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Review Article

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Fast Dissolving Oral Films Technology: A Recent Trend For An Innovative Oral Drug Delivery System

Deepak Sharma [1*], Daljit Kaur[1], Shivani Verma[1], Davinder Singh[1], Mandeep Singh[1], Gurmeet Singh[2], Rajeev Garg[3]

***Corresponding author:**

Deepak Sharma

[1]Department of Pharmaceutics, Rayat-Bahra Institute of Pharmacy, Hoshiarpur, Punjab, 146001, India
[2]Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, 142001, India
[3]Department of Pharmaceutics, ASBASJS Memorial College of Pharmacy, Bela, Ropar, Punjab, 140111, India

Abstract

Over the past few decades, there has been increased interest for innovative drug delivery system to improve the safety, efficacy and patient compliance, thereby increasing the product patent life cycle. In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. Fast dissolving oral films are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve 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. These films have a potential to deliver the drug systemically through intra-gastric, 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. Fast dissolving oral films are found to be satisfactory in many situations like allergic conditions, cold and cough, sore throat, nausea, pain, mouth ulcers, CNS disorders and CVS disorders. Oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, film stabilizing agents, plasticizers, sweeteners, flavours, colors, saliva stimulating agents, surfactants etc. The present review reflects information regarding formulation ingredients, technologies and evaluation tests employed in the preparation of fast dissolving oral films. However, for future growth point of view the fast dissolving oral films sector is well-positioned. It seems that the value of the overall oral thin films market will grow significantly.

Keywords: Fast dissolving oral films, Oral Mucosa, Disintegration, Hydrophilic polymers, Innovative drug delivery, Patented Technologies.

Introduction

Fast dissolving oral films were first introduced in the market as breath fresheners and personal care products such as dental strips and soap strips. However, they are introduced in the United States and European pharmaceutical markets for therapeutic effect [1]. Fast dissolving oral films are most advance form of solid dosage form due to various reasons like flexibility, improved efficacy of API (Active Pharmaceutical Ingredient), dissolution and disintegration within 1 minute with the help of less amount of saliva as compared to dissolving tablet. Thin films have the potential to allow the development of sensitive drug targets that may otherwise not be possible in tablets or liquid formulations [2]. Oral ingestion is the most common and oldest route of administration which consists of tablets, capsules, etc. But this type of ingestion is not suitable for geriatric and pediatric patient suffering from the dysphasia, bedridden and non- compliant patients due to the fear of chocking [3]. So, to overcome this disadvantage bioadhesive mucosal dosage forms have been introduced which includes adhesive tablets, gels, ointments, patches and then in 1970s polymeric films were introduced also known as oral thin films or fast dissolving films or mouth dissolving films or oro-dispersible films or quick disintegrating films and melt in mouth dosage form which was based on the technology of transdermal patches [4]. Today, these are proven to be acceptable for OTC (Over the Counter) medications and are in the early to mid- development stages for prescription drug. Zulpenz is the first oral soluble disintegrating film approved by the FDA as a prescriptions medication [5]. These consists of thin oral films which get absorbed in the buccal cavity with the help of saliva, as hydrating agent without requirement of water and give their effect through pre-gastric absorption from mouth, pharynx and oesophagus as the saliva passes down into the stomach [6].

Physiochemical properties of oral mucosa

Permeability coefficient of a drug is the measure of ease with which the drug can permeate a membrane [7]. Order of permeability is intestine> buccal mucosa> skin [8]. This permeability ranking is based upon the relative thickness and degree of keratinization. Permeability of buccal mucosa is 4-4000 times greater than that

of skin. Due to less permeability of buccal mucosa than the intestine some permeability enhancer has been extensively developed in the buccal drug delivery system like [9];
Aprotinin
23-Lauryl ether
Benzalkonium chloride
Dextran sulphate
Sodium taurodeoxycholate
Hence buccal delivery serves as an excellent platform for absorption of drug. Absorption of oral film takes place either through transcellular route (intracellular route) and paracellular route (intercellular route) [7, 8].
Oral mucosa consists of three layers [7]:
Stratified squamous epithelium (outermost layer)
Lamina propria (intermediate layer)
Submucosa (innermost layer)
Epethelium of oral mucosa is 40-50 cell layers thick which is composed of intercellular ground substance called mucus which consists of proteins and carbohydrates. Mucosal thickness of hard and soft palates, the floor of the mouth, the ventral tongue and the gingival varies from 100-200 um. Submucosal layer secrets gel like secretion known as mucous which consists of 1-5% of water insoluble glycoprotein, 90-99% water and other components like proteins, enzymes, electrolytes and nucleic acids in very small quantities and this composition varies depending upon the origin of secretion in the body [7, 8].
Function of mucous:
Maintains hydrating conditions of oral cavity
Provides adequate lubrication
Provides concentrated protective molecules such as secretory immunoglobulins and also reduces attachment of micro-organisms.
Salivary gland consists of lobules of cell which secrete saliva and parotid through the salivary duct near the teeth submandibular and the sublingual ducts. Minor salivary glands present in the lips, buccal mucosa and in lining of the mouth and the throat. Total amount of saliva secreted per minute is 1-2 ml [3]. Saliva consists of water, mineral salts, salivary amylase (enzyme), mucus, lysozyme, immunoglobulins and blood clotting factors [10]. Saliva and salivary mucin contribute to the barrier properties of oral mucosa. Negative charge of mucin contains sulphydryl group and salic acid responsible for the muco-adhesive phenomenon [9].

