Review Article

Role of freeze drying technology in the development of orally disintegrating films

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Abstract

Amongst Oral Drug Delivery System, Orally disintegrating film Technology (ODFT) has gained much attention. The significant advantages of ODFT are it overcomes difficulty in swallowing of oral dosage forms for the administration to pediatric and geriatric population and it is an alternate platform for molecules that undergo first pass metabolism. Thus it shortens onset time, enhances bioavailability and reduces the probability of first pass side effect. The current review describes recent developments in the oral disintegrating films, which includes various techniques for preparation of film and evaluation of oral disintegrating films. This review highlights role and application of freeze drying technology in formulation of orally disintegrating films and evaluation parameters of ODF.

***Keywords*:** Orally disintegrating film, freeze dried film, flash release, thin film strips

Introduction

Dosage forms like tablet and capsules are popular dosage forms in oral route of administration. But children and geriatric patients finds discomfort in swallowing tablets and capsules as oral dosage forms.

Patients with dysphagia, nausea, and vomiting also pose a problems in terms of keeping an oral dosage form down long enough to dissolve and get to work. Psychiatric patients may resist to dosage regimens of medication and conceal it in their mouth to spit out later (Irfan et al., 2015).

In such situations, a rapidly dissolving/disintegrating oral formulation would provide a better solution. Effective way of medication and patients care with extreme rapidly. The technique of lyophilization is applicable in the development of Dosage forms that dissolve rapidly, and offer quick dispersion (Siow et al., 2016).

For treatment which has issues like migraine or diarrhea, unpredictable onset of action, ODF are useful as it gives rapid onset of action with additional benefit of convenience as it do not require water for administration.

A dosage form that is designed for a purpose to dissolve in the oral cavity and being absorbed rapidly needs to meet a key requirements i.e.it must disperse very quickly so that it does not hang in the mouth and cause discomfort or fail to be absorbed effectively. Furthermore, if it is going to be acceptable to the patients, it must be palatable. A product that tastes unpleasant or has a disagreeable, gritty mouth feel is unlikely to gain acceptance.

The role of lyophilization technique is valuable in development of oral drug delivery systems (ODDS). Freeze-drying is a desiccation process, the advantageous material properties attributed to freeze-drying extend to the preparation of stable pharmaceutical products. The important considerations are formulation and process variables as they may affect the final freeze-dried product characteristics. If the dosage form has rapid disintegration and immediate absorption it is effective method of medication and patient care (Liew and Odeniyi, 2015).

A freeze-drying has created new dimensions in the area of oral drug delivery system, where the properties of the drugs, excipients and characteristics of the final solid dosage form can be modified. With the emergence of new applications, the role of freeze drying technology in ODDS is relevant and promising (Liew and Odeniyi, 2015; Abdelwahed et al., 2006; Siow et al., 2016).

Freeze-drying process

Freeze-drying process involves freeze drying cycle which comprises three stages: freezing (solidification), primary

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drying (ice sublimation), and secondary drying (moisture desorption). The success and the efficiency of each stage in a freeze-drying cycle depend upon process parameters such as pressure, temperature, and duration, and should be designed according to desired physical properties of the formulation. The physical properties of formulations in frozen and freeze-dried solid states should be characterized using advanced techniques (Patel et al., 2013; Siow et al., 2016).

The steps required to lyophilize a product in a batch process are as follows:

- Pretreatment / Formulation
- Loading / Container (Bulk, Flask, Vials)
- Freezing (Thermal Treatment) at atmospheric pressure
- Primary Drying (Sublimation) under vacuum
- Secondary Drying (Desorption) under vacuum

Product Containers and Containment Systems

A suitable container system must be chosen for the product. The product containers which are commonly used are flasks, vials and trays. If possible, it is advisable to pick a container that keeps the maximum thickness of the product to less than ¾" (2 cm). Product trays with removable-bottoms are available when working with vials. The tray is loaded with vials, placed on a shelf in the freeze dryer and then the bottom part of the tray is slid out. It allows the containers to rest directly on shelf and increases the heat transfer to the product.

Special containment systems such as glove boxes are required for freeze drying certain products, especially when toxic materials are present (Siow et al., 2016).

Physical properties of materials and formulation

For successful lyophilization process it is essential to understand the physical properties of materials that are freeze-dried. If the material is amorphous it forms glassy state when frozen. The excipients added to a formulation can affect the thermal characteristics of the product and its ability to be freeze dried in a reasonable amount of time (Liew and Odeniyi, 2015; Abdelwahed et al., 2006; Siow et al., 2016; Patel et al., 2013).

