



INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

ORAL THIN FILM: A STUDY OF APPLICABILITY AS A DRUG DELIVERY SYSTEM.

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ABSTRACT

The oral thin-film technology is still in the beginning stages and but most popular because it fulfils all the need of patients. In due course, these formulations having APIs will be commercially launched using the oral film technology. These can be prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Water-soluble polymers are used as film formers for fast dissolving films. It seems that the value on the whole oral thin film market will grow significantly.

The film has the ability to dissolve rapidly without the need for water provides an alternative to the patients receiving swallowing disorder patient suffering from nausea headache etc. Oral thin films (OTFs) are the most advanced and promising new approaches for drug delivery as it offers more flexibility and comfort. These enable an ease of administration, as there is no need to drink high amounts of liquids or swallow large solid dosage forms Also it improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. OTF offers an alternative to tablets, syrups or suppositories for the treatment of vomiting and nausea, especially for the pediatric population.

Keywords: oral thin films, hydrophilic polymer, nausea, vomiting

INTRODUCTION

Despite of tremendous advancement in drug delivery system the oral route of drug administration is the most important method of administration of drug for systemic effect. About 60% of total dosage forms are administered by oral route, but oral drug delivery system still needs some advancements to be made because of their some drawbacks related to particular class of patient such as geriatric, pediatric & dysphasic patients associated with many medical condition as they have difficulty in swallowing or chewing solid dosage forms .Many pediatric & geriatric patients are unwilling to take solid preparations due to fear of choking due to tablet type of appearance. It is estimated that 50% of population is affected by dysphasia which result in high incidence of non-compliance & ineffective therapy, To overcome this problem it is necessary to design a formulation which rapidly disperses / dissolves in oral cavity without the need of water for swallowing.

So, fast dissolving drug delivery system comes into existence in late 1970's as an alternative to tablet, capsules & syrup for pediatric & geriatric patient .oral thin film was developed on the basis of technologies of transdermal patches.

Fast dissolving film - These film & strip have been developed as a means to quickly release an active agent upon placing the strip on the tongue .A strip or film can be defined as a dosage form that employs a water soluble polymer (hydrocolloidal bioadhesive polymer) which allows the dosage forms to quickly hydrate ,adhere & dissolve when placed in oral cavity to provide rapid local & systemic action.

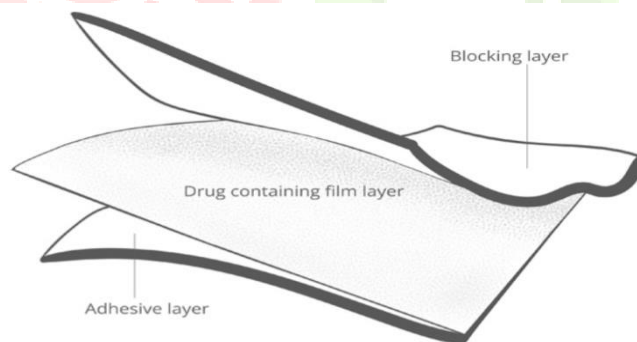
The film are generally thin flexible strips (2×3 cm²) & can be packaged in multidose container or individual packed .A film or strip dissolves instantaneously when placed on the tongue in oral cavity. Fast dissolving drug delivery was pioneered by scientist at Wyeth Laboratories in the UK during the late 1970's which resulting in patenting of "Zydis" drug delivery system.

The oral thin film places as an alternative in market due to the consumer's preference for a fast dissolving product over conventional tablet/capsules. The OTF technique is still in the beginning stages & has bring future ahead because it fullfill all the need to patients.

In north america more than 80 oral thin film brands launched since 2003 the market remain limited when compared to ODTs .However , for future growth point of view the OTF sectors is well positioned .More importantly , prescription OTFs have now been approved in US , EU & Japan which are the three major region. It seems that the value of over all Oral thin film market will grow significantly.

CURE Pharmaceutical Secures Chinese Patent on its Oral Thin Films to Treat Erectile Dysfunction. Oral, quick response, and on demand, also known as a spontaneous oral treatment for erectile dysfunction, is highly needed by both patients and physicians. Vardenafil is selective (fewer side effects) and more effective in difficult-to-treat conditions than sildenafil.

Bilayer-OTF technology provide a potential means of reducing the pill burden for patients as they can administer two or more active pharmaceutical ingredients (APIs) in a single FDC (fixed dose combination) dosage form. Bilayer-OTF has one adhesive layer to ensure drug release through Buccal mucosa and a backing layer that avoids drug release in oral cavity.



