



ORALLY DISINTEGRATING FILM: A REVISIT OF ITS TWO DECADES DEVELOPMENT

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Abstract: For the last two decades, oral drug delivery system was extensively discussed in the pharmaceutical field which includes Orally Disintegrating Film (ODF) due to its advantages over other oral dosage form such as tablet and capsule. ODF can be taken without water and classified as patient friendly dosage form especially for geriatric and pediatric who affected the most with swallowing disorder. ODF manufactured by various methods such as solvent casting method, semi solid casting method, hot melting extrusion, solid dispersion extrusion, rolling method and spraying method. ODF formulated using several chemicals like hydrophilic polymers, plasticizer, saliva stimulating agent, surfactant, sweeteners, API, coloring, and flavoring agents. Validation tests such as thickness test, folding endurance, tensile strength, young modulus, disintegration, and dissolution test performed to analyze the mechanical properties, disintegration, and dissolution profile of the film. Some challenges will be encountered in the process of formulating ODF such as API insolubility, unpleasant taste of API, stability issue, and dose uniformity. Those challenges can be overcome with great formulations, high standard manufacturing methods and ideal storage management. In general, ODF have great potential in pharmaceutical market and can be a good tool to enhance the therapeutic convenient of patient which then lead to advancement of healthcare system.

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are certain pathways involved in explaining how oral drugs being absorbed such as transcellular, paracellular, carrier-mediated transcellular and facilitated transport. Among these pathways, transcellular pathway is the most common mechanism in ODDS. Although oral route is the most preferable administration method, there are still numerous of limitations to it such as the low bioavailability rate, unsuitability to peptide drugs like insulin and vaccine, inconvenient to patient with swallowing mechanism disorder and side effects to gastrointestinal tract. Despite all challenges come across ODDS still considered as prudent delivery system for medication and boundless changes have been made to advance patient acceptability towards ODDS (Homayun et al., 2019; Sheaiikh, 2017).

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Oral Drug Delivery System (ODDS)

Drug can be delivered from site of absorption into circulation via many ways such as through oral, dermal, rectal, intravenous and many more. Different delivery system will give rise to different effects such as the onset of the drugs, percentage of drug absorption into circulation and therapeutic action to the body. Among all different types of delivery system, oral pathway has been the most well-known and significant due to its advantages including simple and convenient administration, cost effective, controllable and safe delivery system (Homayun et al., 2019). The absorption process of ODDS is complicated as the drugs need to be completely dissolved before absorbed into blood vessels located in stomach, intestine or rectal. There

Orally Disintegrating Film (ODF)

For the past two decades, an improved interest is seen to develop patient-friendly and compliant dosage form. Thus, the interest for growing new innovations has been expanding every year. Since the development cost of new drug is very expensive, endeavors are currently being made by pharmaceutical companies to formulate new dosage form of existing drug with enhanced safety and efficacy (Amin et al., 2015).

ODF is the new technology of formulation consumption without water (Saini et al., 2012). ODF (figure 1) is a thin oral strip consist of hydrophilic polymer, active pharmaceutical ingredient, and other excipients. The strip will disintegrate few seconds after wet by saliva in oral cavity (Hussain et al., 2018). This will allow the active pharmaceutical ingredient to be released and absorbed.

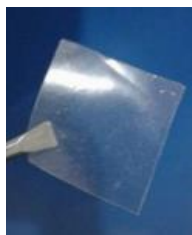


Figure 1: ODF

Manufacturing Methods of ODF

ODF can be formulated using several methods such as solvent casting method, semi solid casting method, hot melting extrusion, solid dispersion extrusion, rolling method and spraying method. ODF can be manufactured by using one or combination methods. Solvent casting method typically being

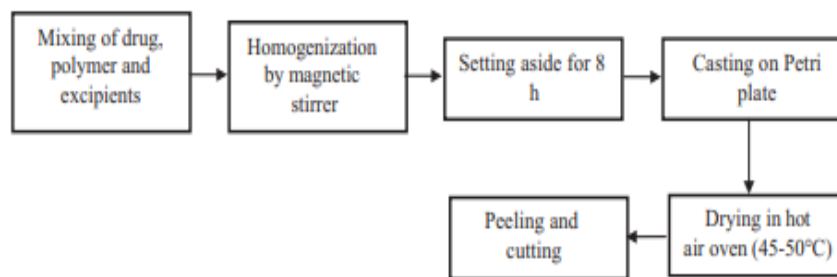


Figure 2. Solvent casting method chart

(Mahboob et al., 2016)

Solvent casting method is an ideal method for thermolabile active pharmaceutical ingredient due to low temperature needed to remove the solvent compared to other methods like hot melting extrusion method. However, oral film formed might contain residual solvent due to low temperature used in drying the film (Amin et al., 2015).