Ideal characteristics of oral films

Should have pleasant taste.
Dose upto 40mg can be incorporated.
Drug should be stable to moisture overtime and soluble in saliva.
Should exhibit suitable tensile strength.
Should not stick to the packing material and fingers.
Should be ionized at pH of oral cavity.
Should be able to permeate the oral mucosal tissue.
Should not be bitter and have quick onset of action.
Drug with smaller and moderate molecular weight are preferable.
Drug should have high first pass metabolism [4, 11].

Advantages of oral films

Convenient dosing.
No water requirement.
No risk of chocking.
Enhanced stability.
Ease of administration.
Bypass of the GIT improves its bioavailability.
Due to low dose, low side effects.
Good mouth feel.
Rapid onset of action in case of mouth sickness and allergic attacks like asthma.
Controlled release of drug facilitates the rate and extent of absorption.
Does not interfere with normal function like talking, drinking etc.
Delivery of those API is possible which are at high risk of degradation in the gastrointestinal tract [9, 12].

Disadvantages of oral films

Packing requires special equipment. So, difficult to pack.
Not suitable for drugs which irritate and are unstable at buccal pH.
Only small dose of drug can be administered.
Hygroscopic in nature. So, longer preservation is difficult.
Drugs which are absorbed only by passive diffusion can be administered by this route.
Restriction of eating and drinking for sometime after consumption of oral film.
Method for preparation is expensive as compared to oral dissolving tablets [7, 13, 14].

Formulation of fast dissolving oral films

Excipients used in oral films are given below as per their categories. All excipients used in formulation should be chemically inert and approved for use in the formulation of oral films. According to the film forming material characteristics, the manufacture of the dosage forms can present different critical issues. Common problems are caused by foaming during the film formation due to the heating of the material or solvent evaporation, the flaking during the slitting and the cracking in the cutting phase [15].

Table 1: Composition of oral thin films [16, 17]

S. No.	Name of the excipient	Quantity
1	Drug	5-30%
2	Film forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Surfactant	Q.S
7	Flavouring agent	Q.S.
8	Colouring agent	Q.S.

Active pharmaceutical ingredient

The selection of API depends upon its potency, dose and therapeutic efficacy. Most suitable API for ODF includes antiulcers, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal antiemetic, neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, anti-alzheimers, expectorants and anitussive [18].

Table 2: List of some marketed products along with their API [19]

S. No.	Drugs	API	Use
1	Benadryl®	Diphenylhydramine HCL (12.5mg or 25mg)	Antiallergic
2	Suppress®	Menthol (2.5mg)	Cough suppressants
3	Klonopin Wafers	Clonazepam (0.125mg,0.25mg,0.5mg, 1mg or 2mg)	In anxiety
4	Theraflu®	Dextromethorphan HBR (15 mg)	Anti allergic
5	Orajel®	Menthol/pectin (2mg/30mg)	Mouth ulcer
6	Gas-X	Simethicone (62.5mg)	Anti flatuating
7	Chloraseptic®	Benzocaine/menthol (3mg/3mg)	Sore throat
8	Triaminic®	Diphenylhydramine HCL (12.5mg)	Anti allergic

Film forming polymer

The selection of polymer is one of the most important and critical parameter for the successful development of oral films because of their tensile strength which depends upon the type and amount of polymer used. At least 45% w/w of polymer should be present based on the total weight of dry film but typically 60-65% w/w of polymer is preferred to obtain desired properties [20]. The polymers can be used alone or in combination to obtain the desired film properties. The film obtained should be quiet enough so that there won't be any damage while handling or during transportation [21].

Ideal properties of the film forming polymers

The polymer employed should be non-toxic, non-irritant.

It should be devoid of leachable impurities.

It should have good wetting and spreading properties.

The polymer should exhibit sufficient peel, shear and tensile strengths.

The polymer should be readily available and should not be very expensive.

It should have good shelf life.

