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A BRIEF REVIEW ON ORAL FILM TECHNOLOGY

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ABSTRACT
The purpose of the current review is to enlighten present and future perspective on oral film drug delivery system. Now-a-days we observe paediatric and geriatric patients facing the problem of dysphasia due to administration of monolithic solid dosage forms, which are also seen in the case of fast dissolving tablets considering the size of the tablets. Hence oral film drug delivery is proved to be better alternative in such cases. The oral films are formulated using polymers, plasticizers, flavors, colors and sweeteners. The oral film is manufactured using solvent casting method, rolling method, extrusion method and solid dispersion method. The films are evaluated for dimensions, disintegration, dissolution, tensile strength and folding endurance. It has many applications like taste masking immediate release and sustained release formulation.

KEYWORDS: Oral strips, Solvent casting technique, Electronic tongue, Packaging.

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INTRODUCTION
Oral route drug administration is considered to be most effective and acceptable form due to its better therapeutic efficacy and good patient compliance. Peroral dosage forms can be distinguished as solid or liquid oral dosage forms in which the prior fall in category of pills, capsules, granules, and powders[1,2] while the latter includes solutions/suspensions or emulsions offering more advantages over monolithic solid dosage forms. However they also possess certain disadvantages such as finding non-toxic excipients and need preservatives, which might cause adverse effects in children, microbiological stability, and also shows problems with the taste masking and dose accuracy[4]. To overcome these problems associated with the liquids dosage forms, Oral Dissolving Tablets (ODTs) were designed in early 19th century, which slowly led to their further development and thus came the existence of Oral Disintegrating Films (ODFs).

Oral medicated strips/films
A strip or film can be defined as a dosage form that employs a water-dissolving polymer (generally a hydrocolloid, which may be a bio adhesive polymer), which allows the dosage form to quickly hydrate, adhere, and dissolve when placed on the tongue or in the oral cavity (i.e., buccal, palatal, gingival, lingual, or sublingual, etc.) to provide rapid local or systemic drug delivery.

Characteristics of an ideal orally soluble film drug delivery system
- Do not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Compatible with taste masking and other excipients[3].
- They posses pleasant mouth feel[5].
- Leave minimal or no residue in the mouth after oral administration.
- They can withstand the rigors of the manufacturing process and post manufacturing handling[6].
- Resistant to environmental conditions such as humidity and temperature[6].
- They are adaptable and amenable to the existing processing and packaging machinery.
- Processing and packaging of strips / films can be done at low costs prices[6].

Advantages of oral films
a) The oral film administered sublingually and buccally deliver the drug with high potential to improve the onset of action, lower the dose, and enhance the efficacy and safety profile of the medicament[7].
b) All single unit dosage forms, soft gels and liquid formulations primarily enter the blood stream via the

gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first pass effects. As a result, such formulations often require higher doses and generally have a delayed onset of action, which can be overcome using current oral film drug delivery systems that avoid these issues and yield quicker onset of action at lower doses[8].

c) Oral film is more stable, durable and quicker dissolving than other conventional dosage forms.
d) Oral film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain a precise amount of the drug.
e) Oral film ensures more accurate administration of drugs.
f) Oral films can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration. These properties are especially beneficial for paediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult.
g) Oral film's ability to dissolve rapidly without the need for water provides an alternative to patients with dysphasia and to patients suffering from nausea, such as those patients receiving chemotherapy.
h) Oral film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations.
i) From a commercial perspective oral film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition.
j) Sublingual Film delivers a convenient, quick-dissolving therapeutic dose contained wioralan abuse-deterrent film matrix that cannot be crushed or injected by patients, and rapidly absorbs under the tongue to ensure compliance[8].

Disadvantages of oral film

Oral disintegrating films have limitations in terms of the amount of drug that can be incorporated in each unit dose. For lyophilized dosage forms, the drug dose must generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. Also, due to the nature of ODTs, special packaging is needed for products that are fragile, which may add to the cost[9].

To avoid these minute problems associated with oral disintegrating Film - Oral Soluble Film came to existence from early 1970s since then a tremendous research work was carried out in this current field to delivery active ingredients through oral cavity, using soluble film technology.

