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MANUFACTURE AND CHARACTERIZATION OF ORAL FILMS AS A DRUG DELIVERY SYSTEM

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ABSTRACT

The tendency of researchers toward innovative drug delivery systems has majorly increased to ensure efficacy, safety and patient acceptability. Discovery and development of new chemical agents is complex, expensive and time consuming process, so recent trends focus on designing and developing innovative drug delivery systems for existing drugs. Out of those, the oral films act as a suitable alternative to patients with swallowing difficulties and also as a more suitable, acceptable and convenient dosage form when compared to the conventional oral dosage forms. The advantages of this drug delivery system may include fast dissolution of the films, the self administrable nature of the technology and the high blood supply of the oral mucosa will enable fast effective treatments for many more conditions. Various approaches are employed for formulating oral films and among which solvent casting and spraying methods are frequently used. Generally, hydrophilic polymers along with other excipients are used for preparing oral films which allow films to disintegrate quickly and release incorporated active pharmaceutical ingredient (API) within seconds. Present review attempts to focus on benefits, composition, approaches for formulation and evaluation of oral films.

Keywords: Oral films, Formulation parameters, Manufacturing methods, Characterization.

INTRODUCTION

Several mucosal surfaces including oral, nasal, rectal, vaginal and ocular have been investigated as delivery routes. Depending on the site, the oral mucosa is 4-4000 times more permeable to that of the skin. Mucosal delivery sites possess the advantage of directly delivering drugs into the systemic circulation and avoiding first pass drug metabolism in the liver and hence pre-systemic elimination of the drug in the gastrointestinal tract. Due to high blood supply and permeability, the oral mucosa is known as an ideal site for the rapid delivery of systemic drugs, for example, in the management of pain, seizures and angina pectoris. The mucosal delivery systems such as rectal, vaginal and ocular delivery systems are restricted to delivery of drugs for local disease rather than systemic drug delivery due to their poor patient acceptability. Nasal delivery also possesses some limitations including the small volume of the nasal cavity, rapid clearance of administered substances and potential disruption of physiological functions of the nasal cavity. Its use for chronic conditions is limited due to the long term administration of drugs across the nasal mucosa can cause irreversible damage to the nasal cilia. However, the oral mucosa is more acceptable and readily accessible as a site for drug delivery. It is more permeable than the skin, is more vascular, has better properties of self repair, less responsive to allergenic and irritant materials and provides a more hydrated environment for solubilization of drugs [7, 12].

The oral cavity comprises three types of oral mucosa; (1) the lining mucosa in the outer oral vestibule

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(the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1) which comprises approximately 60%, (2) the specialized mucosa on the dorsal surface of tongue which comprises approximately 15%, while (3) the masticatory mucosa on the hard palate (the upper surface of the mouth) and the gingiva (gums) which comprises approximately 25% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains that resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized while lining mucosa has a non-keratinized epithelium, which sits on a thin and elastic lamina propia and a submucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa having well papillated surfaces; which are both keratinized and some non-keratinized [19, 21, 25].

The permeability of buccal mucosa is greater than that of the skin (4-4000 times) but less than that of the intestine. Hence buccal delivery serves as an excellent platform for absorption of molecules having poor dermal penetration [7]. The permeability barrier is predominantly comprised of the lipid content of the upper layers of the epithelium. It prevents exogenous and endogenous materials from entering the body across the oral mucosa and also prevents loss of fluid from the underlying tissues to the environment. The epithelium is the major barrier to permeability with the connective tissue. Due to their high level of hydration, connective tissues' provide some resistance to lipophilic materials. After differentiation, supra-basal cells form strong intercellular desmosomal junctions and on their apical surfaces, form membrane coating granules which release lipophilic material into the intercellular spaces ensuring epithelial cohesion. Then this lipophilic material slows the passage of hydrophilic materials across the epithelium [12]. These membrane coating granules present at the uppermost 200 micron layer. The epithelia of oral cavity are composed of an intercellular ground substance which is called as mucus [1, 7]. It consists of proteins and carbohydrates, maintains hydrated condition of the oral cavity, provides adequate lubrication, concentrates protective molecules such as secretory immunoglobulins, and reduces the attachment of microorganisms. The sulfhydryl groups and sialic acid residues of the negatively charged mucin are responsible for mucoadhesion phenomena. The saliva and salivary mucin play an important role in the barrier properties of oral mucosa. The major salivary glands consist of lobules of cells that secrete saliva, parotids through salivary ducts near the upper teeth, submandibular regions (tongue regions), and the sublingual ducts. The minor salivary glands are located in the lips, buccal mucosa, and in linings of the mouth and throat [4, 11]. The total turnover rate of the whole saliva i. e. output from the major and minor salivary glands has a flow rate of 1-2 ml/min at normal physiological conditions. The pH of human saliva has been described previously, with varying results in the wide range of 5.3–7.8, depending on the stimulation state [10].

