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**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**Available online at: <http://www.iajps.com>**Review Article****A PRECISE REVIEW ON FAST DISSOLVING ORAL FILMS****Perumalla Ashok Kumar^{1*}, Dr. Deenanath Jhade²**¹Research scholar, Department of Pharmaceutics, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India.²Associate Professor, Department of Pharmaceutics, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India.**Abstract:**

Orally fast dissolving films (OFDFs) have been introduced in the market recently as they provide convenience and ease of use over other dosage forms such as orally disintegrating tablets. This technology 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, so OFDFs are gaining the interest of large number of pharmaceutical industries. Orally fast dissolving film is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. OFDFs are very similar to postage stamp in their shape, size and thickness. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The present review provides an account of various formulation considerations, method of preparation and quality control of the OFDFs.

Keywords: *Fast dissolving films, Fast disintegration, Oral strips, Tensile strength.***Corresponding Author:****Perumalla Ashok Kumar,**

Research scholar,

Department of Pharmaceutics,

Sri Satya Sai University of Technology and Medical Sciences,

Sehore, Madhya Pradesh, India.

Email ID: perumalalashok@gmail.com

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INTRODUCTION:

Among the different routes, the most agreeable route for the patients is oral route. Most of the pharmaceutical companies have directed their research activity in developing viable dosage alternatives from oral route for pediatrics, geriatric, noncompliant or nauseous patients. Research in the oral drug delivery segment has led to evolution of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet to wafer to the recent development of fast dissolving oral films. Fast dissolving oral film, a novel drug delivery system for the oral delivery of the drugs is an ultra thin film prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity. It is an ultrathin strip (50- 150 microns thick) of postage stamp size with an active agent and other excipients developed on the basis of transdermal patch technology[1]. These evolved from the confectionery and oral care markets over past decade in the form of breath strips and became a novel and widely accepted dosage form by consumers for delivering vitamins and personal care products. These fast dissolving oral films have persistent to extend in sales and launched as patient compliant and convenient products effectively addressing issues for pharmaceuticals as well as nutraceuticals that have been traditionally administered as oral solid dosages. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application [2]. It then rapidly disintegrates in a matter of seconds and dissolves to release medication for oromucosal absorption. Today, fast dissolving oral films are a well proven and world wide accepted technology for the systemic delivery of active pharmaceutical ingredients (APIs).

Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of \$500 million in 2007 and could reach \$2 billion in 2012. Based on upward global growth trends of the

past decade, the fast dissolving dosage market could produce revenues of \$13 billion by 2015



Fig 1: oral thin film

Special features of mouth dissolving films

- ✓ Thin elegant film
- ✓ Available in various size and shapes
- ✓ Unobstructive
- ✓ Excellent mucoadhesion
- ✓ Fast disintegration
- ✓ Rapid release

ADVANTAGES

Fast dissolving oral films being an advanced evolution of fast dissolving drug delivery systems have some outstanding advantages over conventional dosage forms and orally disintegrating tablets. They are:

- ✓ Improved patient compliance.
- ✓ As fast dissolving thin oral films are flexible, they are easy to carry, store and handle, which is not the case with orally disintegrating tablets (fragile and brittle)
- ✓ Precision in the administered dose is ensured from each of the strips as compared to drops or syrup formulations.
- ✓ Water is not needed for administering, so problem encountered in swallowing of tablets or capsules can be evaded.
- ✓ Patients suffering from repeated emesis, dysphagia, and motion sickness prefer this dosage form as they are unable to swallow large quantity of water.
- ✓ Availability of larger surface area leads to fast disintegration and dissolution in the oral cavity.
- ✓ As the oral mucosa is being highly vascularized, drugs directly enter the systemic circulation without undergoing first-pass hepatic metabolism.
- ✓ This results in improved oral bioavailability of molecules. These films can be manufactured through economically feasible nonsophisticated procedures and uncomplicated equipment.

The ideal characteristics of a drug to be selected

- ✓ The drug should have pleasant taste.
- ✓ The drug to be incorporated should have low dose— upto 40 mg
- ✓ The drugs with smaller and moderate molecular weight are preferable.
- ✓ The drug should have good stability and solubility in water as well as in saliva.
- ✓ It should be partially unionized at the pH of oral cavity.
- ✓ It should have the ability to permeate oral mucosal tissue.