Choice of drug candidate

Suitable drug candidate for orally soluble chewable films should posses

- No bitter taste or if it is then it should be masked.
- Good stability in water and saliva.
- Dose should be low as possible.

Unsuitable drug candidate for orally soluble chewable films should include

- Short half-life and frequent dosing.
- Required controlled or sustained release.

With the above mentioned information earlier studies were carried out to deliver lidocaine, as local anaesthetic, for dental applications from polymer films. However, recently several thin-film or strip intraoral dosage form technologies have been developed as a means to quickly release an active ingredient upon administration of the film on the tongue. Thin-film and strip intraoral dosage forms have been developed by several companies including LTS Lohman Therapie-Systeme AG, Zengen Inc., and Lavipharm Laboratories introducing Quick-Dis™ and Slow-Dis™ technology based on a unique solution-coating process where the formulation is dispensed and metered to a controlled thickness onto a moving bed and dried in precision temperature-controlled multi zone ovens, die-cut, and packaged. Generally these films dissolve rapidly (within seconds), to release the drug, whose release can be altered depending upon their thickness, and selection of the polymer matrix[10].

CONCEPT OF FORMULATION FOR FILM DRUG DELIVERY SYSTEM

Film Forming Polymers

A number of polymers are used in the preparation of Oral Soluble film technology. They can be used either individually or in combination, to impart the desired properties into the film. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type and concentration of the polymer used[11]. The various polymers used are Pullulan, Gelatin and hypromellose(Table 1). Pullulan is a natural polymer obtained from no animal origin and does not require chemical modification. Modified starches are also used for preparation of Oral films. The excipients being more economical, it is used in combination of Pullulan to decrease the overall cost of the product. About 50 to 80 percent w/w of Pullulan can be replaced by starch in the production of Oral film with no loss in the properties of Pullulan. Combination of microcrystalline cellulose and maltodextrin has also been used to formulate Oral film[12,13]. The polymer employed should be non-toxic, non-irritant and devoid of leachable

impurities. It should have good wetting and spreadability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Various polymers can be employed to modulate the disintegration property of the oral strip. This is especially used in case of slowly disintegrable oral bio adhesive strips or patches that need to be retained in intact form for longer duration in the oral cavity[14]. Polymers used for OS should have good shelf life and they should not aid in causing secondary infections in the oral mucosa or dental regions. It would be ideal to have a polymer that would have local enzyme inhibition action along with penetration enhancing property. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. Water-soluble polymers are used as film formers which achieve rapid disintegration, good mouth feel and mechanical properties to the films. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxymethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrin and Eudragite[15,16]. Polymerized rosin is a novel film forming polymer. Polymers are categorized according to strip forming capacity such as very poor, poor, average, good, better, best[17].

Active Pharmaceutical Ingredient

The oral dissolving thin film technology has the potential for delivery of variety of APIs. Since the size of the dosage form is limited, high dose molecules are difficult to be incorporated into the films allowing only 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated into the film and up to 10%w/w of dry film weight was incorporated into the oral thin films in the case of multivitamins[18]. The water soluble APIs are present in the dissolved state or in the solid solution form in the films whereas the water insoluble drugs are dispersed uniformly in the strip. APIs can also be added as milled, micronized or in the form of nanocrystals or particles depending upon the ultimate release profile desired. It is always advantageous to have API micronized that adds improvement to the texture of the film showing better dissolution and uniformity in the oral film[19]. Many APIs that can be potentially used for Oral film technology are with bitter taste which makes the formulation unpalatable especially for paediatric formulations. This leads to the very significant unit operation- taste masking, before incorporating the API in the oral dissolving film.

Various methods can be used to improve the palatability of the formulation[20]. Among the techniques employed, the simplest method involves the mixing and blending of bitter tasting API with excipients with pleasurable taste which is termed as obscuration technique. Barrier technologies can also be used to mask the bitter taste which includes complexation, polymeric coating, conversion into micro particles/microcapsules, coated particles or coated granules. Depending on the material employed and type of the taste masking technique and the manufacturing technique, the rate of drug release varies. Hence, the issue of palatability and drug release needs to be balanced to make it advantageous for the development of Oral Soluble film formulation[21].