Polymers interact with the mucin and adhere in one or more of the following ways [25]:

1. Electronic theory: Electronic interactions between polymers, mucin and glycoproteins form adhesion. Electrostatic attraction between positively charged polymers and negatively charged mucin favors the adhesion.

2. Adsorption theory: Chemical interactions between polymers and mucin develop adhesion which is also due to primary chemical bonds or secondary interactions such as van der Waals forces, hydrogen bonds and hydrophobic bonds.

3. Wetting theory: In liquid formulations, the ability of polymers to spread over mucin determines adhesion of a system.

4. Diffusion theory: The mutual diffusion of mucin glycoproteins and polymers to form interpenetrable layer and entanglements forms the adhesion. Factors such as molecular weight, hydrodynamic size affects diffusion of polymers in to mucin.

5. Mechanical theory: Surface roughness on delivery systems determines the adhesion. In this phenomenon, adhesion favors by increased roughness due to increased contact area.

Three methods of diffusion across the permeability barrier of the oral mucosa include [12]

1. Passive diffusion including trans-cellular i.e. through cells and para-cellular i.e. where material passes through lipid rich domains around the cells,
2. Carrier mediated transport, and
3. Endocytosis/exocytosis where material is actively taken up and excreted by cells via the endocytic pathway.

The oral films act as a suitable alternative to patients with swallowing difficulties and also as a more suitable, acceptable and convenient dosage form when compared to the conventional oral dosage forms [3].

This dosage form has some advantages over other oral formulations such as [7, 11] -

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. The disadvantage of most orally disintegrating tablets is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the orally disintegrating tablets. Hence, there is ease of transportation and during consumer handling and storage.
3. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
4. Convenient and accurate dosing.
5. Ease of swallowing for geriatrics and pediatrics.
6. The advantage of ease of swallowing and no need of water has led to better acceptability amongst the dysphagic patients. The difficulty encountered in swallowing tablets or capsules is circumvented. The large surface area

available in the strip dosage form allows rapid wetting in the moist buccal environment. The dosage form can be consumed at anyplace and anytime as per convenience of the individual.
7. Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability.
8. Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
Into this delivery system, a number of molecules can be incorporated including cough/cold remedies (antitussives, expectorants), sore throat, erectile dysfunction drugs, antihistaminics, antiasthmatics, gastrointestinal disorders, nausea, pain and CNS (e.g. anti-parkinsons disease) [7].

MATERIALS AND METHODS

Formulation consideration

The formulation of oral strip involves the intricate application of aesthetic and performance characteristics (taste masking, fast dissolving, physical appearance, mouth-feel etc). From the regulatory perspectives, all excipients which are used in the formulation of oral strip should be Generally Regarded as Safe and should be approved for use in oral pharmaceutical dosage forms The excipients required in the formulation of oral strip are given below as per their categories.

Strip forming polymers

For the preparation of oral strip, a number of polymers are available which can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage to the film while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount of polymer in the formulation. The strip forming polymer serves as the platform for the oral strip and is the most essential and major component of the oral strip. At least 45%w/w of polymer should be used based on the total weight of dry oral strip. Pullulan, gelatin and hypromellose are most commonly used polymers for preparation of oral strip. Pullulan provides highly clear and homogenous films, has low oxygen permeability and low water content which makes it most suitable for the production of oral strip. Due to low cost of modified starches, it is used in combination with pullulan to decrease the overall cost of the product. Generally, 60 to 65%w/w of water soluble polymer is preferred for preparation of oral strip [7].

