

ORALLY DISSOLVING STRIPS: A NEW APPROACH TO DRUG DELIVERY SYSTEM

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Abstract: Recently, fast dissolving strips are ahead significance as an alternative of fast dissolving tablets. The strips are designed to dissolve in the lead contact with mucosa in buccal cavity, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This expediency provides both a marketing advantage and increased patient acquiescence. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. As oral route is most preferred and patient-convenient means of drug administration. Most of the drugs are being taken in the form of tablets and capsules by almost all patients, including adult, paediatric and geriatric patients. However, around 26 – 50% of patients find it difficult to swallow tablets and hard gelatin capsules. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients with fear of choking. Many companies are utilizing transdermal drug delivery technology to develop thin strip formats. In the present review, recent advancements regarding fast dissolving strips formulation and their evaluation parameters, advantage, disadvantage, their formulation aspects are compiled.

Keywords: Fast dissolving strips, oral mucosa, permeability, solvent casting, solvent casting and disintegration

1. INTRODUCTION

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films.[7]

Oral route is most preferred and patient-convenient means of drug administration. Most of the drugs are being taken in the form of tablets and capsules by almost all patients, including adult, paediatric and geriatric patients. However, around 26 – 50% of patients find it difficult to swallow tablets and hard gelatin capsules. These patients mainly include, elderly (who have difficulties taking conventional oral dosage forms because of hand tremors and dysphagia), paediatric patients (who are often fearful of taking solid oral dosage forms, owing to their underdeveloped muscular and nervous systems) and others which include the mentally ill, developmentally disabled, patients who are uncooperative, on reduced liquid-intake plans or nauseated, and travellers who may not have access to water.

However, Mouth Dissolving Tablets (MDT) are associated with certain limitations, such as:

1. Despite the short disintegration/dissolution times of MDT, the fear of taking solid tablets and the risk of choking persists [10].
2. For their production, many MDT requires the expensive lyophilisation process,
3. MDT are sometimes difficult to carry, store and handle (fragility and friability)
4. MDT requires specialized and expensive packaging and processing.

The above mentioned limitations of MDT have paved the way for development of Mouth Dissolving Films (MDF) as fast drug delivery systems. MDF are gaining interest as an alternative to MDT to definitely eliminate patients' fear of choking.[3]

2. CLASSIFICATION OF FAST DISSOLVING TECHNOLOGY:

2.1] LYOPHILIZED SYSTEM:

The technology around these systems involves taking a suspension or solution of drug with other structural excipients, through the use of a mould or blister pack, forming tablet shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. The units are capable of incorporating a range of taste masked materials and have more rapid disintegration than tablet-based systems.[16]

2.2] COMPRESSED TABLET BASED SYSTEM:

Compressed tablet-based systems This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard high density polyethylene (HDPE) bottles or blisters through to more specialist pack designs for product protection, for example, CIMA Labs, PackSolv. The speed of disintegration for fast dissolving tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or superdisintegrate or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail Fuisz Technology. It uses the proprietary Shearform system to produce drug loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies, and generic pharmaceutical companies, for in-house development of line extension and generic fast dissolving dosage forms. [16]

2.3] ORAL THIN FILM (OTF)

Thin film strips: Oral films, also called oral wafers, evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Today, FDFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats. [16]

2.3.1] CHALLENGES IN OTF

Taste masking of bitter and obnoxious drug Taste is an important parameter in case of fast dissolving oral film. Oral film has to remain in contact with oral mucosa until it completely dissolves in saliva in oral cavity. For this, taste of bitter drugs should be masked. So, taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the paediatric and geriatric population [15, 17]. Taste is the ability to respond to dissolved molecules and ions "gatekeeper to the body". Human uses taste receptor cells that are clustered into onion shaped organs called taste buds for detection of taste. A taste bud contains a pore which opens out to surface of the tongue and passing molecules and ions into the mouth to reach to the receptor cells inside [16, 19]. Human have around 10,000 taste buds which appear in foetus at about three months. A single taste bud bears 5000 taste cells and each taste cells have receptors on its apical surface. These are trans-membrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely salty, sour, sweet and bitter. Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids (eg. monosodium glutamate) .[11]

2.3.1.1] Ideal taste masking process and formulation

1. It involves least number of equipments and processing steps.
2. This requires minimum number of excipients for an optimum formulation.
3. There is no adverse effect on drug bioavailability.
4. It requires excipients that are economical and easily available.
5. Manufacturing cost is least.
6. It can be carried out at room temperature.
7. It requires excipients that have high margin of safety.
8. This is a rapid and easy to prepare. [11]

3. FACTORS THAT ARE TAKEN INTO CONSIDERATION DURING THE TASTE-MASKING FORMULATION PROCESS INCLUDE

- Bitterness of the API.
- Required dose load.
- Drug particulate shape and size distribution.
- Drug solubility and ionic characteristics.
- Required disintegration and dissolution rate of the finished product.
- Desired bioavailability.
- Desired release profile.
- Required dosage form.