The Oral Soluble film technology offers advantages in certain clinical situations. For drugs that are projected as local anaesthetic or pain killer, the Oral films has projected improved clinical benefits. Certain pathologies require instantaneous release of the medicament for prompt relief. For instance, in the case of migraine a rapid clinical effect is desired by the individual. Regiospecific delivery of the medicament would be required in the cases of sore throat, cough, allergy and other local oral manifestations. Breath strips also offer superior consumer compliance. Similarly, cases of motion sickness need immediate attention. This dosage form can also be used for natural extracts and neutraceutical including vitamin B12, chromium picolinate, melatonin and possibly CoQ10. (Table 2)

Plasticizers

Plasticizer is an important ingredient for the Oral dissolving thin film formulation. It imparts flexibility to the strip by reducing its brittleness. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer[22]. The plasticizer selection will depend upon its compatibility with the polymer and also solvent employed in the casting of strip. The flow of polymer will be improved with the use of plasticizer that 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 plasticizers in the concentration of 0–20%w/w of dry polymer weight. However cracking, splitting and peeling of the film might occur with the inappropriate use of plasticizer. The Plasticizer employed should impart the permanent flexibility to the film which depends on the volatility of the plasticizer and the type of interaction with the polymer. Plasticizer should be compatible with drug as well as other excipients used for preparation of oral films.

Various studies were carried out in different plasticizers to study their plasticization effect on the gelatin strips

which resulted in observation that malic acid was found to be better plasticizer when compared to citric acid, oleic acid and tartaric acid as it did not crystallize out when the films were dried. Amongst the different grades of polyethylene glycol (PEG); PEG 300 was found to be better plasticizer for gelatin as compared to higher molecular weight PEG. This is because lower molecular weight PEG formed visually superior transparent films and had low water vapour permeation rate[23]. When sugars like mannitol and sorbitol were tested as plasticizers for gelatin strips, sorbitol was found to be better as compared to mannitol since it showed the similar problem like that of citric acid. Maltodextrin can also be plasticized and converted into oral dissolving film with incorporation of glycerine and propylene glycol as plasticizer in the concentration range of 16–20%w/w, and found to be more advantageous by using glycerine over propylene glycol as it shows miscibility problems with maltodextrin either by using solvent casting or hot melt extrusion methods. In some cases certain drug molecules themselves can act as plasticizer[24]. For example, Ibuprofen interacted with Eudragit RS 30 D and played the role of a plasticizer. There are two mechanisms propagated of how the plasticization takes place namely internal plasticization (involving chemical interaction) and external plasticizing effect, the latter mechanism is more proffered as it does not involve chemical interactive alterations in the product.

Saliva Stimulating Agents

The saliva stimulating agents are used to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving film formulations. Generally acids which aroused in the preparation of food are utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the considered as the salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip. Other Oral film ingredients such as sweeteners also act as salivary stimulants. Food grade sugars along with the synthetic sugars are useful salivary stimulants along with acidulents.

Sweetening Agents

Sweeteners have become the significant part of the food products as well as pharmaceutical dosage forms intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more preferred especially in case of paediatric population. Natural sweeteners as well as synthetic sweeteners are used to improve the palatability of the formulations. The traditional source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is dissolved rapidly in the saliva compared to sucrose and dextrose and also sweeter than sorbitol and mannitol for which it is used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, Iso malt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are considered less carcinogenic and do not project bitterness after tasting which is a vital aspect in formulating oral preparations. The sweetness property of the polyols is less than half of that of sucrose except xylitol and maltitol which have similar sweetness as that of sucrose (scale of 0.8–1.0). However the use of such natural sugars is restricted in the case of diabetic patients and diet conscious patients. Due to this reason, the synthetic sweeteners have gained more popularity both in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the synthetic sweeteners followed by acesulfame-K, sucralose, alitame and neotame that fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is an herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200–300 time sweetness but these synthetic sweeteners carry a disadvantage of after taste effect which can be reduced by mixing or blending the natural and synthetic sweeteners. The flavor quality of these synthetic sweeteners is different than the natural sweeteners and is generally disliked by patients accustomed by the natural sweeteners. The amalgamation of sweeteners may lead to synergism and improvement in the taste of the formulations. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow of saliva for the equal time under similar conditions. The stimulant action of sweeteners is dependent on the sweetness value. Fructose has the sweetness value of 1.1 as compared to 0.7 of glucose and 1.0 of sucrose.