To improve the hydrophilicity, flexibility, mouth-feel and solubility of oral strip, mixtures of polymers are used. Copovidone is mixed with poly vinyl pyrrolidone because polyvinyl pyrrolidone films are brittle in nature. Combination of microcrystalline cellulose and maltodextrin has been used in the formulation of piroxicam oral strip.

The polymer should be non-toxic, non-irritant and devoid of leachable impurities, should have good wetting and spreadability property, should exhibit sufficient peel, shear and tensile strengths, should be readily available and should not be very expensive. A number of polymers can be used to modulate the disintegration property of the oral strip. Polymers should have good shelf life and they should not cause secondary infections in the oral mucosa or dental regions.

Mucoadhesive polymers include polycarbophil, cellulose derivatives like hydroxypropyl methylcellulose, poly (acrylic acid) derivatives, sodium carboxymethyl cellulose, hydroxylethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hyaluronic acid, xanthan gum, locust bean gum, guar gum, carrageenan, sodium alginate, agar, acacia, Poly-L (lactide-coglycolide) (PLGA), chitosan, poly (ethylene oxide), poly (ortho esters), poly (hydroxyl butyrate), poly (cyano acrylates), polyphosphazenes, poly vinyl pyrrolidone, poly (vinyl alcohol), Poly(methacrylates) etc. Second generation mucoadhesive polymers include thiolated polymers.

Plasticizers

Plasticizer is a vital ingredient of the oral strip formulation which helps to improve the flexibility of the strip and reduces the brittleness of the strip [7]. Plasticizer improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and the type of solvent employed in the casting of strip. Examples of the some commonly used plasticizers are 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.

The plasticizers are used in the concentration of 0 - 20 % w/w of dry polymer weight. The properties of plasticizer are important to decrease the glass transition temperature of polymer in the range of 40 - 60˚C for non aqueous solvent system and below 75˚C for aqueous systems.

Plasticizer should be compatible with drug and other excipients used in the preparation of strip. Malic acid was found to be better plasticizer as compared to citric acid, oleic acid and tartaric acid because it did not crystallize out when the strips were dried. PEG 300 was found to be better plasticizer for gelatin as compared to higher molecular weight PEG because lower molecular weight PEG formed visually superior films and had low water vapor permeation rate.

In case of sugars, sorbitol was found to be better as compared to mannitol since mannitol crystallizes out from the gelatin strip. Certain drug molecules themselves act as plasticizer. For example, Ibuprofen played the role of a plasticizer by interaction with Eudragit RS 30 D. The two mechanisms of how the plasticization takes place are

internal plasticization (involving chemical interaction) and external plasticizing effect. The chemical structure and concentration of plasticizers play an important role in reducing the glass transition temperature of the polymers.

Active pharmaceutical ingredients

High dose molecules are difficult to be incorporated in oral strip due to the limited size of the dosage form. Generally, active pharmaceutical ingredients can be incorporated in the oral strip in the concentration of 5% w/w to 30% w/w. Multivitamins were incorporated in the oral strip up to 10% w/w of dry film weight with dissolution time of less than 60 seconds. APIs can also be added in the oral strip as milled, micronized or in the form of nanocrystals or particles depending upon the ultimate release profile desired.

Some active pharmaceutical ingredients have bitter taste which makes the formulation unpalatable especially for pediatric preparations. Hence, the taste needs to be masked before incorporating the API in the oral strip. Various methods can be used to improve the palatability of the formulation from which the simplest method is obscuration technique involves the mixing and co-processing of bitter tasting active pharmaceutical ingredient with excipients with pleasurable taste. Barrier technologies that can also be used to mask the bitter taste include complexation, polymeric coating, conversion into microparticles/microcapsules, coated particles or coated granules. Complexation technology involves the use of cyclodextrins, resins which prevents the direct contact of bitter active pharmaceutical ingredient with saliva by surrounding it. For taste masking of bitter drugs, the drug can be matrixes or can be coated with water insoluble polymer. The bitter taste of paracetamol was masked by using the lipidic excipients like hard fat and lecithin.

For the taste masking of active pharmaceutical ingredients, a novel salting out technology was developed which involved coating of drug substance with salting out layer consisting of salt and water soluble polymer. The bitter taste of the drug is masked by the salt which reduced the dissolution of water soluble polymer and drug from the system. The polymer and drug was released and resulted into immediate release of the drug by decreasing the salt concentration in the system. Lag time was generated with subsequent immediate release during this salting-out taste-masking system. The technology was successfully carried out for the taste masking of paracetamol used as model drug.