Taste masking techniques Taste masking with sweeteners and flavours This is very simple and mostly used technique for oral film formulation. Very minimum amount of sweetener and flavour are required for formulation to mask the bitter taste of drug [11]

4. ADVANTAGES OF FAST DISSOLVING ORAL FILM

- Water is not needed for administration of oral film. Film uses saliva in oral cavity for disintegration and dissolution.
- Risk of choking never appears after administration of film.
- Dosage form improves patient compliance.
- It shows rapid disintegrating and dissolution in oral cavity.
- Flexible and portable nature provides ease in transportation, handling and storage.
- Film avoids first pass metabolism due to pre-gastric absorption.
- It reduces side effects associated with drug.

- Film dosage form is generally useful for patient suffering from diseases like motion sickness, repeated emesis and mental disorders. [16]

5. DISADVANTAGE OF FAST DISSOLVING ORAL FILM

- The disadvantage of OS is that high dose cannot be incorporated into the strip. The dose should be between 1-30 mg. There remain a number of technical limitations with use of film strips; the thickness while casting the film. Glass Petriplates cannot be used for casting.
- The other technical challenge with these dosage forms is achieving dose uniformity. [16]

6. THERE ARE THREE SUBTYPES OF ORAL FAST DISSOLVING STRIPS:

- Flash release
- Mucoadhesive melt-away wafer
- Mucoadhesive sustained-release wafers

6.1] FLESH RELEASE WAFER:

Thickness and area of the flesh release wafer are approximate 20-70 μ m and 2-8 cm² respectively. Structurally, it is single-layered, contains hydrophilic polymers of high solubility and solid solution as drug phase. It takes not more than a minute for the strip to dissolve over the tongue, providing either local or systemic action. Mucoadhesive melt – away wafer:

6.2] MUCOADHESIVE MELT AWAY WAFER:

acquires around 2-7cm² area and 50-500 μ m thickness. The system may be single or multi-layered, with suspended drug particle or solid solution as a drug phase. Polymers used are hydrophilic and highly soluble. The strip, when placed inside the mouth, dissolves in a short period and forms a gel. The activity site could be local or systemic.

6.3] MUCOADHESIVE AND SUSTAIN RELEASE:

Mucoadhesive and sustain release film has about 2-4 cm² and 50-250 μ m of area and thickness respectively. It is a multi-layered system, comprising of non-soluble or slightly soluble polymers. The phase of a drug may be a solid solution or suspension. The strip dissolves in maximal 8-10 hours after placing over the buccal or gingival region, with systemic or local activity. [9]

7. IDEAL CHARACTERISTIC OF A SUITABLE DRUG CANDIDATE:

- The drug should have low dose.
- It should have an acceptable taste.
- The drug should have extensive high first pass metabolism.
- The drug should have smaller and moderate molecular weight.
- It should quickly dissolve to release drug instantaneously in mouth.
- The drug to be incorporated should have low dose up to 40 mg
- The drug should have high solubility and high permeability (BCS class I).
- It should be compatible with the other ingredients.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity. [4,7,16]

8. FORMULATION ASPECTS FOR FAST DISSOLVING FILMS

8.1 SELECTION OF API

The film composition usually contains a drug concentration of about 5-30 % w/w. Drugs having small doses are the ideal candidates for incorporation in mouth dissolving films and should possess good stability and permeability through oral mucosa. Selection of excipients Generally Recognized as Safe (GRAS-listed) and accepted excipients are used in the formulation of oral dispersible films.

8.2 POLYMERS

For formulating thin films, multiple synthetic and natural polymers are available which can be used either solely or blended in a mixture, depending on desirability. Fast dissolving films synthesized using natural polymers, such as mucilages and gums, possess greater value due to the ease in availability and administration as well as lesser side-effects. It is the most significant component and required not below 45% w/w of total dry film content.

8.3 PLASTICIZER:

The plasticizer is one of the primary ingredients of mouth dissolving films that makes the strip flexible and less fragile. The concentration of plasticizer used is 20%, as more than 30% leads to difficulty in drying while less than 10% makes the product less flexible.

8.4 SWEETENING AGENT:

Sweetening agents are an essential component of mouth dissolving formulations, to enhance product palatability. Natural and artificial are two types of sweeteners, used either alone or as a part of a blend, in 3-6% w/w concentration. Fructose, glucose, honey, mannitol, sorbitol, liquorice, and glycerol sucrose represent natural sweeteners while artificial sweeteners could be nutritive and non-nutritive. Artificial Sweetener include nutritive include; maltose, fructose, and glucose, polyol; includes mannitol, sorbitol, maltitol,

syrthriol, xylitol, Non-Nutritive include; sucralose, saccharine, neotame and aspartame; Novel sweeteners include; trehalose and tagatose

8.5 COOLING AGENTS:

Cooling agents like monomethyl succinate can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents like WS3, WS23 and Utracoll II can also be used in conjunction with flavors.