ORAL MUCOSAL DRUG DELIVERY –structural features of oral mucosa

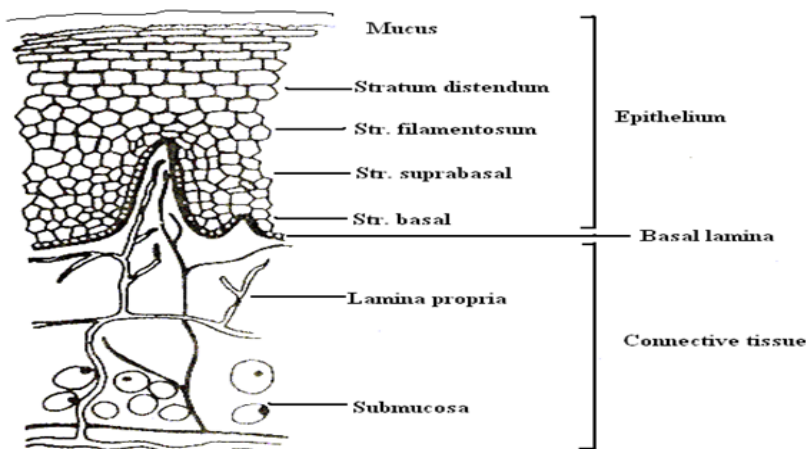


Fig. - Schematic cross section through oral mucosa showing epithelium basal lamina and connective tissue
SPECIAL FEATURES OF MOUTH DISSOLVING FILMS –

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

IDEAL CHARACTERISTICS OF ODF –

- Do not require water to swallow & should dissolve or disintegrate in the mouth within a few second.
- Compatible with taste masking & other excipients.
- They possess pleasant mouth feel and low cost approach.
- Leave minimal or no residue in the mouth after oral administration.
- They can withstand the rigors of the manufacturing process & post manufacturing handling
- Resistance to environmental conditions such as humidity & temperature.
- They are adapted & amenable to the existing processing & packaging machinery.

ADVANTAGES–

- ❖ Oral dissolving films can be administered without water anywhere any time.
- ❖ Due to large surface area, film provide rapid disintegration & dissolution in oral cavity.
- ❖ ODT are flexible & portable so they provide ease in transportation, during consumer handling & storage.
- ❖ Suitability for pediatric & geriatric patients, who experience difficulties in swallowing mentally ill, the developmentally disabled & the patient who are un-cooperative.
- ❖ Beneficial in cases such as motion sickness, acute pain, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- ❖ Stability for longer duration of time as compare to liquid dosage form.
- ❖ Precision in the administered dose is ensured.
- ❖ Drug can absorb directly & can enter the systemic circulation without undergoing first pass hepatic metabolism.
- ❖ The sublingual & buccal delivery of drug via thin film has the potential to improve the onset of action, lower the dosing, & enhance the efficacy & safety profile of medicament.
- ❖ Provide new business opportunity like product differentiation, product promotion, patent extension.

DISADVANTAGES –

- ❖ High dose can not be incorporated.
- ❖ Dose uniformity is a technical challenge
- ❖ Hygroscopic in nature so it must be kept in dry place
- ❖ Shows fragile, effervescence granulation property.
- ❖ Require special packaging for stability & safety.

CLASSIFICATION OF OTF –

- 1) Flash release
- 2) coadhesive melt –away wafers
- 3) Mucoadhesive sustain release wafer

INOVATIVE PRODUCTS HAVING BETTER THERAPEUTIC POSSIBILITY WITH OTF-innovative products may increase the therapeutic possibilities in following indication

- Pediatrics(antitussive,expectorants)
- Geriatrics (antiepileptic ,expectorants)
- Gastrointestinal diseases
- Nausea (Due to cytostatic therapy)
- Pain (e.g. migraine)
- CNS (e.g. antiparkinsonism therapy)
- Erectile dysfunction

MECHANISM OF APPLICATION –

The delivery system is simply placed on a patient's tongue or any oromucosal tissue .instantly wet by saliva due to presence of hydrophilic polymer & other excipients,the film rapidly hydrates & dissolves to release the medication for oromucosal absorption.