Disadvantages

- ✓ High doses cannot be incorporated.
- ✓ Dose uniformity is a technical challenge
- ✓ Active pharmaceutical ingredient
- ✓ Film forming polymers
- ✓ Plasticizer
- ✓ Sweetening agent
- ✓ Saliva stimulating agent
- ✓ Flavoring agent
- ✓ Coloring agent

FORMULATION INGREDIENTS**Drug (1-25%)**

Several class of drugs can be formulated as mouth dissolving films including antiasthmatics (Salbutamol sulphate), antiulcer (Omeprazole), expectorants, antitussives, NSAID'S (Valdecoxib, Meloxicam) .

Water Soluble Polymers (40-50%)

To obtain the desired film properties, polymers can be used alone or in combination. Generally water-soluble polymers are used as film formers as they achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The strength of the film depends on the type of polymer and the amount in the formulation. By increasing the molecular weight of polymer film bases, disintegration rate of the polymer decreases. Polymers frequently used as film formers are water soluble grades of cellulose ethers, polyvinyl alcohol, polysaccharides, polyvinylpyrrolidone K- 90, polyethylene glycols, pullulan, gelatin, carboxmethylcellulose cekol 30, hydroxy propyl methyl cellulose E-3 and K-3, methyl cellulose A- 3, A-6 and A-15, pectin, sodium alginate, hydroxypropylcellulose, maltodextrins and eudragit RD10 .

Plasticizers (0-20%)

Plasticizer enhances mechanical properties such as tensile strength and elongation to the film by

reducing the glass transition temperature of the polymer. It also reduces brittleness of the strip as a result improves its flexibility. Choice of plasticizer depends upon type of solvent used and its compatibility with the polymer. Some of the commonly employed plasticizers are phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and glycerol. Improper use of plasticizer may lead to blooming, film cracking, splitting and peeling of the strip.

Surfactants

Surfactants are used as wetting or solubilising or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed are polaxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is polaxamer 407.

Sweetening agents

Some of the commonly employed sweeteners are dextrose, sucrose, fructose, glucose, isomaltose, polyhydric alcohols (sorbitol, mannitol), etc. Artificial sweeteners like saccharin, cyclamate, aspartame (first generation) and acesulfame-K, sucralose, alitame, neotame (second generation) can also be used.

Saliva stimulating agents

Saliva stimulating agents are used to increase the rate of production of saliva that would help in the faster disintegration of the rapid dissolving strip formulations. Examples of salivary stimulants are citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. Among these the most preferred one is citric acid.

Flavouring agents

The quantity of flavouring agent required to mask the taste depends on the flavour type and its strength. Commonly employed are fruity flavours (vanilla, cocoa, coffee, chocolate, citrus), flavour oils (peppermint oil, cinnamon oil, oil of nutmeg). Flavours can also be chosen from oleo resins, synthetic flavour oils and extract derived from various parts of the plants like fruits, flowers etc.

Colouring agents

Generally incorporated colouring agents are FD&C colours, natural colours, pigments such as titanium dioxide etc .

MANUFACTURE PROCESS OF FILMS [3-8]

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.
- ✓ Semisolid casting

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.

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 entrapment during the solution preparation. Entrapped air tends 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.