8.6 SALIVA STIMULANTS:

Saliva stimulants aid in the rapid dissolution of the film by enhancing saliva production. Citric acid, ascorbic acid, lactic acid, and tartaric acid are some of the examples of saliva stimulating agents, among which citric acid is more recommended. These stimulants are utilized in 2-6% w/w concentration, either combined or used alone.

8.7 COLOURING AGENT:

Colouring agents approved by FDA & C are employed for the development of mouth dissolving thin films. Titanium oxide is one of the examples. The concentration used must not be more than 1% w/w.

8.8 STABILIZING AND THICKENING AGENT:

Stabilizing and thickening agents behave as viscosity enhancers for dispersions before casting. used. Emulsifiers, surface active agents and gums are generally used as thickeners and stabilizers.

8.9 FLAVOURING AGENT:

A wide range of flavouring agents is available to be utilized in a formulation such as mint flavour, fruity flavour and confectionery. Depending upon the type and strength of flavouring agent, up to 10%, w/w can be combined with the formulation, along with cooling agents to amplify mouth feel.

8.10 PERMEATION ENHANCER:

The role of permeation enhancers is to promote drug absorption by improving permeability. Menthol, dextran sulfate, benzalkonium chloride, Apoprotein, sodium taurodexcholate, cyclodextrin, cetylpyridinium chloride, 23 Lauryl ether, azone, and sodium glycodeoxycholate are the commonly employed permeation enhancers.[9]

9. FILM FORMING POLYMERS

Water soluble polymers are utilized such as HPMC E-3, E-5 E-15, K-3., Methyl cellulose A-3, A-6 and A-6, Carboxymethylcellulose, pullulan, maltodextrin, hydroxypropylcellulose cokol 30, polyvinyl alcohol etc. for the preparation of the oral soluble film. They can be utilized individually and also in combination, to impact the desired properties into the film.

The characteristic properties of the film forming polymer

- It must have good shelf life.
- It must have good wetting property.
- It shall have good spread ability property
- It must not aid in causing secondary infections in the oral mucosa/ dental region.
- It must have a good mouth feel property.
- Polymer employed must be non-toxic, non-irritant and devoid of leachable impurities

9.1 STRIP FORMING POLYMERS

The polymers in the formulation can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that they won't be any damage while handling or during transportation. The robustness of the strip will rely upon the type of polymer and its amount. A variety of polymers are available for the preparation of oral strip. On the other side, fast dissolving strip dosage form must have the ability to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously. Various polymers used in the formulation of oral strips are given in table 2. Of the various polymers available pullulan, gelatin and hydromellose are most commonly used for preparation of oral strip. At least 45% w/w of polymers should generally be present based on the total weight of dry oral strip.[6]

Table 1: Strip forming polymers [6]

Strip Forming Polymers	Hydroxyl propyl methyl cellulose (hypromellose)	Hydroxyl propyl cellulose	Starch and modified starch	Pullulan	Gelatin	Carboxymethyl cellulose
Synonym	HPMC, methocel, metolose, benecel.	Hydroxy propyl ether, hyplose, klucel, Nisso HPC	Amido, amylum, pharmGel, fluftex W, Instant pure-Cote, Melogel	Pullulan, 1,6 α linked maltotriose	Byco, cryogel, instgel, solugel	Akulell, blanose, aquasorb, CMCsodium
Molecular weight	10000-1,500,000	50000-1,250,000	50,000-1,60,000	8000-2,000,000	15,000-2,50,000	90,000-7,00,000
Solubility	Soluble in cold water, forming a viscous colloidal solution, in soluble in chloroform, ethane	It is freely soluble in water below 380C forming a smooth, clear, colloidal solution	Starch is insoluble in cold water and ethanol. It swells in water by about 5 to 10% at 370C	It is soluble in hot as well as cold water	Soluble in glycerin, acid and alkali. Swells in water and softens. It is soluble in hot water.	It is easily dispersed in water to form a clear or colloidal solution
Film forming ability	It has a film forming ability in 2 to 20% w/w concentration	5% w/w solution is generally used for film coating	Modified starches have a property to form quick dissolving films	5 to 25% w/w solution forms flexible films	It has very good film forming property.	Carboxymethyl cellulose as good film forming property
Viscosity	Viscosity of various grades ranges from 3mPas-1,00,000mPas	75mPas-6500mPas depending upon the polymer grade	2% w/v aqueous dispersion of starch provides 13mPas viscosity	The viscosity (10% w/w, 300 C) of pullulan was 100 – 180mm ²	4.3-4.7mPas for a 6.67% w/w aqueous solution at 600C	The 1% w/w aqueous solution as viscosities in the range of 5 to 13,000 mpPas.
Melting point	Browns at 190 to 2000 C. Glass transition temperature is 170 to 1800C	It softens at 1300C, chars at 260-2750C	It decomposes at 2500C	1070C		Browns at 2270C chars at 2520C