Semi Solid Casting Method

This method is specifically adopted when the polymer used in making the oral film is an acid insoluble polymer such as cellulose acetate phthalate or cellulose acetate butyrate. Firstly, hydrophilic polymer solution is prepared and mix with acid insoluble polymer solution at ratio 1:4. After adding significant amount of plasticizer, a gel mass is gained and casted by using heat controlled drum to form oral thin film (Joshua et al., 2016).

Hot Melting Extrusion

Initially, hot melting extrusion method is used in preparing granules, transdermal and transmucosal drug-delivery system and sustained release tablets. By using the same concept, ODF can be formulated (Amin et al., 2015). Polymer with low molecular weight and low viscosity is suitable for hot melting extrusion method (Saini et al., 2012). All dry ingredients in solid state will be introduced to heat until melt and mixed by using extruder screw. Finally, the melt is forced into film shape by die to form ODF (Joshua et al., 2016).

This method is commonly used due to several advantages such as no water or diluent needed in this method and uniform fine particles film will be produced due to high intensity and agitation created by the extruder (Amin et al., 2015).

Solid Dispersion Extrusion

used to formulate and manufacture ODF (Joshua et al., 2016; Saini et al., 2012).

Solvent casting method

Solvent casting method (figure 2) is a conventional film making process and most used method in producing ODF by dissolving hydrophilic polymer in suitable diluent like distilled water or ethanol. Then, other chemicals such as API, plasticizer, surfactant, flavoring agent, saliva stimulating agent and sweetener are dissolved in the mixture of the polymer and diluent. Stirring process will be carried out by using magnetic stirrer or high shear homogenizer for several hours until homogenous and slightly viscous solution formed. Air bubbles produced in the solution will be removed by using vacuum pump or sonicator. The solution is then cast on carrier such as petri dish or glass and allow to dry by using oven at temperature of 40°C-50°C for 24 hours. After thin film formed, it is peeled and cut into desired size (Irfan et al., 2016; Mahboob et al., 2016).

Solid dispersion extrusion method is prepared by extruding the API with immiscible components to form solid dispersion. Thin oral film is formed by shaping solid dispersions into dies (Amin et al., 2015)

Rolling Method

In this method, rheology factor should be greatly considered when preparing the suspension or solution by using polymer, polar solvent, and additive except active pharmaceutical ingredient. Water and alcohol or combination of water and alcohol can be used as solvent. Required amount of API is then added into the suspension and mixed by using homogenizer until uniform mixture is obtained. The mixture is rolled to get thin oral film and dried using controlled bottom drying. Lastly, the formed oral film is cut into desired size (Mahboob et al., 2016; Saini et al., 2012).

Spraying Method

Active pharmaceutical ingredient, water soluble polymer and other excipients are dissolved in suitable diluent to form homogenous solution. The solution is then sprayed onto suitable carrier such as glass or Teflon sheet. After drying, film will be peeled off and cut into desired sizes.

Challenges in Formulating ODF

ODF currently is the dosage form of choice in the market due to its patient friendly nature compared to tablets and capsules. Prescription of ODF have been approved in many countries like Japan, United States and Europe countries (Galgate, 2019). However, there are many pharmaceutical industries and formulators encountered with few challenges in developing and forming ideal ODF.

Insolubility of Active Pharmaceutical Ingredient (API)

Solubility of API is the rate limiting parameter to get desired drug concentration in the systemic circulation after administrating ODF orally. Drugs under BCS class II classification will encounter problem in dissolving API with selected solvent during formulation process and to dissolve the ODF with saliva after placing it in the oral cavity. Solubility enhancement procedures should be carried out to certain drugs with low solubility and high permeability in order to overcome this problem (Galgatte, 2019).

Taste Masking of Unpleasant Taste of API

Taste is one of the most important factors for ODF as it will dissolve and remain intact with oral mucosa in oral cavity. It will determine patient compliance especially for geriatric and pediatric population (Amin et al., 2015). Sweeteners and flavoring agent being used to mask the unpleasant taste of API and needed to be in correct the correct amount. This will lead to better taste and high compliance.

There are some factors to be considered during taste masking formulation process such as degree of API bitterness, required dose load in the dosage form, drug particles and sizes, drug solubility and bioavailability (Shelke et al., 2012).

Dose Uniformity

Uniformity of dose in the desired size of ODF is very crucial to be delivered to the patient. This will allow optimum therapeutic effect will be produced after placing the ODF on the tongue. Dose uniformity depends upon several factor like drug and excipients solubility in diluent, viscosity of film formulation and drying temperature (Shelke et al., 2012).