It should not aid in cause secondary infections in the oral mucosa/ dental region.

It should have a good mouth feel property.

It would be ideal to have a polymer that would have local enzyme inhibition action along with penetration enhancing property.

It should not be an obstacle in the disintegration time [22, 23].

Table 3: List of polymers used in oral thin films [20, 24]

Group	Class	Example
Natural	➢ Carbohydrate	Pullalan, pectin, sodium alginate, maltodextrin, Sodium starch glycolate (SSG)
	➢ Proteins	Gelatin
	➢ Resin	Polymerized rosin (novel film former)
Synthetic	➢ Cellulose derivatives	Hydroxy propylmethycellulose (E3, E5, E15, K3, K15, K50), Methylcellulose (A3, A6, A15), Carboxy methylcellulose secekol- 30, Sodium carboxymethyl cellulose, Microcrystaline cellulose, Croscarmellose sodium (CCS).
	➢ Vinyl polymer	Poly vinyl pyrrolidone (K-90, K-30), Poly vinyl alcohol, poly ethylene oxide
	➢ Acrylic polymer	Eudragit (RD-100, 9, 10, 11, 12 and RL-100)

Natural polymers

Pullalan

It is a neutral glucan, with a chemical structure somewhat depending upon carbon source, producing micro-organism like Aureobasidium pullalans and fermentation conditions [25]. The basic structure is a linear - glucan one, made from three glucose units linked -(1,4) in maltotriose units which are linked in a -(1,6) way. The three glucose units in maltotriose are connected by an -(1,4) glycosidic bond, whereas consecutive maltotriose units are connected to each other by an -(1,6) glycosidic bond. The regular alternation of (1 4) and (1 6) bonds results in two distinctive properties of structural flexibility and enhanced solubility [20].

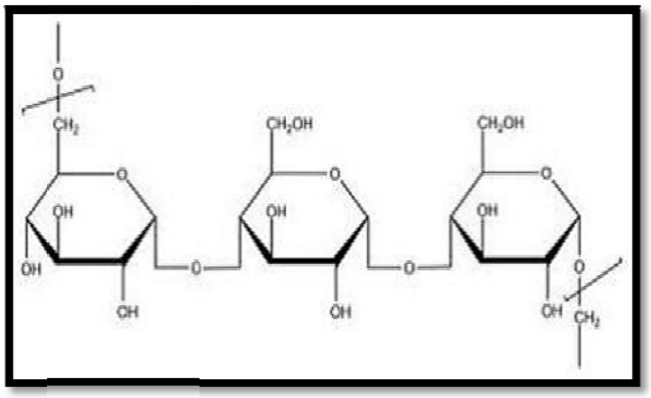

Figure 1: Structure of Pullalan

Salient features

5-25% w/w solution is required to form flexible film.
It is soluble in hot as well as cold water.
Melting point is 107°C.
pH is 5-7.
Pullalan film has 300 times more oxygen barrier than HPMC films and 9 times more stronge than gelatin film [11, 20].

Pectin

Pectin is a heterogeneous grouping of acidic structural polysaccharides. This complex anionic polysaccharide is composed of β-1,4- linked d-galacturonic acid residues, wherein the uronic acid carboxyls are either fully (HMP, high methoxy pectin) or partially (LMP, low methoxypectin) methyl esterified [22].

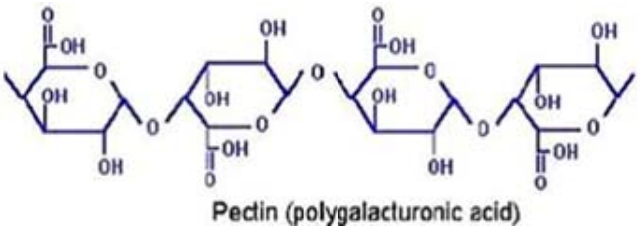

Figure 2: Structure of Pectin

Salient features

Soluble in water but insoluble in ethanol (95%) and other organic solvents.
Melting point is 152°C.
pH is 6.0-7.2.
Molecular weight is 30,000-100,000 [11, 20].

Gelatin

Gelatin is prepared by thermal denaturation of collagen, isolated from animal skin, bones and fish skin. The two types of gelatin are available i.e., Type A from pork skin by acid cessing and Type B from bones and skin of animal by alkaline processing [26].The properties and film forming ability of gelatins are directly related to the molecular weight, i.e., the higher the average molecular weight, the better the quality of the film. Gelatin films were found to dissolve rapidly, excellent carriers for flavors and produce a smooth mouth feel [22].