RECENTS FDA APPROVED FAST DISSOLVING FILMS –

Drug	Year	Use	Company
Suboxone (buprenorphine & naloxene)	Aug 2010	- Sublingual film indicated for maintainance treatment of opiod dependence & should be used as part of a complete treatment plan to include counselling & psychosocial support.	Reckett Benckiser pharmaceuticals inc.
Zuplenz	Jan 2010	Prevention of postoperative emetogenic cancer therapy induced & radiatherapy induced nausea & vomiting	Pharmfilm technology
Ondasetron	23 rd march 2010	Prevention of postoperative emetogenic cancer therapy induced & radiatherapy induced nausea & vomiting i& children adults & children aged above 4 years	APR & Labtec GmbH
Zelapar	Oct-2005	Treatment for parkinson's disease	Valeant pharmaceutical International Inc.
Vardenafil	Mar-2020	Erectile dysfunction	curepharmaceutical.com

DISSOLVING MARKET COMPRISING TECHNIQUE -

DOSAGE FORMS	DESCRIPTION OF THE DOSAGE FORM
Freeze dried wafers	A quick dissolving thin matrix consists of an active pharmaceutical agent which does not require water for swallowing .This freeze dried dosage forms when placed in the mouth disintegrates instantaneously ,release the drug which dissolves or disperse in saliva. The saliva is then swallowed & drug is absorbed the GIT.
Orally Disintegrated tablets ODT	A solid dosage form containing API that disintegrates rapidly, usually in minutes to seconds. It is placed on the tongue, where it releases the drug which dissolves or dispersed in saliva and drug is absorbed across the GIT.
Fast melt tablet /Mouth dissolving Tablets	An Oral tablet that require no intake of liquid. The dosage form dissolves in less than a few min when placed in the mouth.
Oro-dispersing Tablet	A tablet is placed in pateints mouth & the saliva rapidly dissolves the tablet, release API
Buccal gum/chewing gum	A non dissolving polymer matrix modified release dosage form containing the drug & other excipient that must be chewed but not swallowed to promote release of drug from the dosage form in oral cavity.
QUICK Buccal patch /gingivial patch / Odontal patch	A non dissolving thin matrix dosage form composed of one or more polymer film polymer film or layers containing drug & other excipient for specific delivery.
Buccal Tablet	A modified release dosage form to be applied to the buccal cavity & that dissolves in mouth , which is intended to be absorbed through the mucosal lining of the mouth without the need of water .
Spray	A unit actuation pump or aerosol spray for rapid drug absorption through buccal mucosa.
Quick dissolving film or quick dissolving wafers	A fast dissolving polymer film embedded with drug that melts & dissolves in saliva quickly & completely, releasing the drug for absorption through the oral mucosa.

FORMULATION –

Composition –A typical composition contains the following-

Drug - 5-30 %w/w

Water soluble polymers – 45 % w/w

Plasticizer – 0-20 % w/w

Surfactants –Q.S.

Sweetening Agent – 3-6 % w/w

Saliva stimulating agent -2-6% w/w

Fillers, colors, flavors etc. –Q.S.

Contain -

- Active Pharmaceutical Ingredient
- Film forming Polymer
- Plasticizers
- Sweetening agent
- Saliva Stimulating Agent
- Flavoring Agent
- Coloring agent

Active Pharmaceutical agent –

High dose molecule are difficult to be incorporated into the films allowing only 5% w/w to 30 % w/w of pharmaceutical ingredients can be incorporated into the film & up to 10 % of dry film weight was incorporated into the film in case of multivitamins. 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 strips. APIs can also be added as milled , micronised or in the form of nanocrystals or particles depending upon the ultimate release profile desired.It is advantageous to have API micronized that adds improvement to the texture of the film showing better dissolution & uniformity in the oral film.

Choice of drug candidate –

Suitable drug candidate for orally soluble film should possess-

- No bitter taste, if it has, must be maskable
- Good stability in water & saliva.
- Dose should be low as possible as.

Researches have shown interest in development of fast dissolving films for drugs like –Pediatric – antitussive,expectorant,antiasthamatic

Geriatric – antiepileptic,expectorant

Gastrointestinal diseases

Nausea,pain,CNS(e.g. antiparkinsonism)

CATEGORY	EXAMPLES
Selective serotonin reuptake inhibition	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram & alaproclate
Antiemetics	Ondasetron, granisetron, palonosetron, dronabinol, aprepitant, ramosetron, metopromine, trimethobenzamide.
5HT3 antagonist	Alosetron, Granisetron, palonosetron, tropisetron
Anti-epileptic	Carbamazepin, clonazepam, diazepam, divalproex sodium, fosphenytoin, gabapentin, lamotrigin, zonisamide
Anti-migrane	Amlotriptan, eletriptan, frovatriptan, sumatriptan
Dopamine D1 & D2 antagonist	Amisulpride, bromperidol, cabergoline, domperidon
Statins	Atovastatin, cerivastatin, lovastatin, simvastatins

FILM FORMING POLYMER –

A no. of polymer 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.