Sweetening agents

The sweet taste in formulation is main factor in case of pediatric population. To enhance the palatability of the mouth dissolving formulations, natural sweeteners as well as artificial sweeteners are used in the preparation of oral strip. Sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

The classical source of sweetener is sucrose that is derived from cane or beet in the form of liquid or dry state, dextrose, fructose, glucose, liquid glucose and maltose. In comparison to sucrose and dextrose, the sweetness of fructose is perceived rapidly in the mouth. Fructose is widely used as a sweetener due to its greater sweetening power than sorbitol and mannitol [7]. Some sweeteners like polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol are used in combination because they additionally provide good mouth-feel and cooling sensation. These are less carcinogenic and do not have bitter after taste. Xylitol and maltitol have similar sweetness as that of sucrose (scale of 0.8 - 1.0).

The artificial sweeteners have gained more importance in food and pharmaceutical preparations because of restriction of natural sugars in the case of diabetic patients or the people who are on diet. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners whereas acesulfame-K, sucralose, alitame and Neotame fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness respectively while Neotame and alitame have more than 2000 and 8000 time sweetening power respectively as compared to sucrose. A herbal sweetener, Rebiana, which is derived from plant Stevia rebaudiana (South American plant), has more than 200–300 time sweetness. But these artificial sweeteners give the after taste effect. The combination of natural and artificial sweetener can reduce this disadvantage of artificial sweeteners. The oral strips of valdecoxib were prepared by using aspartame as a sweetener. Maltodextrin was used as sweetening agent for the oral strip of piroxicam.

Saliva stimulating agents

Saliva stimulating agents are used to increase the rate of production of saliva that improves the disintegration of the rapid dissolving strip formulations. Acids such as citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid can be utilized as salivary stimulants [13]. Citric acid is the most preferred salivary stimulant. These are used alone or in combination in concentration of 2 to 6%w/w of weight of the strip.

Sweeteners also act as salivary stimulants. Food grade sugars as well as synthetic sugars including glucose, fructose, xylose, maltose, and lactose are useful salivary stimulants. The stimulant action of sweeteners depends on their sweetness value. Fructose has the sweetness value of 1.1 whereas glucose has 0.7 and sucrose has 1.0. Due to lower concentration requirement, the artificial sweetener is preferred than the natural sugar as saliva stimulating agent. The comparison between the salivary stimulation using citric acid and other sugars is given in Table 1.

Flavoring agents

Depending upon the ethnicity and liking,

perception for the flavors changes from individual to individual. Age plays a significant role in the taste fondness. The geriatrics likes mint or orange flavors while younger generation like fruit punch, raspberry flavors. Flavors are also used alone or in the combination. The selection of flavoring agent is also dependent on the type of drug to be incorporated in the formulation. For example, mint flavor used for products used for indigestion. Flavoring agents can be selected from synthetic flavor oils (peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg); oleo resins, extract derived from various parts of the plants like leaves, fruits (fruity flavors like vanilla, cocoa, coffee, chocolate and citrus) and flowers. Few examples of fruit essence type are apple, raspberry, cherry, pineapple, etc. The amount of flavor required to mask the taste depends on the flavor type and its strength. Flavors are added up to 10% w/w in the oral strip formulations. Monomethyl succinate as a cooling agent can be added in the oral strip to improve the flavor strength and to enhance the mouth-feel effect of the product.

Coloring agents

FD&C approved coloring agents or pigments such as titanium dioxide are incorporated in oral strip in the concentration levels up to 1%w/w [13]. Coloring agents are incorporated when some of the formulation ingredients or drugs are present in insoluble or suspension form.

Stabilizing and thickening agents

The stabilizing and thickening agents are used in the preparation of oral strip to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. The examples of thickening agents and stabilizing agents include natural gums like xanthan gum, locust bean gum, carragenan and cellulosic derivatives, etc. These can be used in the concentration up to 5%w/w. Other ingredients include surfactants and emulsifying agents. These are added in small amount to improve the strip properties.