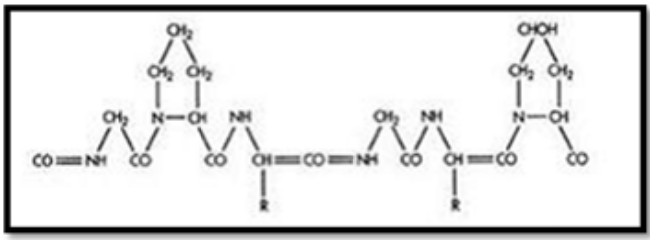

Figure 3: Structure of Gelatin

Salient features

Soluble in acid, alkali, gycerine and hot water.
It has very good film forming ability.
Swell in water and softens [11, 20].

Sodium alginate

Sodium alginate consists of sodium salt of alginic acid which is a mixture of polyuronic acid composed of residues of D-mannuronic acid and N-guluronic acid [20].

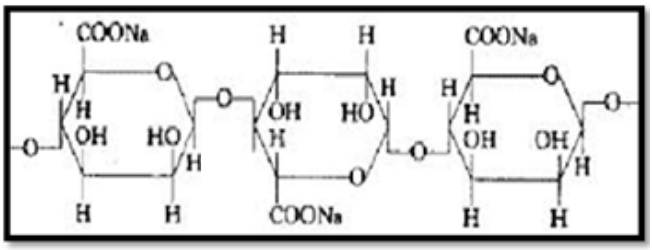

Figure 4: Structure of Sodium alginate

Salient features

Alginate solution has gelling capacity in the presence of calcium.
A mixture of starch and alginate to form edible film improve the mechanical properties of film.
Melting point is > 300°C.
Slowly soluble in water and form colloidal solution [11, 22].

Maltodextrins

Maltodextrin is typically composed of a mixture of chains that vary from three to seventeen glucose units long. Maltodextrins are classified by DE (dextrose equivalent) and have a DE between 3-20. Higher the DE value, shorter glucose chains, higher sweetness, higher the solubility and the lower heat resistance [22].

Salient features

It is soluble in alcohol, ether, benzene and chloroform.
Mechanical properties can be improved by the addition of plasticizer such as dibutyl sebacate (DBS).
It has an excellent anti-oxidation property and high softening point [20, 23].

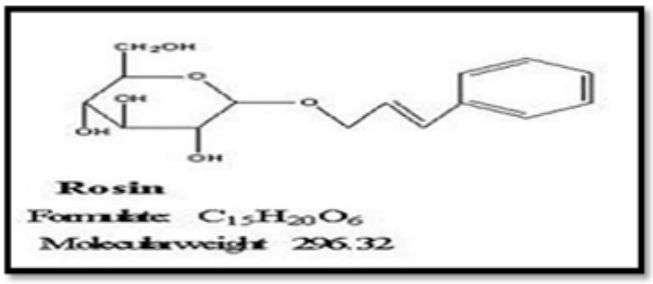

Figure 5: Structure of Maltodextrins

Starch

Biopolymer starch is composed of glucose units and having two main constituents are, amylose and amylopectin. Amylose constituent is a linear one, having long chain of -D glucose units linked together by -1,4 glycoside linkages and only slightly branched. The amylopectin constitutes -1,4 linkages of glucose units, interlinked by - 1,6 linkages and having a branched structure.

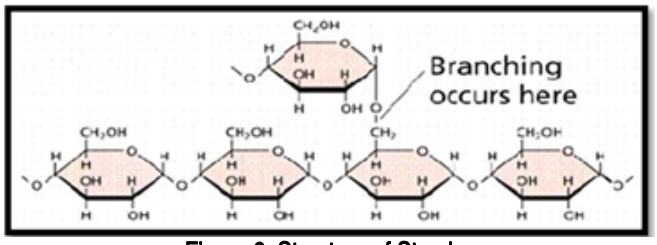

Figure 6: Structure of Starch

Recently, Hu et al have developed starch films from oxidized potato starch (OPS) with glycerol as a plasticizer. For example, pre-gelatinized starch includes lycoat (NG73), modified starch, amylase rich starch [20].

Salient features

It is insoluble in cold water and ethanol.
It swells in water by about 5 to10% at 37°C.
It decomposes at 250°C.
2% aqueous dispersion of starch provides 13 mPa s viscosity [6, 11].

Synthetic polymers

Hydroxy propylmethyl cellulose

HPMC polymer has a high glass transition temperature and is classified according to the content of substituent's and its viscosity which affects the solubility-temperature relationship. Lower grades of HPMC like Methocel E3, E5, and E15 are particularly used for film formation because of their low viscosity [7].