Requirements –

- 1) The polymer should produce a film which is tough enough so that there won't be any damage while handling or during transplantation
- 2) Polymer must be water soluble with low mole weight & has excellent film forming capacity.
- 3) Polymer should improve hydrophilicity, flexibility, mouth feel & solubility characteristic of FDT.
- 4) It should give proper stiffness property to film.
- 5) Disintegration time 7 physicochemical property is depend on polymer concentration & nature.

A water soluble polymer are used as film former which achieve rapid disintegration, good mouthfeel & mechanical property. Some of the water soluble polymer used as film former are polyethylene oxide, acrylic based polymer, sodium CMC, HPMC, synthetic copolymer of PEG-PVA, sodium alginate.

Natural gum also used in preparation of film such as – guar, xanthum, acacia, arabic or tragacant.

Most widely used polymer is pullulan, a natural polymer obtain from no. of animal origin & does not required chemical modification. Pullulan is an a 1,6 –linked maltotriose produced from the fungus aureobasidium pullulans. Modified starch are also used for preparation of oral film. Many the excipients being more economic. It is used in combination of pullulan to decrease the overall cost of product. About 50-80 % in production of oral film with no loss in properties of pullulan.

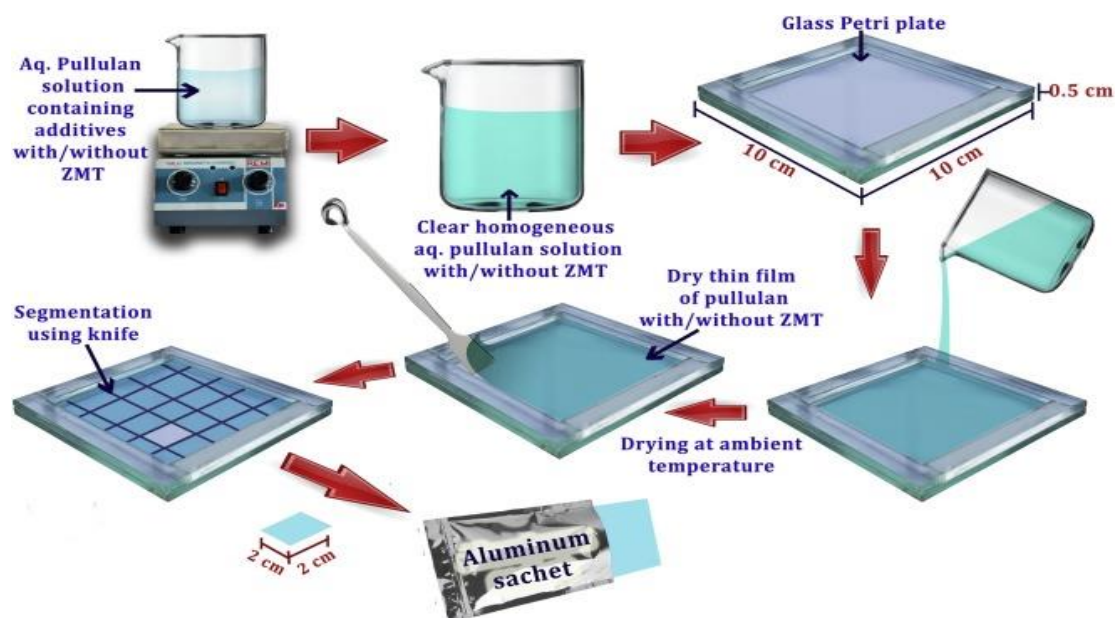
IDEAL PROPERTIES OF POLYMER –

- Non toxic
- Non irritant
- Devoid of leachable impurities
- Should have good wetting & spreadability
- Should exhibit sufficient peel shear & tensile strength
- Easily available & cost effective
- Should have good shelf life
- Should have local enzyme inhibition action along with penetration enhancing property.

Many different polymers for use in oral film are proposed in the literature & various research groups have introduced different material. The polymer used alone or in combination to improve hydrophilicity, flexibility, mouth feel & solubility characteristics of fast dissolving films. The stiffness of strip depend on the type of polymer & amount of it. Polyvinyl pyrrolidone films are brittle in nature & therefore copovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating films. Combination of microcrystalline cellulose &

maltodextrin has been used to formulate fast dissolving films of piroxicam made by hot melt extrusion technique. In this case microcrystalline cellulose is used to render the film non sticky & smooth. Microcrystalline cellulose was also used to decrease the disintegration time & improve the dissolution of drug from the films.