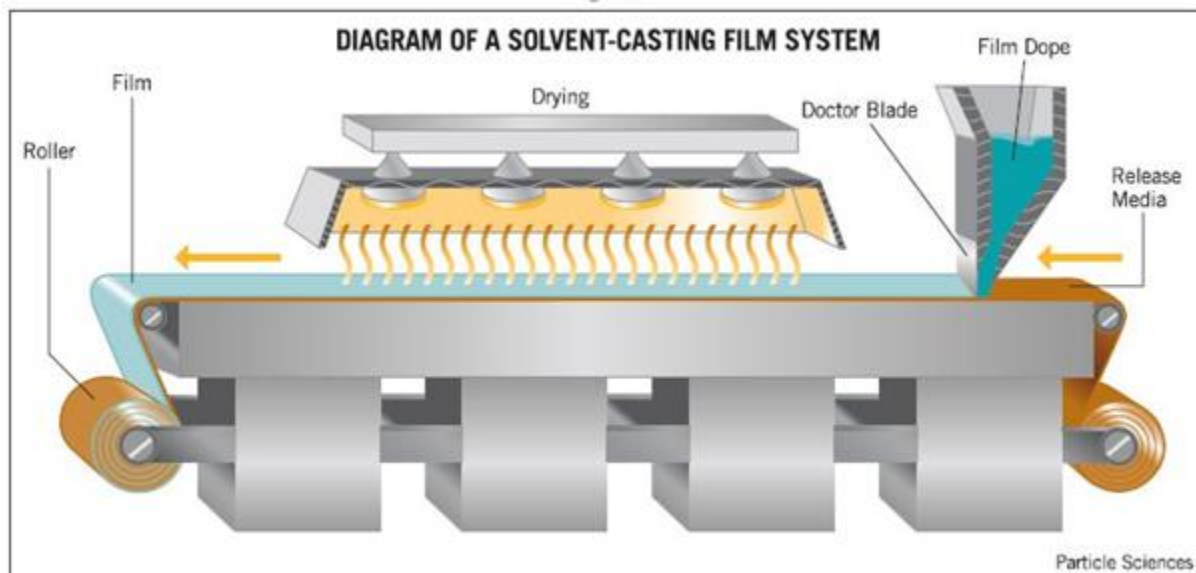


Fig 2: Solvent casting film method

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. 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. 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 70° C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polymer.