10. METHODS OF MANUFACTURING FAST DISSOLVING FILMS

Following are the methods of manufacturing for fast dissolving films:

- Solvent casting method
- Semisolid casting method
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method[7]

10.1 SOLVENT CASTING METHOD [7]

In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both

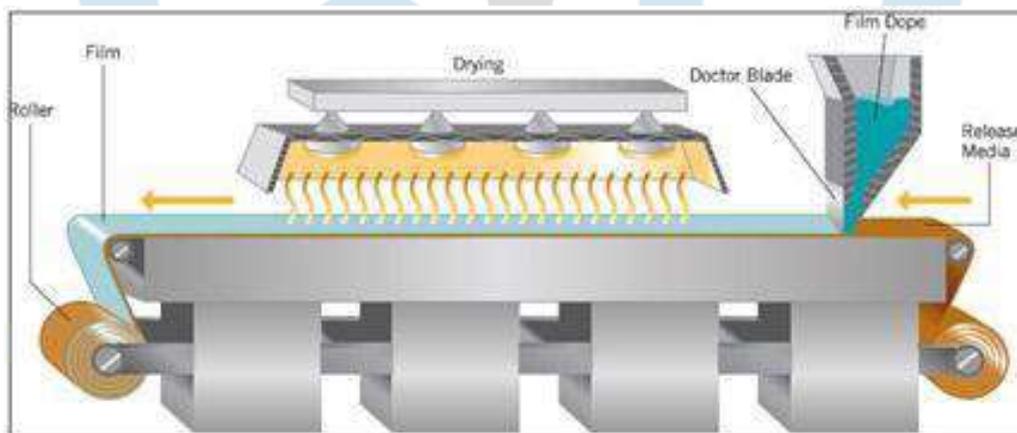
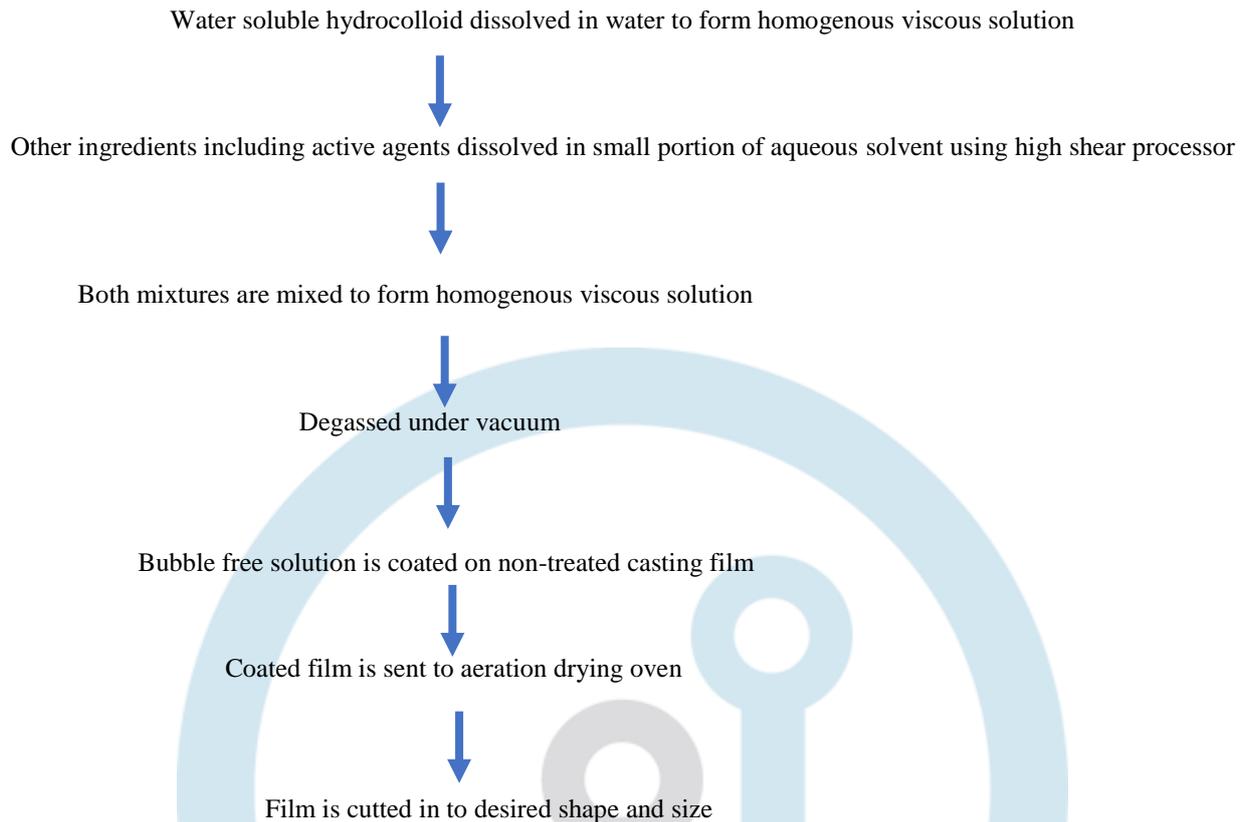


Figure 1: Solvent casting method

10.1.1 Advantages

- Great uniformity of thickness and great clarity than extrusion.
- A typical relative standard deviation (RSD) for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1.2% RSD.
- Films have fine gloss and freedom from defects such as die lines.
- Films have more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 μ m.