Freeze drying process

The Freeze drying is involves following three steps:

Freezing Step

It is the first step which involves the cooling of liquid suspension, and formation of ice crystals of solvents. This results in increase in concentration of remaining liquid. As the liquid suspension becomes more concentrated, its viscosity increases which will there after induce the inhibition of further crystallization. The small amount of water remains in the liquid state and does not freeze which is called bound water (Liew and Odeniyi, 2015; Abdelwahed et al., 2006).

Primary Drying Step

It involves sublimation of ice from the frozen product. In this step, Heat is transferred from the shelf to the frozen solution through the tray and the vial, and conducted to the sublimation front, the ice sublimes and the water vapor formed passes through the dried portion of the product to the surface of the product, then water vapor is transferred to the condenser from the surface of the product through the chamber, and the water vapor condenses on the condenser and drained out. At the end of sublimation step a porous plug is formed. Its pores correspond to the spaces that were occupied by ice crystals.

Secondary Drying Step

It involves the removal of absorbed water from the product. This is the water which did not separate out as ice during the freezing, and did not sublimate in previous step (Liew and Odeniyi, 2015; Abdelwahed et al., 2006).

Classification of fast disintegrating technology

The fast disintegrating technologies can be divided into three main groups (Chaurasiya et al., 2016).

i. Lyophilized systems

ii. Compressed tablet-based

iii. Thin films strips

Lyophilized systems: This system has been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. It involves technology systems taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems (Chaurasiya et al., 2016).

Compressed tablet-based systems: System is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. The speed of disintegration for fast dissolve tablets compared with a standard tablet is achieved by

formulation using water soluble excipients, or super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is biovails fuisz technology. It uses the proprietary shear form system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast dissolve dosage forms (Chaurasiya et al., 2016).

Thin films (OTF): Oral films, also called oral wafers are group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTFs are a proven and accepted technology for the systemic delivery of API is for over-the-counter (OTC) medications and are in the early to mid-development stages for prescription drugs(Chaurasiya et al., 2016).

Classification of oral film

There are three different sub types:

1. Flash release

2. Mucoadhesive melt-away films

3. Mucoadhesive sustained-release films

These three types of oral films are differentiated from each other in following table(Chaurasiya et al., 2016).

Oral films formulation components:

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Sweetening agent
- Saliva stimulating agent
- Flavoring agent
- Coloring agent

Active pharmaceutical ingredients

A typical composition of the film is 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in OFDFs. Multivitamins upto 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OFDFs. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste (Liew and Odeniyi, 2015; Irfan et al., 2015; Lee et al., 2017).

Table 1. Types of Films and their properties

Sr.No.	Property/sub type	Flash release	Mucoadhesive melt-away films	Mucoadhesive sustained release films
1	Area (cm^2)	2-8	2-7	2-4
2	Thickness (mm)	20-70	50-500	50-250
3	Structure	Film: single layer	Single or multilayer system	Multi-layer system
4	Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	Low/non-soluble polymers
5	Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
6	Application	Tongue (upper palate)	Gingival or buccal region	Gingival, (other region in the oral cavity)
7	Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
8	Site of action	Systemic or local	Systemic or local	Systemic or local

Table 2. List of molecules eligible for incorporation in Orally disintegrating films (Irfan et al., 2015; Lee et al., 2017)

Molecules	Therapeutic category	Dose
Betamethasone	Corticosteroid (Anti ulcer)	0.5–10.0 mg
Nitroglycerin derivatives	Vasodilator	0.3–0.6 mg
Zolmitriptan	Antimigraine	2.5 mg
Domperidone	Antiemetic	10 mg
Desloratidine	Antihistaminic	5.0 mg
Diphenhydramine hydrochloride	Antihistaminic	25.0 mg
Loperamide	Antidiarroheal	2.0 mg
Famotidine	Antacid	10.0 mg
Flurazepam	Anxiolytic, Anticonvulsant	15.0–30.0 mg
Chlorpherinamine maleate	Antihistaminic	4.0 mg
Domperidone	Antiemetic	10 mg
Oxycodone	Opoid Analgesic	2.5–10.0 mg
Diclyclomine	Muscle Relaxant	25.0 mg
Omeprazole	Proton pump inhibitor	10.0–20.0 mg
Cetrizine	Antihistaminic	5.0–10.0 mg
Ketoprofen	Anti–inflammatory	12.5–25.0 mg

Film forming polymer

Since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity, the final film that is used must necessarily be water soluble. In order to prepare a thin film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. The polymers can be used alone or in combination to improve hydrophilicity, flexibility, mouthfeel and solubility characteristics of fast dissolving films. The stiffness of the strip depends on the type of polymer and the amount of polymer in the formulation (Irfan et al., 2015; Bhyan et al., 2015; Lee et al., 2017).