API and all other excipients like polymers, plasticizer, sweetening agents, and many more should be fully dissolved in the diluent like distilled water or alcohol. This will allow uniform distribution of API in the film formulation. Next, the viscosity of the mixture needs to be adjusted. Too high mixture viscosity due to the hydrophilic polymer activity will lead to difficulties in transferring the mixture into the petri dish for drying and will affect the uniformity if the dose in the film. Lastly, drying time and temperature should be below melting points of the API and excipients. High temperature and too long drying time will degrade the API and will disturb the uniformity of the ODF produced (Amin et al., 2015; Shelke et al., 2012).

Stability against Humidity

In formulating ODF, hydrophilic polymer used usually around 40%-60%. This will give rise to unstable state of ODF towards humidity or high ambient water content. It will easily absorb the water and liquefied due to dissolution of the film. After the film being formulated, it needs to be stored at specified place such as in the desiccator which contain silica gel to absorb the moisture. Stability of ODF against humidity is one of the biggest challenge and very difficult to overcome (Galgatte, 2019)

ODF Formulation and Agents

In formulating any dosage forms, formulation plays important role in maintaining the high standard and quality of the medication which then lead to safe, effective, and patient friendly medication delivered to patient. Ideal formulation for ODF need to comply and consist of ingredients which are Generally Regarded as Safe (GRAS listed) (Amin et al., 2015). General composition for ODF is shown below:

Active Pharmaceutical Ingredient (API)

Various pharmacological classes of drug can be formulated and incorporated into ODF dosage form such as anti-emetic, vasodilator, anti-asthmatic, antihypertensive and many more.

There are some important properties of the drug to produce good quality of ODF. Common properties like high solubility and high permeability (BCS class I), low dose, non-bitter and quick onset will help in forming good ODF (Irfan et al., 2016; Saini et al., 2012).

Hydrophilic Polymer

To successfully develop ODF, hydrophilic polymer is the most important chemicals as it acts as film former agents and provide mechanical strength to the ODF. They can be used alone or in combination with other polymers. Hydrophilic polymer is water soluble and will dissolve when intact with saliva in buccal cavity and will also determine the dissolution rate of the film. Usually, the polymer should present in the formulation at least 45% and can be up to 65% from the total weight of the dry film (Mahboob et al., 2016; Panda et al., 2012).

Example of hydrophilic polymers are hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC) and carboxymethyl cellulose (CMC), starch and many more (Sharma, 2018). Ideal ODF can be develop if the hydrophilic polymers are non-toxic, non-irritant, should not hinder with the disintegration time of ODF, should have good mechanical properties, should exhibit sufficient tensile strength, should possess good spread ability and should possess adequate shelf-life (Irfan et al., 2016).

Plasticizer

Plasticizer is used to help hydrophilic polymer in enhancing the mechanical strength of the film such as tensile strength and its elongation. It also may improve the flow and prevent brittleness of the film. Plasticizer should be compatible with the API and other excipients. Improper plasticizer selection will lead to splitting and cracking to the final film formed (Joshua et al., 2016). Common examples of plasticizer are phosphate esters, ester of oleate, polyethylene glycol and glycerol (Panda et al., 2012)

Sweetening Agent

Some active pharmaceutical ingredients are bitter in nature. Sweetening agent is used to mask the bitterness of the drug and will lead to increase patient compliance. Generally, sweetener concentration is around 3% to 6% either alone or used in combination. Sweetener can be divided into two which are natural and artificial sugar. Natural sugar is less used due to complication in diabetic patients where they can lead to hyperglycemia while artificial sugar like mannitol, saccharin and aspartame are not affecting blood sugar level and commonly used in formulating ODF (Joshua et al., 2016).

Saliva Stimulating Agent

Saliva stimulating agent is needed to increase the secretion of the saliva so that the oral disintegrating film will be disintegrate and dissolve fast in the mouth. Citric acid or ascorbic acid can be used at 2-6% w/w alone or in combination as saliva stimulating agent (Saini et al., 2012).

Flouring Agent

Any US-FDA approved flavoring agent such as lavender oil, peppermint oil, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers can be incorporated into the formulation. It can be used alone or in combination and should be compatible with API and other excipients and can be added up to 10% (Joshua et al., 2016; Saini et al., 2012).

Coloring Agent

Coloring agent is used to impart interesting color which intend to enhance the ODF elegance. Common example of coloring

agents like titanium oxide or food dye approved by FDA can be incorporated up to 1% w/w (Mahboob et al., 2016).