10.1.2 Disadvantages

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.[6]

10.2) HOT MELT EXTRUSION:

Hot melt extrusion is commonly used to prepare granules, sustained-release tablets, and transdermal and transmucosal drug-delivery systems. In the hot melt extrusion drug mixed with carrier in the solid form. Extruder having extra facility with heater it melt the solid form carrier and drug then this melt is placed in the dies and cut into specific shape

E.g. Maltodextrin can be used to produce fast-dissolving films with a high drug loading capacity by hot-melt extrusion technology.

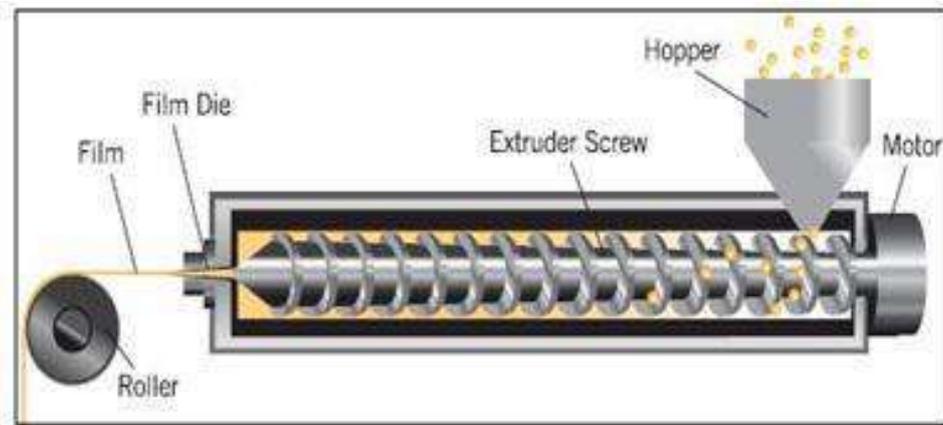


Figure 2: Hot melt extrusion method.

10.2.1 Advantages

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the APT may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.
- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high shear methods.

10.2.2 Disadvantages

- Thermal process so drug/ polymer stability problem.
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers[6,7]

10.3) SEMISOLID CASTING

In this method a solution of water soluble film forming polymer should be prepared and the resulting solution should be added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was made in ammonium or sodium hydroxide. Then suitable amount of plasticizer should be added to form a gel mass. Finally, the gel mass should be casted in to the films or ribbons using heat controlled drums. The thickness of the film formed will be in the rapid of 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer must be 1:4 in this method.[13]

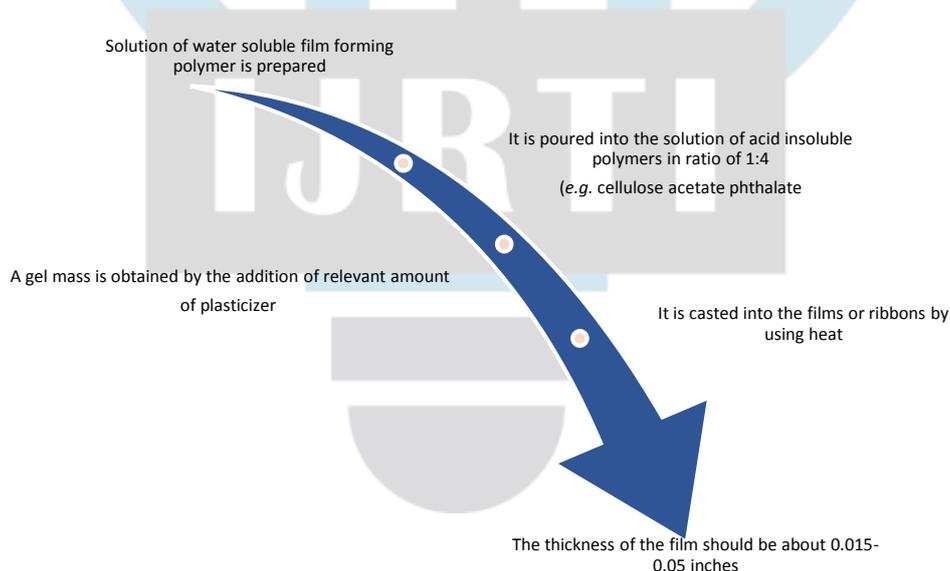


Figure 3: Semisolid casting

10.4) SOLID DISPERSION METHOD

In this method, in the presence of amorphous hydrophilic polymers, one or more active ingredients are dispersed in an inert carrier in a solid state.