Methods for manufacturing of oral films

Methods employed for manufacturing of oral films are as follows -

Solvent casting method

Solvent casting method is the most commonly used method for the preparation of oral films using water soluble excipients, polymers and drug which are dissolved in de-ionized water [2, 30]. A homogenous mixture is obtained by means of high shear forces generated by a shear processor. Then, the prepared solution is poured onto the petri plate and the solvent is allowed to dry by exposing it to high temperature.

In solvent casting technique, film forming polymer is soaked in an appropriate solvent for overnight. The type of API that has to be incorporated in oral film governs the selection of a suitable solvent depending on physico- chemical properties of API such as melting point, shear sensitivity and polymorphic form. Compatibility of drug with solvent and other excipients is also important. Deaeration of the mixture is carried out with the help of a vacuum pump (Fig. 2) [13].

Semi-solid casting method

Flow map of semi-solid casting method is given below in Fig. 3 [13].

Hot melt extrusion

In this technique, a mixture containing drug, polymer and excipients is extruded under high temperature to form a homogenous mass and then this homogenous mass casted to form smooth films. This is a solvent free process; however, the major drawback of this process is processing of thermolabile substances due to the use of high temperature during extrusion (Fig. 4) [13].

Solid dispersion extrusion

The flow map of solid dispersion method is given below in Fig. 5 [13].

Rolling method

Plot of rolling method is shown in Fig6. For rolling onto the drum, the prepared solution should possess specific rheological properties [13].

Spray technique

In spray technique, drug substance, polymers and all other excipients are dissolved in a suitable solvent to form a clear solution and then this clear solution is sprayed onto suitable material such as glass, polyethylene film of non-siliconized Kraft paper or Teflon sheet (Fig. 7) [13].

Characterization and evaluation

Films are characterized for following parameters:

1. Organoleptic evaluation

Special controlled human taste panels are used for such purpose. This in vivo taste evaluation is carried out on human volunteers. In vitro taste evaluation of oral films 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.

2. Mechanical properties

2.1. Thickness test& weight variation

Thickness of a film is determined by using calibrated digital micrometer and mean average is calculated [2, 6, 27].Three readings from all the batches are determined and average is calculated. Weight variation of a film is calculated in triplicate by cutting the film and determining weight of each film. Uniformity in thickness is directly proportional to dose accuracy of the film.

2.2. 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. The 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 are used to evaluate dryness of films in paint industry but are also adoptable for assessing orally fast disintegrating films. Some newly invented instruments are useful in performing dryness or tack test.

2.3. Tensile strength

This test is performed to measure the mechanical strength of films [24]. Tensile strength is maximum stress applied at which the film breaks and can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below [7, 9, 31]:

Tensile strength = [load at failure / (strip thickness ×strip width)] ×100

2.4. Percent elongation

Strain is defined as change in length of film divided by its initial length of the film specimen [7]. Percent elongation is related quantitatively to the amount of plasticizer used in film formulation which is determined by the following formula:

Percentage elongation = (change in length / initial length) × 100

Increased plasticizer concentration in the film enhances elongation of the strip.

2.5. Tear resistance

Tear resistance of film is the intricate function of its ultimate resistance to rupture. Maximum force required to tear the film is measured as tear resistance value. The rate of loading employed is 2 in/min to determine the magnitude of force required to initiate tearing in the film specimen [7, 20]. Tear resistance value is the maximum amount of force necessary for tearing is generally found near the tearing onset.

2.6. Young's modulus

It is the measure of film stiffness [20]. It is found as ratio of applied stress to the strain in the elastic deformation region and is determined by the following formula:

Young's modulus = [slope / (strip thickness × cross head speed)] × 100

It can also be written as:

Young's modulus = force at corresponding strain / (cross-sectional area × corresponding strain)

The characteristics of the films such as hardness and brittleness are related with Young's modulus and tensile strength. A hard and brittle film shows higher value of tensile strength and Young's modulus with small elongation.

2.7. Folding endurance

Folding endurance value is number of times the film is folded without breaking and is measured by repeatedly folding a film at the same point until it breaks [22, 28]. Higher folding endurance value shows the more mechanical strength of a film and mechanical strength is governed by plasticizer concentration so it is clearly evident that plasticizer concentration indirectly affects folding endurance value.

3. Swelling property

Simulated saliva solution is used to check the swelling property of films [16, 18]. Initial weight of film is determined and is placed in pre-weighed stainless steel wire mesh. This mesh is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant pre-determined time intervals until no more increase in weight. Degree of swelling is determined by formula [15, 29]:

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.