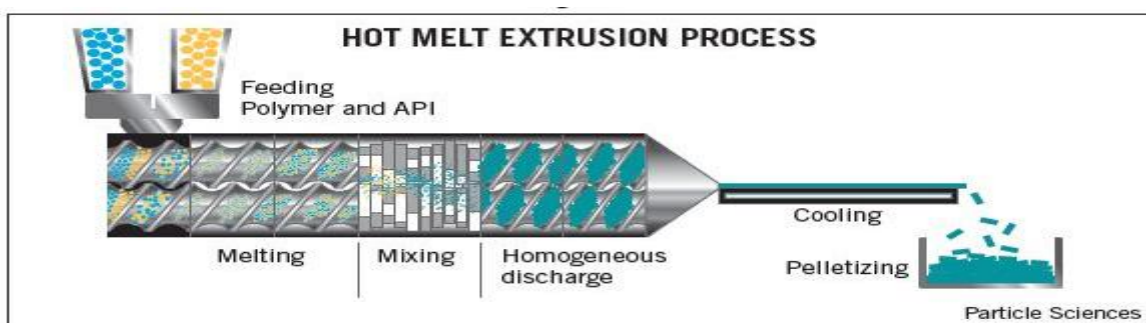


Fig 3: Hot melt extrusion process

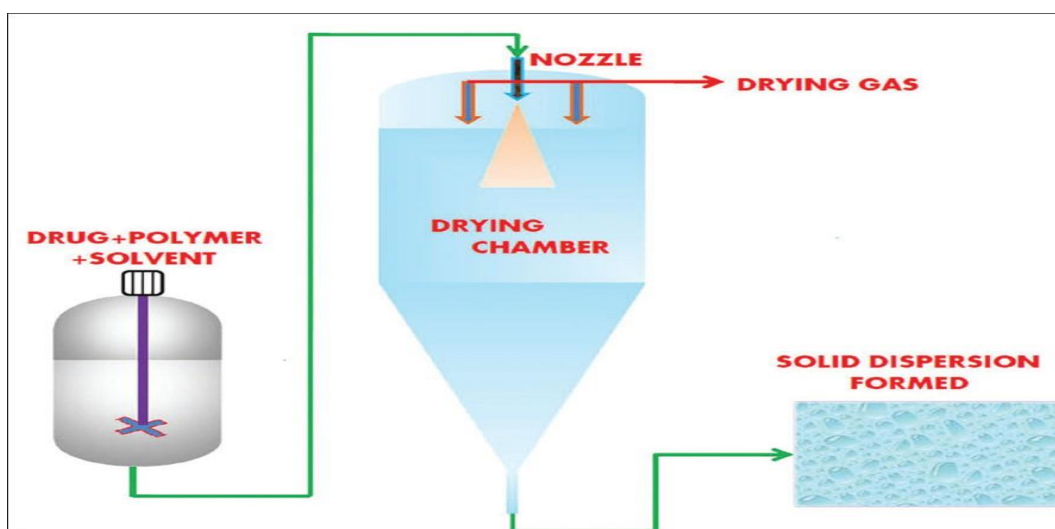


Fig 4: Solid dispersion Extrusion

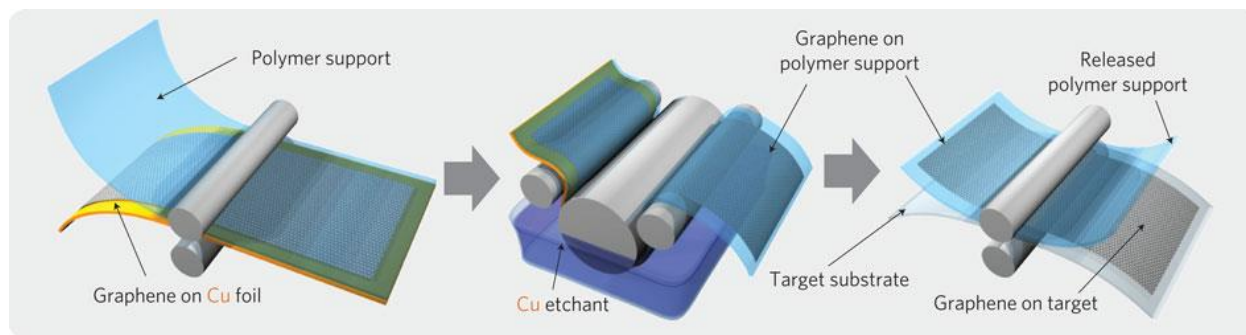


Fig 5: Rolling method

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. 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.

Semisolid casting

In semisolid casting method firstly a solution of watersoluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches.

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°C/65% RH and/or at 40°C/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 space³⁴. 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 packet 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 packet.

APPLICATIONS OF FILM DELIVERY SYSTEM [9-19]

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 fresheners. 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.

Evaluation

Mechanical properties

- ✓ Thickness
- ✓ Dryness/tack test
- ✓ Tensile strength
- ✓ Percent elongation
- ✓ Young's modulus
- ✓ Tear resistance
- ✓ Folding endurance

Organoleptic test

Swelling test

Surface pH test

Contact angle

Transparency

Assay/Content Uniformity

Disintegration test

In-vitro Dissolution test

Thickness

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations.

Dryness test/tack tests

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-to touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OFDF. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip.

Percent elongation

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

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

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

Tear resistance

Tear resistance of plastic film or sheeting 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 Newtons (or pounds-force).

Folding endurance

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

Organoleptic evaluation

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 and drug release by modified pharmacopoeial methods 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.

Surface pH of film

Surface pH of the films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the colour of pH paper was observed and reported.

Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed.

The degree of swelling was calculated using parameters

$$\alpha = wt - wo/wo$$

wt is weight of film at time t,

and wo is weight of film at time zero.

Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows:

$$\text{Transparency} = (\log T_{600})/b = - \epsilon c$$

Where T₆₀₀ is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

Assay/ Content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.

Disintegration time

Disintegration of orally fast dissolving films requires USP disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films strips.

Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. 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 strip to float onto the dissolution medium when the paddle apparatus is employed.

CONCLUSION:

The growing success and popularity of fast dissolving oral film recently in global market is evidence to the need for effective taste masked, "without water" pharmaceutical formulations. Fast dissolving oral films being a natural evolution of fast dissolving drug delivery systems have prominent advantages over conventional dosage forms and orally disintegrating tablets. Due to their immense importance during the emergency cases such as allergic reactions and high patient compliance, fast dissolving oral films have evolved as consumer friendly dosage forms. So many of the pharmaceutical companies are launching this technology as these films can be manufactured through non-sophisticated, uncomplicated equipment and procedures. Due to these, fast dissolving films have economically feasible developmental futuristic opportunities.

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