Flavoring Agent-

Perception for the flavors changes from individual to individual depending upon the ethnicity and liking. 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. The selection of flavor is also dependant on the type of drug to be incorporated in the formulation. For example, mint flavor is generally added

in products used for gastric related ailments like indigestion. The acceptance of the oral disintegrating or dissolving formulation by an individual 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. Flavoring agents can be selected from synthetic flavor oils, oleoresins, 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. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferably up to 10%w/w flavors are added in the OS formulations. Cooling agents like monomethyl succinate can be added to improve the flavour strength and to enhance the mouth-feel effect of the product. Other cooling agent's likeWS3, WS23 and Utracoll II can also be used in conjunction with flavors.

Colouring Agents

Pigments such as titanium dioxide or FD & C approved colouring agents are incorporated (not exceeding concentration levels of 1 percent; w/w) in OS.

MANUFACTURE PROCESS OF FILMS

One (or a combination) of the following processes may be used to manufacture the oral films:

- Solvent casting
- Hot-melt extrusion
- Solid dispersion extrusion
- Rolling method.

Solvent Casting Technique

The method of solvent casting technique involves preparation of the film base which involves the mixing of suitable film forming excipients along with drug in a suitable solvent or solvent system. Once the solution is prepared, the film casting process is performed wherein a film of desired thickness is casted onto a moving inert substrate, where suitable rollers are employed for guiding the solution onto the substrate. The clearance or tolerance between the roller and the substrate determines the required thickness of the film; this process is used in large scale production wherein glass or teflon plates can be used as inert support material to cast a film at the laboratory scale. The formed strip is then subjected to drying process to remove the solvent[25].

The selection of solvent essentially depends on the API to be incorporated into the film. The physicochemical properties of the API like heat sensitivity, shear sensitivity, the polymorphic form of the API employed, compatibility of the API with solvent and film based excipients are to be critically studied. The predominant factors to be considered are liquid rheology, desired mass to be casted and uniformity of drug content. Solvent systems used in the preparation of solution or suspension should be selected carefully and more preferably from ICH Class 3 solvent list.

Heating processes can be used to assist the complete dissolution of materials. Mixing may cause formation of air bubbles and their entrappment during the solution preparation. Entrapped air tend to produce uneven films. Deaeration step is imperative to get a uniform film which may be achieved by vacuum assisted machines.

Another important aspect is the moisture present in the solution. It is observed that moisture can cause changes in the mechanical properties of the films such as tensile strength, flexibility, folding endurance, Young's modulus, elongation etc. Hence care should be exercised by using suitable humidity controls in the manufacturing production area. The solution is subjected to continuous mixing process in order to keep the viscosity and concentration unchanged. The solution or suspension may be kept under controlled temperature condition to achieve the desired viscosity of the material.

Hot Extrusion Process

Hot melt extrusion (HME) is commonly used to prepare granules, sustained-release tablets, and transdermal and transmucosal drug delivery systems. This technique involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting method[26]. In this process API and other ingredients are mixed in dry state which are subjected to heating process and then extruded out in molten state. These processes do not involve use of any solvents systems. The molten mass thus formed is used to cast the film. The films are further cooled and cut to the desired size. The main disadvantage of this process is high temperature used in the process might degrade thermolabile APIs. The critical step is the casting and the drying process. Optimization of speed of casting and drying time are important from the commercial scale output. Hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix (<2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters, and possibility to scale up. Repka et al. prepared chlorpheniramine maleate (CPM) topical HPC films by hot melt extrusion technique using hydroxy propyl cellulose as polymer.

Solid Dispersion Extrusion

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic

polymers and also using methods such as melt extrusion[27]. This involves a drug which is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of suitable polymer, obtainable below 70º C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polymer.

Rolling Method

In this method, the film is prepared by pre-mixing of an active ingredients and excipients followed by subsequent addition of the solvent. The pre-mix or master batch which includes the film- forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank .Then a pre-determined amount of the master batch is controllably fed via a first metering pump and control valve to either or both of the first and second mixers. The required amount of the drug is added to the desired mixer through an opening in each of the mixers. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan through the second metering pumps. The film is finally formed on the inert substrate and carried away via the support roller[28]. Thus the wet film is then dried using controlled bottom drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film.