Validation Tests

There are several validation tests should be run to categorize the quality of the ODF film formed. Validation tests are divided into mechanical test, organoleptic test, content uniformity test, disintegration test and in vitro dissolution test (Saini et al., 2012). Mechanical test aims to evaluate physical characteristics of the film which is the most importance element in getting patient acceptability. Organoleptic test will be conducted to the film which meant to determine the ability of the sweetening agent to mask the unpleasant taste of API. Content evaluation will be based on the standard assay method stated for specific API in pharmacopeia. Content uniformity is determined by estimating the API content in individual strip. Lastly, disintegration and dissolution will be the most important tests to determine bioavailability of the ODF after being produced. It will be based on the time taken of the ODF to disintegrate after in contact with water or saliva water and the dissolution rate of the film (Irfan et al., 2016).

Thickness Test

Thickness test should be done at 5 different points i.e. from center and 4 corners by using calibrated digital Vernier caliper and then mean thickness is calculated (Saini et al., 2012). Uniformity of the thickness is important to ascertain as it is directly proportional to the dose accuracy of the film (Irfan et al., 2016).

Tensile Strength Test

Tensile strength test is the maximum stress applied to the film until its break by using machine such as Instron or Monsanto tester (Liew et al., 2016). It can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below:

Young Modulus Test

Young's modulus or elastic modulus is the measure of stiffness of the strip (Mahboob et al., 2016). It is represented as the ratio of applied stress over strain in the region of the elastic deformation as follows:

Folding Endurance Test

Lastly, mechanical test to evaluate the physical characteristics of the film is folding endurance test. It is run with 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 (Saini et al., 2012)

Disintegration Test

Other test should be implemented is disintegration test. Disintegration test is the medium used to determine the time for the film to dissolve after in contact with some amount of solvent or diluent like distilled water. There are no official guidelines available for determining the disintegration time of ODF (Bhyan, Jangra, Kaur, & Singh, 2011). Normally, the disintegration time for the film is between 5s-30s which varies based on the formulation and composition of the ingredients in the production of the film (Irfan et al., 2016).

Dissolution Test

In vitro dissolution testing can be performed using standard basket or paddle apparatus prescribed in pharmacopeia. There are several criteria to be fulfilled such as 300 ml phosphate buffer with pH of 6.8, 900 ml of 0.1 N HCL, temperature of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and rotation of 50rpm. Sample drug will be analyzed by using UV spectrometer to get the API released in the medium (Irfan et al., 2016).

Organoleptic Test

Organoleptic test will be conducted to the film to ensure the ability of the sweetening agent to mask the unpleasant taste of the Amlodipine. This 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 (Saini et al., 2012). There are several methods to test the efficiency of the sweetening agents to mask the unpleasant taste of the API such as E-tongue evaluation and human taste panel sensory/in vivo taste masking evaluation (Al-Kasmi, Al Rahal, El-Zein, & Nattouf, 2018).

ODF Research Projects in Two Decades

Table 1. ODF Research Projects

No	Drug candidate	ODF manufacturing method	Disintegration time	Reference
1.	Promethazine HCL	Solvent Casting	26.3 - 52.7s	(Hussain et al., 2018)
2.	Mosapride citrate	Solvent Casting	1 – 11 s	(Elmeshad et al., 2011)
3.	Amlodipine Besylate	Solvent casting	20.67 – 723.33 s	(Maheswari et al., 2014)
4.	Dextromethorphan Hydrobromide	Solvent Casting	14 – 37 s	(Kunwarpuriya et al., 2015)
5.	Etoricoxib	Solvent Casting	31 – 38 s	(Senthilkumar et al., 2015)
6.	Diphenhydramine HCL	Solvent Casting	32.63 – 41.88 s	(Samantha et al., 2016)
7.	Lisinopril	Solvent Casting	9.2 – 18.4 s	(Phasate et al., 2015)
8.	Zolmitriptan	Solvent Casting	33.33 – 57.33 s	(Shelke et al., 2012)
9.	Itraconazole	Solvent Casting	90.6 – 151.8 s	(Karagianni et al., 2020)
10.	Ondansetron	Solvent Casting	330 – 420 s	(Koland et al., 2010)

Table 1 shows numerous ODF studies which includes various type of APIs. Most commonly method being used was solvent casting method due to its high successful rate in making ODF and disintegration time for all film mentioned accordingly.

CONCLUSION

ODF technology is rapidly expanding for the last two decades contributed to the enhancement of advance drug delivery system. Numerous APIs including OTC products and

nutraceuticals could be incorporated in this oral dosage form. ODF combined the convenience properties of liquid dosage form with accuracy and stability of solid dosage form. As stated by Technology Catalyst and scholars in this area, ODF has a great potential in the pharmaceutical market for the next 5 to 10

years if all the limitations of this dosage form overcome well by good formulations and high-quality method.

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