Plasticizer

Plasticizer is a vital ingredient of the fast dissolving films. Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. The chemical structure and concentration of plasticizers plays an important role in alleviating the glass transition temperature of the polymers. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of film. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug (Irfan et al., 2015; Lee et al., 2017; Bhyan et al., 2015).

Sweetening agents

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients (Irfan et al., 2015; Bhyan et al., 2015; Lee et al., 2017).

Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Eg. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip (Bhyan et al., 2015).

Flavoring agents

Preferably up to 10%w/w flavors are added in the OFDF formulations The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The selection of flavor is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from synthetic flavor oils,

oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type (Irfan et al., 2015; Bhyan et al., 2015; Lee et al., 2017).

Coloring agents

FD & C approved coloring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. Eg. Titanium dioxide (Irfan et al., 2015; Lee et al., 2017).

Method of Preparation of Orally disintegrating Films

One or more of the following process can be used combinly to manufacture the orally disintergrating films by the application of freeze drying technology (Irfan et al., 2015; Liew and Odeniyi, 2015).

- Solvent casting
- Semisolid casting

Freeze drying (FD) method

The weighing boats were stored in a freezer at 20°C for 2 h to freeze the sample. The frozen samples with the weighing boat were then transferred into the freeze dryer to freeze dry under vacuum suction for 6 h. The film was removed from the weighing boat and stored in a desiccator (Liew and Odeniyi, 2015).

Characterization and evaluation

Characterization of films is accomplished via following tests:

Organoleptic evaluation

Special controlled human taste panels are used for such purpose. This in vivo taste evaluation is carried out on human volunteers. The evaluation of ODFs by *In-vitro* taste is performed by using taste sensors for screening. Both in vivo and in vitro techniques analyze the taste masking ability and sweetness level of taste masking agents (Liew and Odeniyi, 2015; Irfan et al., 2015).

Mechanical properties

Thickness test

Thickness of a film is determined by using calibrated digital micrometer and then subsequently mean average is calculated. Generally, three readings from all the batches are determined and average is calculated. The Weight variation test of a film is calculated in triplicate by cutting the film and determining weight of each film. Uniformity in thickness is important to ascertain as it is directly proportional to dose accuracy of the film (Chaurasiya et al., 2016; Kathpalia and Patil, 2017; Irfan et al., 2015).

Dryness test/Tack test

This test is performed to find out the ability of a film to get adhered to a piece of paper pressed between strips. Obstinacy with which the film adheres with the piece of paper or any