EVALUATION OF ORAL FILM

Organoleptic Evaluation

Color is a vital means of identification for many pharmaceutical products and is also usually important for consumer acceptance. The color of the product must be uniform within a dosage form.

Odor is also be important for consumer acceptance of oral dosage forms and can provide an indication of the quality of oral strips or films as the presence of an odor in a batch could indicate a stability problem. However, the presence of an odor may be characteristic of the drug (e.g. vitamins), added ingredients (e.g. flavoring agent).

Taste is also essential factor for the consumer acceptance and many companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product. Taste preference is however subjective and the control of taste in the production of oral soluble films is usually based on the presence or absence of a specified taste[29].

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high throughput taste screening of oral pharmaceutical formulations. Experiments using electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste-masking formulation.

Electronic Tongue

Electronic tongue is also called as artificial tongue or taste sensor. The first multi-sensor system for liquid analysis was based on a poor selectivity approach introduced by Toko *et al* in 1990 and termed it as taste sensor system. Later this was named as "Electronic tongue". This multi-sensor array system shows the perfect correlation of the instrument with that of human perception for various substances. The test was carried out for the liquid samples that are directly analyzed without any preparation, whereas solids require a preliminary dissolution before measurement[30]. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds. A potentiometric difference between each sensor and a reference electrode is measured and recorded by the E-Tongue software.

Thickness

The thickness of film can be measured by digital micrometer screw gauge or digital vernier callipers at different planned locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose distribution in the film. The thickness of film should be in range of the 5-200 micrometer. The thickness of the film can be adjusted depending upon the surface area and thickness of different areas in mouth. The thickness of different parts of mouth is mentioned as following. (Table 4)

Dryness Test/Tack Tests

Dryness is the property is to measure the water or used solvent content. Tack is the tenacity with which the film adheres to an accessory (a piece of paper) that has been pressed into contact with the film. Instruments are also available for this study.

Tensile Strength

Tensile strength is the maximum stress (applied at one point) required for a oral film to breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

Tensile strength = Load at failure × 100 / Strip thickness × Strip width

Percent Elongation

When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increases.

%elongation = Increase in length of strip × 100 Initial length of strip

Tear Resistance

Tear resistance of the oral film is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm (2 in.)/min is employed and is

designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds-force).

Young's Modulus

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's modulus = Slope × 100/Strip thickness × cross - head speed

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Folding Endurance

Folding endurance is determined by repeated folding of the film till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Disintegration Time

The disintegration time limit of orally films is 90s or less. Although, no official guidance is available for oral fast disintegrating films/strips, but for orally dissolving tablets is 30s or less is described in Center for Drug Evaluation and Research, this may be used as a qualitative guideline for quality control test at development stage. By modifying the Pharmacopoeial disintegrating test apparatus may be used for this study[31]. Typical disintegration time for strips is 5–30s.

Dissolution Test

Dissolution testing can be performed using the standard USP paddle over disc and basket or paddle apparatus described in any of the pharmacopoeia. The volume of the dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the film to float onto the dissolution medium when the paddle apparatus is employed. Another method to determine the drug release from the oral film via conductivity[32].

Assay/Drug Content and Content Uniformity

The test for the content uniformity is carried out taking a sample film of size 1×1 cm^2 which is placed in a beaker containing 10 ml of a suitable medium. The contents were stirred in a cyclo-mixer to dissolve the film which was transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at particular wavelength using a standard assay method described for the particular API mentioned in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual film. Limit of content uniformity is 85–115%.

Contact Angle

Contact angle measurements are performed at room temperature with a goniometer (AB Lorentz and Wettre, Germany). A drop of double distilled water was placed on the surface of the dry film. Images of the water droplet were recorded within 10 seconds of deposition by means of digital camera. Digital pictures were analyzed by image 1.28v software (NIH, USA) for angle determination. A minimum of five measurements are taken at different positions of the film. The contact angle was measured on both sides of the drop and average is taken[33].

Storage and Packaging

Owing to the preparation of film considered to be quite interesting, even the storage of the film gained the sense of attention in order to dispense in such a manner that it reaches to the expectations of both storage properties required to be maintained along with easy packaging and also easy withdrawal of the drug delivery system by the patient.