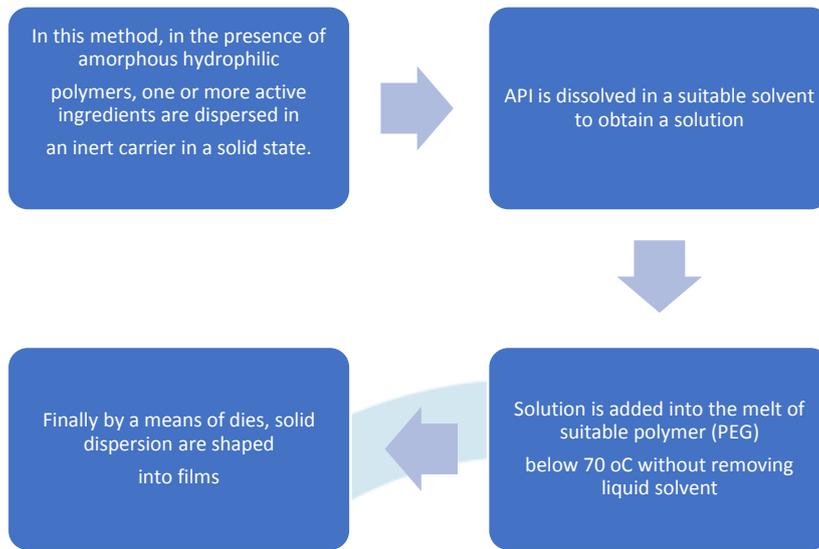
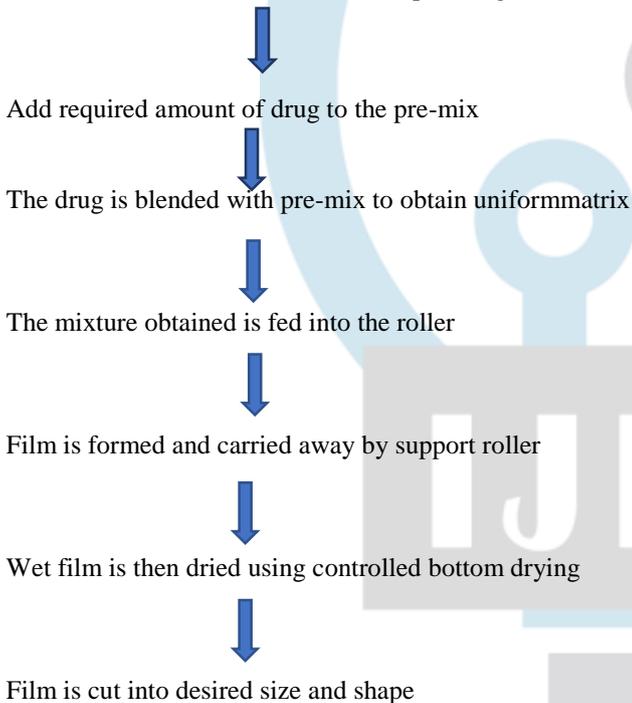


Figure 4:Solid dispersion method

10.5) ROLLING METHOD

Initially a pre-mix is prepared by film forming polymers, Polar solvent and other additives except a drug



In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes.[7]

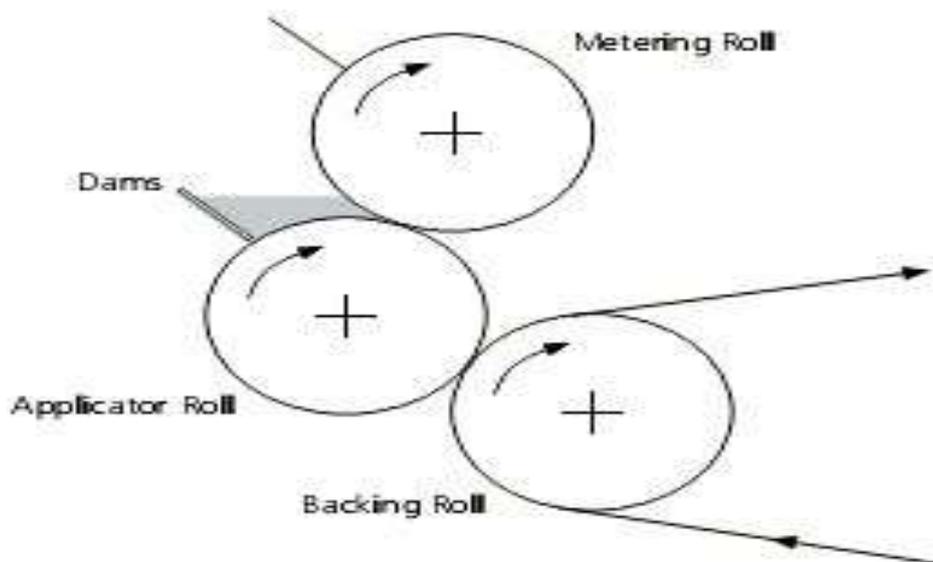


Figure 5:Rolling method[7]