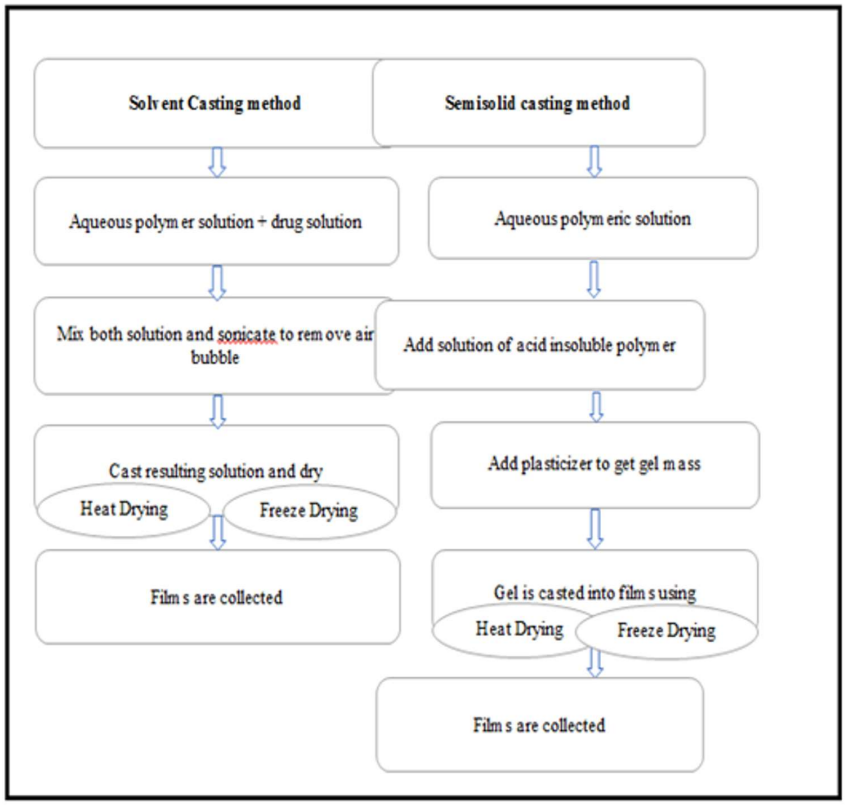

Figure 1. Method of preparation of orally disintegrating Films

other accessory pressed in between the films is known as tack. Almost there are eight stages of film drying process which are identified viz dry-to touch, dry-to-recoat, dry hard, set-to-touch, dust-free, dry-through, tack-free and dry print-free. Primarily these tests are used to evaluate dryness of films in paint industry but are also adoptable for assessing orally fast disintegrating films. Dryness or tack test can also be performed by with the help of some newly invented instruments (Irfan et al., 2015).

Tensile strength

Tensile strength is defined as maximum stress applied at which the film breaks. Basically, this test is performed to measure the mechanical strength of films. It can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below:

Tensile strength

= (Load at failure / Strip thickness x Strip width) x 100

Percent elongation

Upon exerting stress on a film, the specimen stretches which is referred as strain. Strain is defined as change in length of film divided by its original/initial length of the film specimen. The percent elongation test is related quantitatively to the amount of plasticizer used in film formulation. Increased plasticizer concentration in the film generally results in enhanced elongation of the strip (Irfan et al., 2015). It is determined by the following formula:

Percentage elongation = (Change in length / Initial length) x 100

Tear resistance

The intricate function of tear resistance test of film is ultimate resistance to rupture. The maximum force required/applied to tear the film is measured as tear resistance value. This test is typically attributed to plastic industry. The rate of loading employed is 2 inch/minute which is planned to determine the magnitude of force required to initiate tearing in the film specimen. The maximum amount of force necessary for tearing is generally found near the tearing onset which is ranked as tear resistance value (Irfan et al., 2015; Lee et al., 2017).

Young's modulus

It is the measure of film stiffness. It is found as ratio of applied stress to the strain in the elastic deformation region. It is determined by the following formula:

Young's Modulus

= (Slope / Strip thickness x Cross head speed) x 100

It can also be written as:

Young's modulus = Force at corresponding strain / Cross-sectional area x Corresponding strain Hardness and brittleness are characteristics of the films which are related with Young's modulus and tensile strength. A hard and brittle film depicts higher value of tensile strength and Young's modulus with small elongation (Irfan et al., 2015; Lee et al., 2017).

Folding endurance

Folding endurance is another procedure to estimate the mechanical properties of a film. It is measured by repeatedly folding a film at the same point until it breaks. Folding endurance value is number of times the film is folded without breaking. The higher folding endurance value indicates the more mechanical strength of a film. A direct relation exists between mechanical strength and folding endurance of films (Chaurasiya et al., 2016; Lee et al., 2017; Patel et al., 2016).

Swelling property

Simulated saliva solution is used to check the swelling studies of films. Initial weight of film is determined and is placed in pre-weighed stainless steel wire mesh. This mesh containing film is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant predetermined time intervals until no more increase in weight (Irfan et al., 2015). Degree of swelling is determined by these parameters:

Degree of swelling = Final weight (w_t) ¬ Initial weight (W_0) / Initial weight (W_0)

W_t= weight of film at time interval t

W_0= weight of film at time 0

Transparency

Transparency of a strip is determined by using a UV-spectrophotometer. This test is performed by inspecting visual appearance of the formulation. The film are cut into rectangular shapes and placed on the internal side of the photometer cell. Transmittance of the film is worked out at 600 nm wavelength (Irfan et al., 2015). Formula for determining transparency is given as:

Transparency = (logT600)/b = -€c,

T600= transmittance at 600 nm, b= film thickness (mm), c= concentration

Contact angle

Contact angle of a film is usually measured at room temperature with the help of a device known as goniometer. On the dry film surface, a drop of double distilled water is placed. Water droplet images are recorded within 10 seconds after the placement of drop with the help of a digital camera. These digital pictures are analyzed by using image 1.28V software for determining contact angle. Contact angle is measured on both sides of droplets and mean is calculated. Contact angle is determined at least five times at

different positions to have a clear idea about the nature of films (Irfan et al., 2015).