GLANCE OF FORMULATION –



Formulation & evaluation of strip -

Sr. No.	Polymer used	Film forming capacity	appearance	Disintegration time (sec)
1	HPMC E -15+PEG400	Good	Transparant	120
2	HPMC E-15+GLYCERINE	Good	Transparant	92
3	HPMC K4M	Very poor	-	-
4	HPMC E-5	Average	Semitransparent	127
5	PVA	Average	Transparant	52
6	PVP	Very poor	-	-
7	GELATIN	Very poor	-	-
8	EUDRAGITE RL100	Very poor	-	-
9	HPMC E-15+PULLALAN	Poor	-	-
10	PVA+PVP+GLY	Average	Transparant	64
11	PVA+PVP+PEG400	Average	Transparant	52
12	HPMC E-15+PVA	Average	Transparant	78
13	HPMC E-15+PVP	Average	Transparant	67
14	HPMC E-15 +PVA+MCC	Poor	-	-
15	PULLALAN + PVA	Very poor	-	-
16	HPMC E-15+MCC	Better	Semitransparent	42
17	PULLALAN +GUAR GUM+XANTHUM GUM+CARRAGENON	Best	Transparant	19

PLASTICIZERS –

Plasticizers helps to improve the flexibility of strip & reduce the brittleness of film. It significantly improves the film forming properties by reducing the glass transition temperature of polymer. Selection of plasticizer will depend upon its compatability with polymer & also the type of solvent employed in the casting of film. The flow of polymer will get better with the use of plasticizer & enhances the strenght of polymer. Typically the plasticizer use in the range of 0-25 % w/w of drug polymerweight plasticizer employed should impart the permanent flexibility to film which depend on the volatility of plasticizer & type of interaction with polymer.

Rationale for use –

The mechanical properties such as tensile strenght & elongation to film have been improved by addititon of plasticizers.

Inapropriate use may cause –

- Film cracking
- Splitting & peeling of strip
- Also affect the absorpation rate of drug

It should be noted that the properties of plasticizers are important to decrease the glass transition temperature of polymerin the range of 40-60°C for non aq. Solvent system & bellow 75°C for aq. System.

SURFACTANT –

Surfactant are used as solublising or wetting or dispersing agent so that the film is getting dissolved within second & release active agent immediately . Some of the commonly used are sodium lauryl sulphate, benzalkonium chloride , benzthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilising ,wetting & dispersing agent.

SWEETNING AGENT –

Natural sweeteners – Sweeteners have become the important component for those nutraceuticals as well as pharmaceutical products whose dissolution occures in the oral cavity. The classical source of sweetener is sucrose, dextrose,fructose,glucose,liquid & isomaltose.Fructose is sweeter than sorbitol & mannitol .Polyhydric alcohols such as sorbitol, mannitol & isomalt can be used in combination as they additionally provide good mouth feel & cooling sensation . Polyhydric alcohol are less carcinogenic & do not have after taste which is a vital aspect in formulating oral preparation.

Artificial Sweetener – The artificial sweeteners have gained more popularities in food & pharmaceutical preparation .The artificial sweeteners can be classified in I & II generation sweeteners which are given below in table. Acesulfame –K & sucralose have more than 200 & 800 times sweetening power as compare to sucrose. Rebiana which is a herbal sweeteners ,derived from plant stevia rebaudiana has more than 200-300 time sweetness .

First generation	Second generation
Saccharin	Acesulfame -K
Cyclamate	Sucralose
Aspartame	Alitame

SALIVA STIMULATING AGENT –

More saliva production help in the faster disintegration of the fast dissolving film formulatio so the formulations may contain acids which are used in the preparation of food as salivary stimulants,citric acid being the most preferred amongst them.

FLAVORS –

Any flavor can be added ,such as intense mints ,sour fruit flavors or sweet confectionery flavors 15. The amount of flavor needed to mask the taste depends on the flavor type & its strength.

COLOR – Pigments such as titanium dioxide or a full range of colors are available ,including FD &C colors, EU colours , natural colours & custom pantone –matched color.

PERMEATION ENHANCER –

Permeation enhancer plays important role for better absorption. So if we want to absorb the drug mostly in mouth as drug release from formulation then there is the need of permeation enhancer .some e.g. of permeation enhancer given-

Aprotinin
 23-lauryl ether
 Azon
 Benzalkonium chloride
 Cyclodextrin
 Dextran sulfate
 Menthol
 Sodium glycodeoxycholate
 Sodium taurodeoxycholate

TECHNIQUE FOR TASTE MASKING –

Various techniques available for masking bitter taste of drugs

1. Taste masking with ingredient such as flavors sweeteners & amino acid
2. Polymer coating & conventional granulation
3. Ion Exchange resin
4. Spray congealing with lipids
5. Formulation of inclusion complexes with cyclodextrin
6. Freeze drying process
7. Preparing multiple emulsion
8. Miscellaneous, using gelatin, gelatin starch ,mucosomes lecithin ,surfactants,salts or polymeric membrane.