After sizing of the films into desired dimensions they are to be stored in the controlled conditions at 25^0C/65% RH and/or at 40^0C/75% RH in a stability chamber for about 12 months as mentioned in the ICH guidelines Q1A. In order to prevent from any contamination the films are clamped to the slide frames to maintain the films from contacting from any surfaces and also from each other and this also helps in saving the space[34].There are different varieties of packaging processes available for fast dissolving films. Single packaging is quite widely used in the case of the pharmaceutical products which generally involve an aluminium pouch used for the packaging format.

APR-Labtec has developed the special designed packaging system called Rapid card, a proprietary and patented packaging system for the Rapid films. The rapid card resembles that of a credit card that can hold three rapid films on either side. They are stacked upon each other and can be easily taken out individually just by sliding with a single finger. Further these quick dissolving strips or films are available in a number of flavors which are packed into a small disposable plastic or metal packlet with a proper hermetic sealing containing 20 to 32 strips per pack. The non-adhering films are stacked upon each other and a single strip can be easily dispensed by placing a finger on the strip and moving it forward with a sliding motion, thus dispensing the strip out of the packlet.

APPLICATIONS OF FILM DELIVERY SYSTEM

Taste Masking: Oral film systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients on contact with the taste buds and hence, taste masking of the drugs becomes critical to make it

patient compliant. An important aspect of thin oral film technology is the masking of the bitter and poor taste of drug formulations. One method of taste-masking is encapsulation, the coating of drug particles with polymers sufficient to mask the taste of the drug particle while maintaining the ability to release the drug for absorption.

Orally Disintegrating Films: Oral thin film disintegration property is based on the polymers used. The film disintegrates rapidly within seconds in contact with water or saliva, releases the drug in the mouth and promotes gastrointestinal absorption.

Vaccination: Oral thin film can be used to deliver vaccines by quickly dissolving in mouth and in saliva. Rotavirus vaccine is prepared in US by Johns Hopkins University in 2006. Rotavirus vaccine is a room temperature stable quick-dissolving oral thin film delivery system for vaccines that will make vaccinations almost as simple as breath freshners. This delivery system exhibits many advantages not available in current products which include improved patient compliance, improved bioavailability, reduction in the costs associated with storage, distribution, handling and administration.

Sustained Release Film: Sustained release oral film is applicable in hospital preparations and drug carriers using polymer Chitin and chitosan derivatives as excipients and drug carriers in the pharmaceutical field. Chitosan is used as excipients in oral dosage form. Films prepared using chitin or chitosan have been developed as wound dressings, oral mucoadhesive and water-resisting adhesive by virtue of their release characteristics and adhesion.

COMMERCIAL TECHNOLOGIES AND MARKETED PRODUCTS

Over-the-counter and neutraceutical market followed into OST after breath fresheners with a range of fast dissolving strip products prepared for active ingredients such as vitamins, herbal extracts and non herbal extracts. Pfizer had introduced Listerine® pocketpaks® in 2001 for bad breath and Novartis had introduced their famous Triaminic and Theraflu brands in OS form. Biofilm is utilizing this technology for the brand extension of the existing pharmaceuticals products along with the neutraceuticals targeting population of specific age group which include aphrodisiac, energy boosters, vitamins and appetite suppressor. Biofilm has also targeted to improve in the life style of consumers by developing and commercializing the Oral film by incorporating various neutraceuticals like energy boosters which are Oral film products to target especially students, drivers etc. which contain a mixture of caffeine, green tea extract and guarana to maintain energy levels.

CONCLUSION

This brief review on oral films concludes with the note that they are considered as a most promising and important drug delivery system today because of their rapid disintegration, improved dissolution properties especially with paediatric and geriatric patients. Even though most of the formulation today are developed as ODTs, oral film has gain more popularity because of their easy portability, improved patience compliance and ease of administration. They can be applied by both oral and buccal routes. Apart from being used as medicated films (local anaesthetics, vitamins supplements, and cold – allergy remedies) they can also be used for refreshing the breath. This technology is growing in fast pace challenging most of the pharmaceuticals companies to develop oral films for a wide range of active pharmaceuticals ingredients.