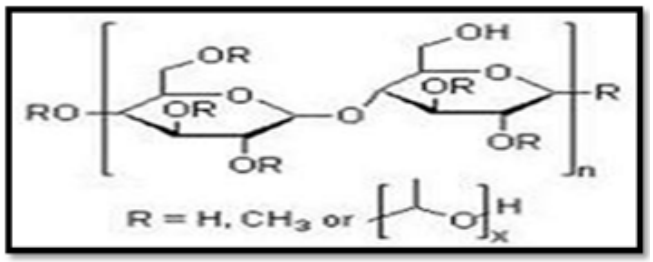

Figure 7: Structure of Hydroxy propylmethycellulose

Salient features

Soluble in cold water, forming a viscous colloidal solution.
Insoluble in chloroform and ethanol [11].

Hydroxypropyl cellulose

Hydroxypropyl cellulose is partially subsituted polyether of cellulose [22].

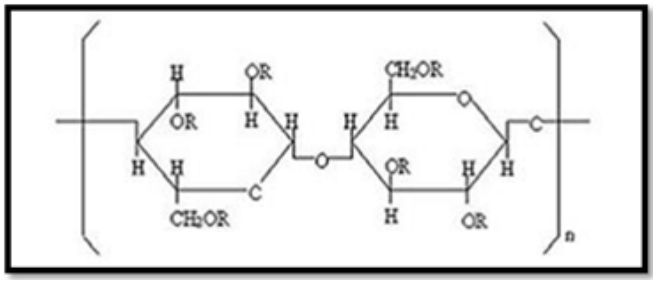

Figure 8: Structure of Hydroxypropylcellulose

Salient features

5% w/w is generally used for film coating.
It is freely in water, in many cold and hot polar organic solvents.
Molecular weight is 50,000-1250000 kDa [11, 20].

Polyethylene glycol

PEG is produced by the interaction of ethylene oxide with water, ethylene glycol or ethylene glycol oligomers [23]. The starting materials used for synthesis of PEG polymers with low Poly dispersity index (PDI) (narrow molecular weight distribution) are Ethylene glycol and its oligomers. Reactions catalyzed by anionic polymerization result in PEGs with low PDI [27].

PEG

Figure 9: Structure of Polyethylene glycol

Salient features

It is soluble in water and in various organic solvents like acetonitrile, chloroform and methylene chloride.
Molecular weight of PEG ranges from 100,000 to 8,000,000.
Melting point is 65-70°C .
pH ranges from 8-10 [11, 20, 22].

Kollicoat

Kollicoat is a new pharmaceutical excipient that was developed as a coating polymer for controlled release tablets. It is a polyvinyl alcohol-polyethylene glycol graft copolymer whose polyvinyl alcohol moiety provides good film forming properties and polyethylene glycol part acts as an internal plasticizer leading to good flexibility properties [20].

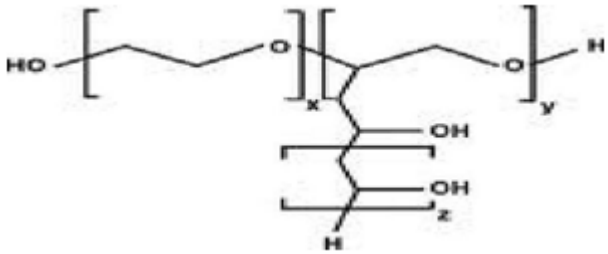

Figure 10: Structure of Kollicoat

Salient feature

It is used to form transparent film [11].

Polyvinyl alcohol

It is synthesized by the polymerization of vinyl acetate to polyvinyl acetate which is then hydrolysed to get PVA. The crystallizability and solubility of PVA is affected by the extent of hydrolysis and content of acetate group present in PVA [27].

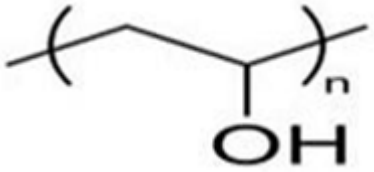

Figure 11: Structure of Polyvinyl alcohol

Salient feature

It has melting point of 230°C and 180-190°C for fully hydrolysed and partially hydrolysed grades, respectively [27, 28].

Polyvinyl pyrrolidone

It is a branched and more complicated polymer than linear polymer, though it lies in a two-dimensional plane. It is also known as polyvidone. It is synthesized by polymerization of vinylpyrrolidone in water or isopropanol [27].

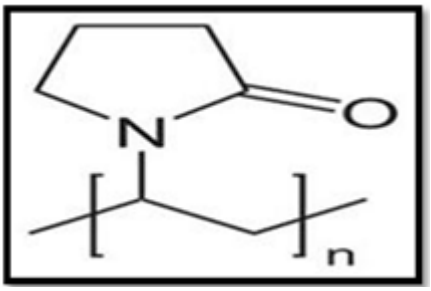

Figure 12: Structure of Polyvinyl pyrrolidone

Salient feature

In dry form it readily absorbs upto 40% of its weight in atmospheric water [29].