METHODS OF PREPERATION OF ORAL THIN FILM

Various approaches to manufacturing of rapid dissolving film are classified as follow –

1. Casting & drying
 - a. Solvent casting
 - b. Semi-solid casting
2. Extrusion
 - a. Hot melt Extrusion
 - b. Solid dispersion
 - c. Freeze drier wafer

From above methods mainly solvent casting & hot melt extrusion method is used for making fast dissolving film, so brief discussion of these two method are given below.

1) Casting & drying -

a) Solvent Casting –

Principle- water soluble ingredient are dissolved in water & API & other agent are dissolved in suitable solvent to form a clear viscous solution ,resulting solution were mixed & casted as a film & allowed to dry to form film.

Procedure –

The RDF is preferred formulated using the solvent casting method ,whereby the water soluble ingredients are dissolved to form a clear viscous solution.The API & other agents are dissolved in smaller amounts of solution ,& combined with the bulk .This mixture is then added to aq. Viscous solution. The entrapped air is removed by vacuum.The resulting solution is casted as a film & allowed to dry, which is then cut into pieces of the desire size.water-soluble hydrocolloids used to prepare RDFs including : hydroxyl propyl methyl cellulose (HPMC) , hydroxyl propyl cellulose(HPC) ,Pullulan, sodium alginate,pectin,carboxy methyl cellulose (CMC) POLYVINYL ALCOHOL (PAV)

Flow chart -

Water soluble polymer in water
(homogenous viscous solution)

API + Other ingredient -dissolved
in small amount of solvent
(Using high shear processor)

Both mixtures are mixed to form homogenous viscous solution then Degassed Under Vacuum then Bubble free solution is coated on non treated casting film then Coated film solution is coated on non –treated casting Film is cutted in to desired shape & size

Advantages -

1. Great uniformity of thickness & great clarity then Extrusion.
2. Film have fine gloss & freedom from defects such as die line.
3. Film have more flexibility & better physical properties.
4. The preferred finished film thickness is typically 12-100 µm .
5. Various thicknesses are possible to meet API loading & dissolution needs.

Disadvantages -

1. The polymer must be soluble in a volatile solvent or water.
2. A stable solution with a reasonable minimum solid content & viscosity should be formed.
3. Formation of a homogeneous film & release from the casting support must be possible.

Example of fast dissolving films prepared by solvent casting method

Sr.No.	Drug	Polymer	Plasticizer	Sweeteners
1	Ondasetron	PVA,PVP,Carbopol 934P	PEG , PEG 400	Mannitol or sodium saccharin
2	Masltodextrin	PVA	Glycerol	Glycerine
3	Salbutamol	HPMC	Glycerol	Aspartame

b) Semisolid casting –Principle- The gel mass is casted which is prepare by using additionally acid insoluble polymer & plasticizers in the solution of water soluble film forming polymerin appropriate amount.

Procedure –

In semisolid casting method firstly a solution of water soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer 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.

Preparation - Solution of water soluble film forming polymer is prepared, Resulting solution is added to a solution of acid insoluble polymer (Cellulose acetate Phthalate, cellulose acetate butyrate) Appropriate amount of plasticizer is added so that gels mass is obtained, Finally the gel mass is casted in to the film or ribbons using heat controlled drums.. The ration of the acid insoluble polymer to film forming polymer should be 1:4

Advantages –

The thicknes of the film should be about 0.015 -0.05 inches.

Multiple casting techniques may be selected on the basis of fluide rheology, desired applied mass, & required dosage form uniformity.

2) Extrusion –

A) Hot melt extrusion –

principle – Polymer is propelled continuously along a screw through regions of high temperature & pressure where it melted & compacted & finally forced through a die to give the final object.

In this method the mass is prepared first under the control of temperature & steering speed. Afterwards, the film is coated & dried in aa drying tunnel. Then follows a slitting & in the last step the film are punched & sealed.

Procedure-

The API & other ingredients are mixed in dry state which are subjected to heating process & then extruded out in molten state. These processes do not involves use of any solvent system. The molten mass thus formed is used to cast the film. The film are further cooled & cut to the desire size.

Flow chart –

The drug is mixed with carrier in solid form

↓
Extruder having heaters melt the mixture

↓
Finally the melt is shaped in films by the dies.

Advantages –

1. Without use of any solvent or water.
2. fewer processing steps.
3. Compressibility properties of the API may not be of important.
4. Better alternative for poorly soluble drugs.
5. More uniform dispersion because of intense mixing & agitation.
6. less energy compared with high shear method.
7. continuous operation possibilities.
8. minimum product wastage.
9. good control of operating parameter & possibility to scale up.