REFERENCES

1. Biradar SS, Bhagavati S, Kuppasad J. Fast Dissolving Drug Delivery Systems: A Brief Overview, the Internet Journal of Pharmacology. 2006; 4.
2. Habib W, Khankari R, Hontz J. Fast-dissolving drug delivery systems, critical review in therapeutics, Drug Carrier Systems, 2000; 17(1):61-72.
3. Rathbone MJ, Hadgraft J. Absorption of drugs from the human oral cavity, International Journal Pharm. 74 (1991); 9–24.
4. Dr Breitkreutz jorg, Heinrich-Heine-University Dusseldorf, Institute of Pharmaceutics and Bio pharmaceutics, University 1, 40225 Dusseldorf, Germany ,Pharmaceutical Medicine.
5. Liang AC, Chen, Li-Lan H. Fast-dissolving intraoral drug delivery systems, Expert Opinion., 2001; 11(6):981-986.
6. "Oral Thin Films," in Orally Disintegrating Tablet and Film Technologies, 5th ed., Technology Catalysts International, Falls Church, VA, 2008.
7. Dixit RP, Puthli SP. Oral strip technology: Overview and future potential, Journal of Controlled Release, v;139: 97.
8. Chang R, Goo X, Burnside BA, Couch R. Fast-dissolving tablets, Pharm Tech., 2000; 24(6):52-58.
9. Quick Dissolving Oral Dosage Forms: Scientific and Regulatory Considerations from a Clinical Pharmacology and Bio pharmaceutics Perspective, Intraoral Delivery Systems, An Overview, Current Status, and Future Trends, Drug Delivery to the Oral Cavity Molecules to market. 2005:344.
10. William R, Pfister and Tapas K. Intraoral Delivery Systems, An Overview, Current Status, and Future Trends, Drug Delivery to the Oral Cavity Molecules to market. 2005:20.
11. Corneille C. Quick dissolving strips: from concept to commercialization, Drug Delivery Technology. 2006;6(2): 68–71.
12. Scott R, Cade D, X He. Pullulan film compositions, U.S. Patent 7,267,718, Sept. 11, 2007.
13. Franchiser C, Slominski G, Meyer S. Disintegrable oral films, U.S. Patent 2007/ 0202057; Aug. 30, 2007.
14. http://www.hughes-medical.com/products/fast-dissolving-film.htm
15. Cilurzo F, Paola M, Andrea C. Maltodextrin Fast –Dissolving Film: A Feasibility Study, Pharma Films Srl, Milano Italy.
16. Chien MJ, Tirol G, Chien C, Schmitt R. Film forming polymers in oral films. Poster presented at the 2006 Annual

Meeting and Exposition of the American Association of Pharmaceutical Scientist Oct. 29– Nov.2AAPS. 2006; 1-5.
17 Kulkarni AS, Deokule HA, Mane MS and Ghadge DM. Exploration of different polymers for use in the formulation of oral fast dissolving strip,JCPR 2010; 2(1): 33-35.
18 Sakellariou P, Rowe RC, White EFT. An evaluation of the interaction and plasticizing efficiency of the polyethylene glycols in ethylcellulose and hydrokypropyl methylcellulose films using the tensional braid pendulum, Int J Pharm. 1986;31: 55–64.
19 Hariharan M, Bogue A. Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms, Drug Del. Technol., 2009;9(2): 24–29.
20 Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches, Drug Dev. Ind. Pharm. 2004;30:429–448.
21 Szejtli J, Szente L. Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins, Eur. J. Pharm. Biopharm. 2005;61(3): 115–125.
22 Sakellariou P, Rowe RC. Interactions in cellulose derivative films for oral drug delivery, Prog. Polymer. Sci. 1995;20:889–942.
23 Palmieri A, Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients, Pharmaceutical press, London, 2006; pp. 790 791.
24 Kennedy SW, Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients, Pharmaceutical press, London, 2006; pp. 792–793.
25 Corniello CM. "Quick-Dissolve Strips: From concept to commercialization". Tech. 2006;6(2):68-71.
26 Hoffmann & Baron, LLP (6900 Jericho turnpike, Syosset, NY, 11791, US) United States Patent Application 20080226695.
27 Anand V, Kataria M, Kukkar V, Saharan V, Choudhury PK. The latest trends in the taste assessment of pharmaceuticals, Drug Discovery Today 2007;12:257–265.
28 Murray OJ, Dang W, Bergstrom D. Using an electronic tongue to optimize taste masking in a lyophilized orally disintegrating tablet formulation, Pharm. Technol. (2004); pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?Id=112227.
29 Hung-Weichen, Ren-Jang Wu, Horn-How Chen. and Yih-Lu Sun. ISNCGS. 2004; 31.
30 Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Sugiyama T. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film, Int J Pharm. 2009;368(1–2): 98–102.
31 Preparation and characterization of fast dissolving Oral films for paediatric use, on at a dissertation at Heinrich University. April 2009.
32 Pfizer had introduced Listerine® pocketpaks® in 2001 http://www.listerine.com/product-pocket-paks.jsp.
33 Novartis had introduced their famous Triaminic http://www.triaminic.com
34 Biofilm is utilizing this film technology for the brand extension http://www.biofilm.co.uk.