11. EVALUATION PARAMETER

11.1 Thickness test

Thickness specifies the dose accuracy of drug in the film. It is measured by a micrometer screw gauge or calibrated digital Vernier callipers at five different strategic locations and the mean value is calculated which indicates the final thickness of the film. The thickness of the film should be in the range of 5-200 μ

11.2 Dryness test/tack test

Give no to each test 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.

11.3 Percent elongation

The strain is the stretching of the strip after stress application. The division of strip deformity to actual strip measurements gives the value of strain. Higher the plasticizer content higher will be the strip elongation. 322.4 • } 63.3% is the conventional value for % elongation

$$\% \text{ Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

11.4 Tensile strength

It is the maximum stress applied to a point of film at which the strip specimen breaks. A film should have good tensile strength. Weight at which the film breaks is known as load failure. Tensile strength is calculated by the applied load at rupture divided by the cross-sectional area of the strip.

$$\text{Tensile Strength} = \frac{\text{Load at failure} \times 100}{\text{strip thickness} \times \text{strip width}}$$

11.5 Tear resistance

It is the maximum resistance required to tear the film. A very low rate of load of 51 mm/min is applied. Its unit is Newton or pounds force.

11.6 Folding endurance

It indicates the brittleness of the film. It can be done manually, as the number of times the film folded without breaking or without any

11.7 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:

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{cross-head speed}}$$

11.8 In vitro disintegration time

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

11.9 In-vitro dissolution test

Amount of drug substance that goes into the solution per unit time under standard conditions of temp, solvent concentration and liquid/solid interface is called dissolution. A standard basket or paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing. When paddle type dissolution apparatus is used, it's difficult to perform dissolution study of oral film as they can float over the dissolution medium. Selection of the dissolution media depends on the sink conditions and the highest dose of drug. During dissolution study, the temperature of the medium should be maintained at 37 ± 0.5 °C and rpm at 50.

11.10 Drug 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%.

11.11 Surface pH test

The surface pH of fast dissolving strip can cause side effects to the oral mucosa, so it is necessary to evaluate the surface pH of film. The surface pH of film should be 7 or close to neutral. For this purpose, a combined pH electrode can be used. With the help of water, OS was made slightly wet and the pH was measured by bringing electrode in contact with surface of oral film. This study should be done on at least six films of each formulation and their mean \pm SD can be calculated.

11.12 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. Determine the transmittance of films at 600 nm. The transparency of the films can be calculated as follows:

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

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

11.13 Permeation studies

Even though permeability of oral mucosa is 4000 times greater than that of skin, permeation studies should be carried out. To study the permeability, modified Franz diffusion cell can be used along with porcine buccal mucosa. Determination of % yield of buccal patches[42] Percentage yield of buccal patches can be calculated by the following formula:

$$\% \text{ yield} = \text{Mass of the buccal patches obtained} / \text{Total weight of drug and polymer} \times 100$$

11.14 Organoleptic test

As the film disintegrates in the oral cavity, it should have acceptable organoleptic characteristics like colour, flavour and taste. An oral thin film should have attractive colour as they are administered to children and should be uniform. Flavours used in the formulation should provide good odour and should mask the taste of polymer, drug and other excipients. Taste is an important factor in patient acceptance. Specially controlled taste panels are used for the physical evaluation. Electronic tongue technique is also used which is based on the principle of potentiometric titration method

11.15 Contact angle

It gives the information about wetting behaviour, disintegration time and dissolution of oral film. This can be performed with the help of goniometer at room temperature. For this purpose, double distilled water should be used. A dry film is taken and a drop of double

distilled water is placed on surface of the dry film. Images of water droplet are taken by a means of digital camera within 10 s of deposition. Digital pictures should be analysed by image J 1.28v software (NIH, USA) for angle determination.

11.16 Scanning electron microscopy

Scanning electron microscopy is an important method to study the surface morphology of the film between different excipients and drug. A film sample is taken and placed in sample holder and at $\times 1000$ magnification and various photomicrographs were taken using the tungsten filament as source of electron

11.17 Stability studies

Stability testing of the prepared formulation is mainly done to check whether it is a stable product or not. It is also used for the determination of effect of temperature and humidity on the stability of the drug for the proper storage, initially the formulation is wrapped in a butter paper followed by aluminium foil wrapping over it, then this is packed in an aluminium pouch and heat sealed. Formulation should be stored at 45°C / 75 % RH for 3 months. During the period of stability studies, triplicate samples are taken at three sampling intervals i.e. 0, 1 and 3 month and films should be evaluated for physical changes and drug content.