Content uniformity

Contents of a film are determined by standard assay method specified for individual drug in different pharmacopoeia. This test is performed on 20 samples using analytical techniques. The acceptance value of the test is less than 15% in accordance with Japanese pharmacopoeia. According to USP27, the contents should range from 85-115% with the standard deviation of less than or equal to 6%. The content uniformity test is performed to estimating drug contents in individual film (Patel et al., 2016; Chaurasiya et al., 2016; Kathpalia and Patil, 2017).

Disintegration time

The disintegration apparatus mentioned in official pharmacopoeias is used for determining the time required for disintegration of a film. Normally, the disintegration time is the function of composition of film as it varies with the formulation and generally ranges from 5-30 seconds. There are no official guidelines available for determining disintegration time of orally fast disintegrating films. The test is performed by one of the method given below for determining disintegration time of film:

1. Slide frame method

A drop of distilled water is poured onto the film clamped into slide frames placed on petri dish.

Time taken by the film to dissolve is noted.

2. Petri dish method

A film is placed onto 2 ml distilled water taken in petri dish. The time require by film to dissolve completely is considered as the disintegrating time (Irfan et al., 2015).

***In-vitro* dissolution test**

Standard official basket or paddle apparatus is used for conducting dissolution studies on films. Sink conditions should be maintained during dissolution. Sometimes while performing this process, film floats over the medium making it difficult to perform the test properly. This problem is more likely to occur in case of paddle method thus the basket apparatus is mostly preferred. Media used are 6.8 pH phosphate buffer (300ml) and 0.1 N HCl (900ml). Temperature is maintained at 37 ± 0.5^{0}C and rotation speed of 50 rpm is usually adjusted. Samples of drug dissolved are collected at pre-determined intervals and are analyzed by using UV-spectrophotometer. Despite of its extensive use, dissolution test is still prone to noteworthy in accuracy and tests let down (Irfan et al., 2015; Chaurasiya et al., 2016; Kathpalia and Patil, 2017).

Visual inspection and surface morphology

Visual inspection of a prepared orodispersible film can performed by Scanning Electron microscopy and gives information about color, homogeneity and transparency. For surface morphology, scanning electron microscopy is performed. Absence of pores and surface uniformity depict good quality of films (Liew and Odeniyi, 2015; Irfan et al., 2015).

Surface pH

The pH value of a film is usually determined by putting the prepared film in petri dish and subsequently film is made wet by using distilled water and noting pH by touching the film surface with a pH meter electrode. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation (Liew and Odeniyi, 2015; Irfan et al., 2015).

Moisture uptake and moisture loss

Percent moisture loss is a parameter that determines the hygroscopicity of a film. Usually, this parameter is determined by first finding the initial weight of the film, afterwards, putting this film in a dessicator for three days. Dessicator contains calcium carbonate. After three days, strips are taken out and weighed again. Moisture loss is determined by applying the following formula (Irfan et al., 2015).

Percentage moisture loss = Initial weight ¬ Final weight / Initial weight x 100

Moisture uptake of a film is determined by first cutting the film with the dimension of 2 x 2 cm^2. Afterwards these strips are exposed to environment with a relative humidity of 75% at room temperature for 7 days. Moisture uptake is determined as percent weight gain of the strips.

Percentage moisture uptake = Final weight - Initial weight / Initial weight x 100

Conclusion

Oral disintegrating films with good mechanical and release properties can be prepared using freeze-drying technique. Oral thin films are intended for application in the oral cavity and they are innovative and promising dosage form specially for use in pediatrics and geriatrics. They combine the greater stability of a solid dosage form and a good applicability of a liquid and thus bridges the gap between two ideas, incorporating positive elements from both solid and liquid dosage form into an elegant, stable and effective delivery vehicle. So they are of great importance during the emergency cases such as allergic reactions and asthmatic attacks whenever immediate onset of action is desired. Today, OTFS are a proven and accepted technology for the systemic delivery of AIP for over-the-counter (OTC) medications and are in the early-to-mid development stages for prescription drugs.

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Conflict of Interest

We declare that we have no conflict of interest.

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