Table 1: Different types of Polymers Used For Oral Strips/ Films

S.NO	POLYMERS USED	FILM FORMING CAPACITY	APPEARANCE	DISINTEGRATION TIME (SEC)
1	HPMC E-15+PEG400	Good	Transparent	120
2	HPMC E-15+ GLYCEINE	Good	Transparent	92
3	HPMC K4M	Very Poor	-	-
4	HPMC E-5	Average	Semitransparent	127
5	PVP	Very Poor	-	-
6	GELATIN	Very Poor	-	-
7	EUDRAGITE RL100	Very Poor	-	-
8	HPMC E-15+ PULLULAN	Poor	-	-
9	PVA+PVP+GLY	Average	Transparent	64
10	PVA+PVP+PEG 400	Average	Transparent	52
11	HPMC E-15+ PVA	Average	Transparent	78
12	PULLULAN +PVA	Very Poor	-	-
13	HPMC E-15+ PVP	Average	Transparent	67
14	HPMC E-15+MCC	Better	Semitransparent	42
15	PULLULAN +GUAR GUM+ XANTHAN GUM+CARRAGENON	Best	Transparent	19

Table 2: List of few active molecules eligible for incorporation in strip dosage forms

Molecule	Levocetirizine	Chlorhexidine gluconate	Diclyclomine	Famotidine	Ketoprofen	Loperamide
Therapeutic category	Antihistaminic	Antimicrobial	Muscle Relaxant	Antacid	Anti–inflammatory	Antidiarroheal
Dose	5.0–10.0 mg	0.12%	25.0 mg	10.0 mg	12.5–25.0 mg	2.0 mg

Table 3: List of sweetening agents commonly used in oral disintegrating formulations

STIMULANT	Aspartame	Fructose	Glucose	Sodium saccharin	Sucrose
MOLARITY	0.034	1.17	1.17	0.42	1.17
FLOW RATE (ml/min)	0.82	0.97	0.52	1.04	0.74
TIME REQUIRED FOR RETURNING TO INITIAL FLOW RATE (min)	6.8	8.7	6.7	10.5	6. 3

Table 4: **List of some Human Epithelia Characteristics**

	BUCCAL	SUBLINGUAL	GINGIVAL	PALATAL
THICKNESS	500-600	100-200	200	250
KERATIZATION	NO	NO	YES	YES

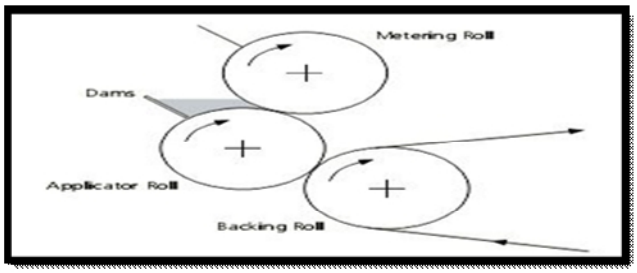

Figure 1. Rolling machine for film production.

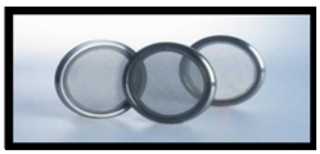

Figure 2. Standard USP paddle over disc