Disadvantages –

1. Thermal degradation due to use of high temperature.
2. Flow properties of the polymer are essential to processing
3. Limited polymers are available
4. All excipients must be devoid of water or any other volatile solvent

B) Solid dispersion –

Principle –

The term “solid dispersion” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymer & also using method such as melt extrusion .this involves a drug which is first dissolved in a suitable liquid solvent & 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.

Procedure-drug is dissolved in a suitable liquid solvent

Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70°C

Finally the solid dispersion are shaped into the film by means of dies.

Precautions while preparing solid dispersion –The selected solvent or dissolved drug may be miscible with the melt of the polyethylene glycol & polymorphic form of drug precipitated in the solid dispersion may get affected by the liquid solvent used.

Quality control tests :Mechanical property testing - Thickness

It can be measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

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 OS as well . 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 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 as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Load at Failure} \times 100}{\text{Strip thickness} \times \text{Strip Width}}$$

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.

$$\% \text{ Elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of film}}$$

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) .

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:

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

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 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 .

Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast Initial length of strip disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30sec. Small amount of medium is use for analysis & hence the drug substances could not be measured by spectrum analysis.

I) Slide frame method – one drop of distilled water was dropped by a pipette onto the oral film .Therefore the film were clamped into slide frames & were place in petri dish . The time until the the film dissolve & caused a hole within the film was measured.

II) Petri dish method – 2 ml of distilled water was placed in a petri dish & one film was added on the surface of the water & the time measured until the oral film was dissolved completely.

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 & hence the stainless steel wire mesh with sieve opening of approximately 700µm used to dip FDS into the dissolution medium.

Assay/drug content and 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.

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 .

Stability testing –

For stability testing the oral thin film were stored under controlled conditions of 25 °C/ 60°C RH as well as 40°C / 75°C over a period of 12 months according to ICH guideline.during storage the morphological properties,mass thickness,tensile properties,water content & dissolution behavior was checked. Consecutively pH & content uniformity during storage are displayed.

TECHNOLOGIES –

1) SOLULEAVES - Technology is used to produce a range of oral delivery films that can incorporate active ingredients, color & flavors. SOLULEAVES films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients & flavors. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal pain therapeutic areas as well as delivering nutritional products. SOLULEAVES films can also be designed to adhere to mucous membrane & to release the active ingredient slowly over 15 minutes.

2) WAFERTAB – is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrips. The system provides rapid dissolution & release of actives when the strip comes into contact with saliva in mouth. The WAFERTAB filmstrip can be flavoured for additionally improved taste masking. The active ingredient is precisely dosed & integrated into the body of a pre-manufactured XGEL film, thus preventing exposure to unnecessary heat & moisture & potentially enhancing product stability. The WAFERTAB system lends itself to many possibilities for innovative product design enabling multiple film with different actives to be bonded together. WAFERTAB can be prepared in a variety.

3) FOAMBURST – is a special variant of the SOLULEAVES technologies where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST manufacturers as a means of carrying & releasing flavours.

4) XGEL – film is at the heart of Meldex International's intellectual property, used in all its film system & its ingestible dosage delivery technologies. XGEL film provides unique product benefits for healthcare pharmaceutical product: it is a non-animal derived, approved on religious ground & is suitable for vegetarians, the film is GMO free & continuous production processing provides an economic & competitive manufacturing platform. XGEL film can be taste masked, colored, layered & capable of being enteric properties & having the ability to incorporate the active ingredient. The XGEL film systems can be made to encapsulate any oral dosage form, & can be soluble in either cold or hot water. The film is comprised of a range of different water-soluble polymers, specially optimised for the intended use.

5) MICAP – MICAP PLC signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the Bioprocess water-soluble film. The developments will be aimed at providing new delivery mechanisms for the \$1.4 bn global market for smoking cessation products.

PACKAGING – A variety of packaging options are available for fast-dissolving film. Single packaging is mandatory for films, which are pharmaceutical products, an aluminum pouch is the most commonly used packaging format. APR – Labtec has developed the rapid card, a proprietary & patented packaging system, which is specially designed for the rapid films. The rapid card has the same size as a credit card & holds three rapid films on each side. Every dose can be taken out individually. The material selected must have the following characteristics:

- ❖ They must protect the preparation from environmental conditions.
- ❖ They must be FDA approved.
- ❖ They must meet applicable tamper-resistant requirements.
- ❖ They must be non-toxic.
- ❖ They must not be reactive with the product.
- ❖ They must not impart to the product taste or odors.