Gum Carrageenan

These sulphated polysaccharides are extracted from cell wall of various red seaweeds belonging to family Rhodophyceae. The main sources for carrageenan are the Chondrus crispus, Eucheuma cottonii and Eucheuma spinosum species [22].

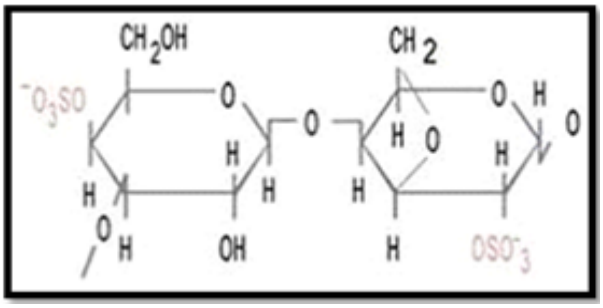

Figure 13: Structure of Gum Carrageenan

Salient features

Films made from carrageenan were found to be less opaque than those obtained from starch [22].

Chitosan

Water soluble derivatives of chitosan have been synthesized by chemical modification like carboxymethylation of chitosan results in formation of N-carboxymethylchitosan which is soluble in wide

range of pH. So, their main drawback related to solubility can be overcome by this method. Chemical modification results in the formation of hydrophilic chitin which has more affinity to water or organic solvents [27].

Table 4: Few examples of drugs with type of polymer used [11, 26, 30]

Oral films	Polymer used
Amlodipin Besylate	Sodium alginate
	HPMC-E5
Famotidine	HPMC, sodium carboxy methyl cellulose, PVA
Ondansetron hydrochloride	Polyvinylalcohol, polyvinyle pyrrolidone, Carbopol E5
Glipizide	HPMC, sodium carboxymethlcellulose, carbopol-934P and
Domperidone	PVA
Valdecoxib	HPMC, Eudragit EPO
Cetrizine hydrochloride	Pullulan gum
Verapamil	HPMC-E6, Maltodextrin
Levocitrazine dihydrochloride	Eudragit EPO, HPMC E5 LV, PVA

Plasticizer

Plasticizer used in the formulation should be compatible with the type of polymer used as it reduces the glass transition temperature and improves flow of the polymer. So, it helps to improve the flexibility of the strip and reduces the brittleness of the strip [31]. It is also reported that the use of particular plasticizer also affect the absorption rate of the drug. Various defects associated with the inappropriate use of the plasticizer are cracking, blooming, pilling and splitting of the strip [32]. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer in the range of 40-60°C for non-aqueous solvent system and below 75°C for aqueous system.

Different types of polymers which get plasticized with different polymers like [22]:

Cellulosic hydrophillic polymers were easily plasticized with hyroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols.

Less hydrophillic cellulosic polymers were plasticized with esters of citric acid and phthalic acid.

Polymer like polyvinyl alcohol easily gets plasticized with glycerol.

Both hypromellose as well as polyvinyl alcohol films get plasticized with diethylene glycol.

Table 5: Advantages of plasticizers over other plasticizers [22]

Plasticizer	Better than	Reason
Malic acid	Citric acid, Oleic acid, Tartaric acid	As it does not crystallized out when films were dried
PEG-300 (low molecular weight)	PEG (High molecular weight)	As they formed visually superior transparent films and had low water vapour permeation rate
Sorbitol	Mannitol	As it does not crystallized out when films are dried [31]

Table 6: Few examples of drugs with the type of plasticizer used [20]

Oral films	Plasticizer used
Montelukast sodium	Glycerine
Ropinirole hydrochloride	PEG-400
Triclosan	Propylene glycol
Sertraline	Propylene glycol or PEG-400
Metaclopramide hydrochloride	Glycerol
Telmisartan	Propylene glycol
Dicyclomine hydrochloride	PEG-400
Tianeptine sodium	PEG
Amlodipine besylate	Glycerol
Livocitrazine dihydrochloride	Glyerine, dibutyle phthalate

Saliva stimulating agent

The purpose of these agents is to increase the production of saliva that would helps in the faster disintegration of the oral thin film. Citric acid, malic acid, lactic acid, ascorbic acid ad tartaric acid used to stimulate salivary secretions. These agents can be used alone or in combination between 2 to 6 % w/w of weight of the strip [6, 18].

Flavouring agent

Any flavor which is USFDA approved can be used to mask the bitter taste of the formulation. These agents can be selected from the synthetic flavor oils, oleo resins. Extract derived from various parts of the plants like leaves, fruit and flowers. The amount of flavor to be used depends upon the type of flavor used. Flavors that can be added are essential oils like menthol, intense mints like peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary flavors such as vanillin, chocolate. They can be used alone or in combination [18, 33].