11.18 Packaging

Valuable packing with a unique process and consideration is required for protecting an oro-dispersible thin film. For this, multiple packing materials are accessible, among which aluminium pouch is the most common option. Individual packing is compulsory for oral films. Rapid card, a packaging system patented by APR –Labtec, is specially designed for fast dissolving thin films, having a size equivalent to credit card and has a tendency of holding 3 strips on every side [64].

Characteristically, packaging material must;

- Have FDA approval
- Be non-toxic and non-reactive
- Protect the formulation from the environment.
- Satisfy tamper-resistance criteria.

11.18.1 Plastic, foil or paper pouches

The pliable pouch is thought to provide not only a tamper-resistant packaging but also high degree environmental protection .

11.18.2 Single pouch and aluminum pouch

Fast dissolving thin film pouch is peelable, with great preventive qualities, and has a clear presentation. 2 structure combination, having one side transparent and other low-priced foil lamination, can be used. The lamination should have zero transmission of air and moisture. Packaging can be used in both nutraceuticals as well as pharmaceutical applications. The single pouch keeps the product and formulation intact form. It's the most commonly used packaging.

11.18.3 Blister card with multiple units

Blister card comprises 2 parts i.e. a cavity for holding the product and a lid stock sealing it. The selection of blister type depends on how many degrees of protection is needed, as semi-flexible blister is also an option. Plastic is generally used for making the blister cavity while

aluminium foil for the lid stock.[6,7,16]

12. PATENTED TECHNOLOGIES

12.1 xgel:

XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

12.2 soluleaves:

This is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. Solute leaves technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form.

12.3 wafertab:

Wafertab is a patented delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting.

12.4 foamburst:

Foam burst is a new patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt-in-the-mouth sensation [9,33].

12.5 micap:

Micap Signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the Bio Progress water-soluble films.[6]

13. CLINICAL AND REGULATORY ASPECTS:

In the US Food and Drug Administration, if the product is bioequivalent to that of the existing oral product of the drug, an Abbreviated New Drug Application (ANDA) route is followed. There are no clinical studies related in this generic approval process (section 505(j) of the Food, Drug and Cosmetics Act). The example of aforementioned case would be a comparative bioequivalence between ODT formulation and OTF product. However, developed oral film product may also display a different target pharmacokinetic profile correlated to the existing marketed product. The OTF is classified as "new dosage form" and the section 505(b)(2) approval process needs to be followed. In this case, a new clinical study would be needed. The benefit of a new clinical study is that it would award three years of marketing exclusivity to the product. In the Europe, Marketing Authorization approval (Abridged Application) is important as per the European Medicines Evaluation Agency guidelines. Either of the two modes i.e. the decentralized procedure or the mutual recognition route can be accepted. The Ministry of Health, Labor and Welfare is primarily answerable for product approvals in Japan.[13]

Table 2 : Various patents in United States on fast dissolving oral films/strips[13]

Title	United States Patent	Issued	Inventors	Assignee	Appl.No	Filed
Fast dissolving orally consumable films containing a taste masking agent	7,648,712	Jan 19,2010	Bess; William S. (Edison, NJ), Kulkarni; Neema (Randolph, NJ), Ambike; Suhas H. (West Hill, CA), Ramsay; Michael P. (Ajax, CA)	McNeil-PPC (Skillman, NJ)	11/429,547	May 5, 2006
Process for manufacturing thin film strip	6,824,829	Nov.30, 2004	Nov.30, 2004 Craig j.berry	Aupac packaging,inc.	10/226,451	Aug.23,2002
Fast dissolving orally consumable film	7,025,983	Apr.11,2006	Sau Hung Spence Leung,Robert S. Leone,Lori D. Kumar, Neema Kulkarni, Albert F. Sorg	Warner Lambert Company LLC.	09/836,474	Apr.18,2001
Fast dissolving orally	2003/0208931	Nov. 13,	Lori D. Kumar,	Warner Lambertv	10/423,398	Apr.25,2003

Table 3: List of some marketed product available as fast dissolving strip[16]

PRODUCT	API	MANUFACTURER	USES
Listerine	Cool mint	Pfizer,inc	Mouth ulcer
Benadryl	Diphenhydramine HCL	Pfizer	Antiallergic
Suppress	Methanol	Innozen,inc	Cough suppressant
Klonopin wafers	Clonazepam	Solvay pharmaceuticals	Antianxiety
Theraflu	Dextromethorphan	Novartis	antiallergic
Orajel	Methanol/pectin	Del	Mouth freshner
Gas-x	Simethicone	Novartis	Antiflatuating

Chloraseptic	Benzocaine/methanol	Prestige	Sore throt
Sudafed PE	Phenylpinephrine	Wolters Kluwer health,inc	Congestion
Triaminic	diphenhydramine	Novartis	Antiallergic

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