1) Foil paper & plastic pouches – The flexible pouch is a packaging concept capable of providing not only a package that is tamper-resistant, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminium pouches.

2) Single pouch & Aluminium pouch – Soluble film drug delivery pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The foil lamination has essentially zero transmission of both gas & moisture. The package provides a flexible thin film alternative for nutraceutical & pharmaceutical applications. The single dose pouch provides both product & dosage protection.

3) Blister card with multiple units – The blister container consists of two components: the Blister, which is the formed cavity that holds the product, & the lid stock, which is the material that is sealed to the blister. The blister package is formed by heat – softening a sheet of thermoplastic resin & vacuum drawing the softened sheet of plastic into a countered mould. After cooling the sheet is released from the mould & proceeds to filling station of packaging machine. The semi-rigid blister previously formed is filled with the product & lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

Barrier films – many drug preparations are extremely sensitive to moisture & therefore require high barrier films. Several materials may be used to provide moisture protection such as polychlorotrifluoroethylene film. Polypropylene does not stress crack under any condition. It is an excellent gas & vapour barrier. Lack of clarity is still a drawback.

APPLICATIONS OF FAST DISSOLVING BUCCAL FILMS :

Vaccines –

Fast dissolving buccal films can be delivered in the form of vaccine which is stable at room temperature so it is quickly dissolved in mouth & in saliva. Rotavirus vaccine prepared in United States is a room temperature stable fast dissolving buccal film delivery system for vaccines that will make vaccination almost as simple as freshening your breath. This delivery system exhibits many advantages which include: improved patient compliance, improved bioavailability, reduction in the costs associated with storage & distribution, handling & administration.

Controlled & sustained release film:

Sustained release buccal film is applicable in hospital preparation & various polymers like chitin & chitosan derivatives are used as excipients. They contribute to expansion of application, decrease toxicity, wound dressing, oral mucoadhesive & water resisting adhesive by virtue of their release characteristics & adhesion.

Taste masking- Taste masking is an essential requirement for fast dissolving tablets for commercial success. Fast dissolving buccal films dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds & hence this property becomes critical for the patient compliance. In taste masking, drug with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers by solvent evaporation & solvent extraction techniques. These polymers microspheres showed efficient taste masking & complete dissolution in a short period.

Orally Disintegrating films-

Fast dissolving buccal films are based on a water soluble polymer. The film has the ability to dissolve rapidly without the need for water provides an alternative to the patients receiving swallowing disorders & to patient suffering from nausea, such as those patients receiving chemotherapy.

Cost – containment policies :

Expensive process & equipment, such as lyophilization & require special & expensive packaging systems due to their fragility & friability. MDFs/OTFs, on the other hand are much more economical to produce & pack & multiple affordable packaging options are available, such as pouches, blister, rapid cards as well as multiple dispenser (especially indicated for OTC market).

Consumer –friendly alternatives :

ODTs are sometime difficult to store ,carry & bundle due to their extreme fragility & friability ;complex packaging systems are often required in order to secure the product’s stability over time.They are also very hygroscopic in order to secure fast dissolution when orally administered.This means that any packaging system must preserve integrity & stability over time.

MDFs/OTFs as a non-patient infringement alternative :

On July 2005 ,the US FDA approved a suitability petition for the registration of a famotidine OTF version through an ANDA procedure . This means that ANDA of novel OTF products substituting ODTs represents a viable option to gel MDF/OTF products approved in the US quickly ; in addition ,the use of MDF products automatically certifies that no patent infringement of odt products can happen.

LIST OF SOME MARKETED PRODUCTS AVAILABLE AS FDF-

Brand name	Manufacturer or Distributer	API (Strength)	Use
Klonopin wafers	Solvay Pharmaceuticals	Clonazepam (0.125,0.25,0.5,1,2mg)	Treatment of anxiety
Listerine Cool Mint Pocket packs	Pfizer	Cool mint	Mouth fresheners
Sudafed PE	Wolter Kluwer Health	Phenylephrine	Relieving congestion
Suppress	InnoZen	Menthol (2.5mg)	Cough suppressant
Triaminic	Novartis	Diphenhydramine HCl (12.5 mg)	Anti-allergic
Theraflu	Novartis	Dextromethorphan HBR (15 mg)	Cough suppressant
Orajel	Del	Menthol/pectin (2/30mg)	Mouth ulcer
Gas -X	Novartis	Simethicon (62.5 mg)	Anti-flatulating
Chloraseptic	Prestige	Benzocaine/mentho (3/3 mg)	Sore throat
Benadryl	Pfizer	Diphenhydramine HCL (12.5/ 25 mg)	Antiallergic

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