Sweetening agents

Both natural and synthetic sweetners are used to improve palatability of the mouth dissolving formulations [34].

Table 7- Types of sweetening agents [16, 18]

Natural		Synthetic	
Sucrose	Mannitol	First generation:	Saccharin
Dextrose	Sorbitol		Cyclamate
Fructose			Aspartame
Glucose		Second generation:	Acesulfame-K
Liquid glucose			Sucralose
Isomaltose			Alitame and Neotame

Colouring agents

Various colouring agents used are FD & C colours, EU colours, natural colours and custom Pantone-matched colours. FD&C approved colours are used in the concentration not exceeding 1% w/w in the manufacturing of oral thin films, such as titanium oxide, silicon dioxide, zinc dioxide etc. [34, 35].

Surfactant

Surfactant as solubilizing or wetting agent in the formulation so that film get dissolved within few seconds and releases active ingredient to produce an effect. Some commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens etc. Palaxamer 407 is the most important surfactant used in oral thin films [34, 35].

Manufacturing of fast dissolving oral films

One or combination of following methods can be used for the preparation of fast dissolving oral films:

3.1. Solvent casting method
3.2. Semisolid casting method
3.3. Hot melt extrusion method
3.4. Solid dispersion extrusion
3.5. Rolling method

Solvent casting method

In this method, prepared solution is poured into the petri dishes and covered with the inverted funnels to allow the evaporation of solvents. These are kept at 20-25 °C for 24-48hrs depending upon solvent system used. Patches obtained are 15-20mm in diameter, 0.2-0.3mm thick and are carefully pull out from the petri dishes [36, 37, 38, 39, 40].

Water soluble ingredients are mixed at 60 °C by stirring at 1000 rpm
Results in viscous solution
Addition of polymers in above solution by using high shear process
Addition of drug
Vaccum is applied for the removal of entrapped air
Pour the solution in a glass mould
Dry in oven at 40-50 °C
Cut into pieces of desired size

Advantages

Great uniformity of thickness
Great clarity then extrusion
More flexibility
Better physical properties
Finished film thickness is 12-100um

Disadvantages

Polymer must be soluble in a volatile solvent or water
Viscosity should be formed

Semisolid casting method

In this method, acid insoluble polymer and film forming polymer ratio should be 1:4. The films thickness formed by this method is about 0.015-0.05 inches [39, 40, 41].

Prepare a solution of water soluble film forming polymer
Prepared solution is added to the solution of acid insoluble polymer, prepared in ammonium or sodium hydroxide like cellulose acetate phthalate, cellulose acetate butyrate.
Appropriate amount of plasticizer is added to obtain a gel mass
Gel mass is casted into the film or ribbon using heat controlled drums
Mixture is degassed under vacuum

Bubble free solution is coated on non-treated casting film
Coated film is dried in aeration drying oven and cut into desired shape and size

Hot melt extrusion method

The processing temperatures should be 80°C in 1st zone, 115°C in 2nd zone, 100°C in 3rd zone and 65°C in 4th zone. The screw speed should set at 15 rpm to set the granules inside the extruder for approximately 3-4 min. [25]
Drug and polymer are blended in sigma blade mixer for 10 min.
Plasticizer is added slowly
Granulation of mixture in the presence of anti-sticking agent
Granules are stored overnight and sieved through 250um sieve
Dried granules are fed into the extrude
Processing is done for 3-4 min. at temperature as mentioned above
Extudate is pressed at temperature 65 °C to obtain a film of thickness 200 um

Advantages

Improved bioavailability of poorly soluble compounds
Cost effective process with reduced production time and reduced number of unit operation
Capability of sustained, modified and targeted release
Better content uniformity
Have stability at varying pH and moisture levels

Disadvantages

Thermal process. So, requires drug and polymer stability
Require high power input
Binders with low melting point are at the risk of melting or softening of the binder during handling and storage of the agglomerates
Binders with high melting point require high melting temperatures and can contribute to volatility problems especially for heat labile materials

Solid dispersion extrusion

This method involves dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers [42].
Immiscible drug is dissolved in suitable solvent

Solid dispersions are prepared by incorporating above solution into melted polyethylene glycol: below 70°C
Finally dispersions are shaped into the films by means of dies

Precaution while preparing by this method

Suitable solvent should be selected while dissolving a drug otherwise polymorphic form of drug may get precipitated in the solid dispersion.