4. Transparency

Transparency of a strip is determined by using a UV-spectrophotometer. This test is performed for visual appearance of the formulation. Film specimens 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. Transparency is determined by formula:

Transparency = (log T600) / b = -€c

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

5. Contact angle

Contact angle of a film is measured at room temperature with the help of a device known as goniometer (Fig. 1.8). A drop of double distilled water is placed on the dry film surface. With the help of a digital camera, water droplet images are recorded within 10 s after the placement of drop. These digital pictures are analyzed by using image 1.28 V 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.

Fig. 1.8: Goniometer

6. 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 [16].According to Japanese pharmacopoeia, the acceptance value of the test is less than 15%. According toUSP27, the contents should range from 85% to 115% with the standard deviation of less than or equal to 6%. Content uniformity is worked out for estimating drug contents in individual film.

7. Disintegration time

The disintegration time is the function of composition of film as it varies with the formulation and generally ranges from 5 to 30 seconds. Disintegration apparatus mentioned in official pharmacopoeias is used for determining the disintegration time of a film [5, 26]. Mostly, the USP disintegration apparatus is used for this test. There are no official guidelines available for determining disintegration time of orally fast disintegrating films. Two methods for determining disintegration time of film are:

7.1. Slide frame method

In this method, a drop of distilled water is poured onto the film clamped into slide frames placed on petri dish and time taken by the film to dissolve is noted.

7.2. Petri dish method

A film is placed onto 2 ml distilled water taken in petri dish and time taken by the film to dissolve completely is considered as the disintegrating time.

8. In-vitro dissolution test

Standard official basket or paddle apparatus is used for conducting dissolution studies on films [1, 14].Sink conditions should be maintained during dissolution. Sometimes film floats over the medium in case of paddle method thus the basket apparatus is mostly preferred. Media used are 6.8 pH phosphate buffer (300 ml) and 0.1 N HCl (900 ml). This test is carried out at the temperature of 37 ± 0.5˚C and rotation speed of 50 rpm. Samples of drug dissolved are collected at pre-determined intervals and are analyzed by using UV-spectrophotometer.

9. Visual inspection and surface morphology

Visual inspection of a prepared orodispersible film gives information about color, homogeneity and transparency. Scanning electron microscopy is performed for surface morphology. Absence of pores and surface uniformity depicts good quality of films.

10. Surface pH

The pH value of a film is usually determined by putting the film in petri dish and is made wet by using distilled water [4]. pH is noted 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.

11. Moisture uptake and moisture loss

Percent moisture loss is a parameter that determines the hygroscopicity of a film. In this test, the initial weight of a film is noted and then the film is placed in a dessicator for three days. Dessicator contains calcium carbonate. After three days, films are taken out and weighed again. Moisture loss is determined by the following formula.

Percentage moisture loss =[(initial weight - final weight) / initial weight] × 100

Moisture uptake of a film is determined by cutting the film with the dimension of 2 × 2 cm^2. These strips are then exposed to environment with a relative humidity of75% 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] × 100

PACKAGING OF ORALLY DISINTEGRATING FILMS

Packing considerations are critical for storage, protection and stability of dosage form. Packaging for oral thin films includes foil paper or plastic pouches, single pouch, aluminum pouch, blister packaging with multiple units and barrier films. Barrier films are most commonly used for moisture sensitive drugs. The films are manufactured by a laminating process and packaging costs are comparable to tablets. Films can be packaged in single or multiple dose packages. Single dose packaging provides primary stability of the product and avoids potential fusing of some multi dose packaging formats. Multiple dose packaging is more expensive to develop but is less expensive to manufacture in large quantities [8].

Table 1. Data on comparison between the salivary stimulation using citric acid and other sugars [7]

Stimulant	Molarity	Flow rate (mL/min)	Time required for returning to initial flow rate (min)
Citric acid	0.26	1.68	7.3
Glucose	1.17	0.52	6.7
Fructose	1.17	0.97	8.7
Sucrose	1.17	0.74	6.3
Aspartame	0.034	0.82	6.8
Sodium saccharin	0.42	1.04	10.5

The resting salivary flow rate was 0.34 mL/min.

Fig. 1. Schematic representation of the different linings of mucosa in mouth [21]

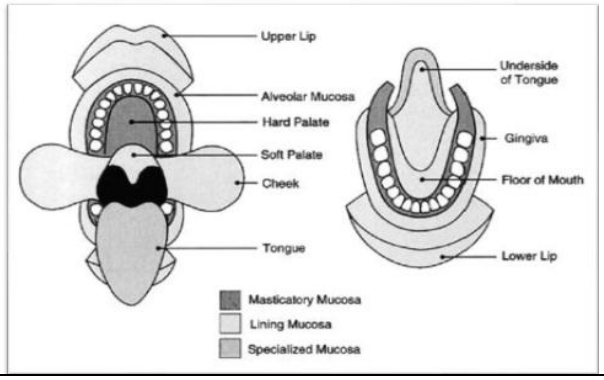


Fig. 2. Flow chart of solvent casting method

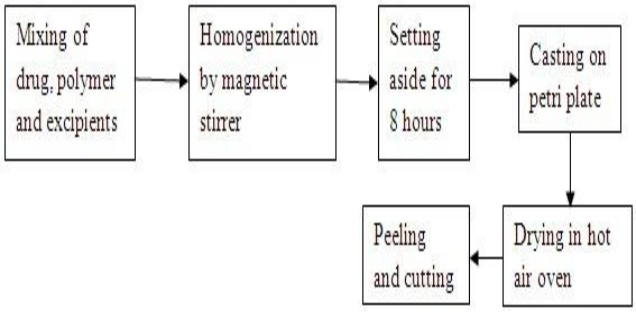


Fig. 3. Flow map of semi-solid casting method

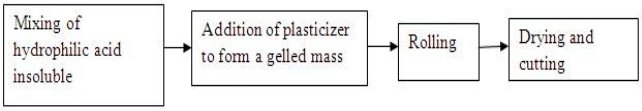


Fig. 4. Flow chart of hot melt extrusion method

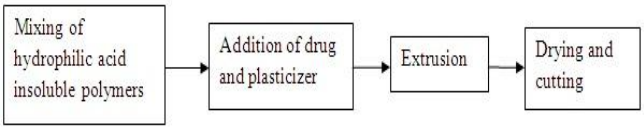


Fig. 5. Flow map of solid dispersion method

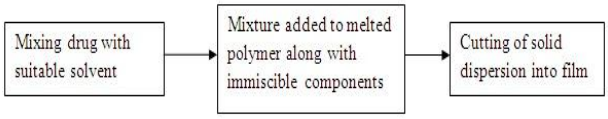


Fig. 6. Plot of rolling method

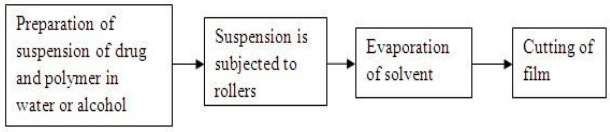
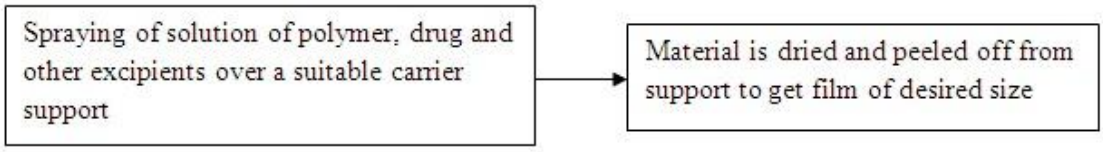


Fig. 7. Flow map of spray method



CONCLUSION

The aim of any drug delivery system is to reach the desired site and give the desired therapeutic action without or minimal side effects. An ideal buccoadhesive system adheres to the site of attachment for a few hours, releases the drug in a controlled fashion, facilitates the rate and extent of drug absorption, does not cause any irritation or inconvenience to the patient, does not interfere with the normal functions (talking, drinking etc.) and that provides unidirectional drug release toward the mucosa and hence the oral films are one of the novel approaches in the field of pharmaceutical sciences. The oral films are widely available for hypertension, acidity, allergy, pain, etc. and act as a suitable alternative to patients with swallowing difficulties and also as a more suitable, acceptable and convenient dosage form when compared to the conventional oral dosage forms.

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