Rolling method

In this solution or suspension containing drug is rolled on a carrier, solvent used is water or mixture of water and alcohol
Film is dried on a roller and cut into the desired shape [38, 39, 43, 44]

Patented technologies of fast dissolving oral films

XGel

XGel film technology is developed by BioProgress which causes a revolution in the product offerings and manufacturing methods which is now available to the pharmaceutical industry. These films may be coloured or printed during manufacture for branding and coding which is quite helpful in product identification and also developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare pouches [45]. These films enhance the stability of product. [46]

Soluleaves

In this technology, the film on coming in contact with saliva releases its active ingredients, during this film adhere to the mucous membrane in order to release the drug slowly in 15 min. This method is useful for those who have difficulty in swallowing conventional tablets [45]. This technology is applied to flavoured products such as mouth fresheners, confectionery and vitamins [46]

Wafertab

Wafertab is a drug delivery system which incorporates pharmaceutically active ingredients into an ingestible film strip. When film came in contact with saliva it provides rapid dissolution and release of active ingredient [47]. The Wafertab film strip can also be flavoured for additionally improved taste masking. The active ingredient is integrated into the body of a fused.

Foamburst

Foamburst is a new patent granted in September 2004 which is for capsules made of formed film. During production an inert gas is blown into the film, results in a film with honeycomb structure as a capsule which dissolve rapidly and causing a melt-in-the mouth sensation. The void in the film may be gas-filled, empty or filled with other materials to produce specific taste burst characteristics or deliver active drugs [47].

Micap

In 2004 Micap plc signed an agreement to combine its expertise in micro encapsulation technology with the BioProgress water soluble films. Their main aim is to provide new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs) [46].

Rapid film™

It is a novel thin film technology developed by Applied Pharma Research (APR), a leading Swiss R&D company whose main focus is innovative drug delivery, in conjugation with Labtec GmbH. Dr. Paulo Galfetti, Head of Licensing & Business Development states that this technology is of great importance when rapid onset of action is required. Galfetti advices, this technology can be used with poorly soluble drugs. [48] Rapid film is a thin film containing drug with area of 1-10 cm sq. Disintegration occurs completely within 20 seconds. For example: Donepezil Rapidfilm®, Olanzapine Rapidfilm®. [49]

Table no. 8: Some patents on oral thin films

Country	Patent Number	Title	Inventors
US	20110305768A1	Quick dissolving oral thin film for targeted delivery of therapeutic agents	Hai-Quan Mao et al [50]
WO	2012103464A2	Oral thin film vaccine preparation	Brian Pulliam [51]
WO	2013085224A1	Bitter taste masked oral thin film formulation of Sildenafil citrate	Dae-Kun Song et al [52]
US	6177096B1	Water soluble film for oral administration with instant wettability	Horst Georg Zerbe et al [53]
EP	1680079A2	Rapidly disintegrating films for delivery of pharmaceutical and cosmetic agents.	Scott D Bamhart et al [54]
EP	2509631A4	Ph sensitive compounds in taste masking within oral thin film strips	A Mark Schobel et al [55]
WO	2012053006A2	Improved oral fast dissolving films comprising combination of polymers and method of preparation thereof	Rajesh Jain et al [56]
US	6596298B2	Fast dissolving orally consumable films	Sau-Hung Spence Leung et al [57]
WO	2014183054A1	Thin film with high load of active ingredient	Eric Allen et al [58]
US	7579019B2	Pharmaceutical carrier device suitable for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al [59]

Previous work done on fast dissolving oral films

Deepthi et al in 2014, formulated and evaluated fast dissolving oral films of Zolmitriptan by solvent casting method. This film of zolmitriptan was evaluated using sodium alginate, xantham gum, sodium starch glycolate and guar gum at different concentrations on the basis of flexibility, tensile strength and stickiness of the film. The F5 formulation showed 98.5% of drug release within 6 minutes which was desired for fast absorption. This was indicated that the formulation was stable because there was no degradation of the film at high temperature and humidity conditions [60].

Farhana Sultana et al in 2013, prepared and evaluated fast dissolving oral thin films of caffeine anhydrous using HPMC-2910 (15 cps), sodium alginate and kollicoat IR white in various concentrations. In-vitro studies have shown that film prepared by using kollicoat IR white were more porous and its disintegration time was found to be 12 sec. and cumulative % release was 99.89% within 240 seconds. Films prepared by using HPMC have shown its disintegration time of 13sec. and its cumulative % release was 100% within 120 sec. So, film prepared by using HPMC were found to be more flexible, smooth and have shown faster release of drug within short time [61].

C.L. Bhingare et al in 2013, formulated and evaluated mouth dissolving films of Zolpidem tartrate by exploring the combination of polymers, hydroxypropyl cellulose (EF-P) with hydroxymethyl cellulose K-15 by solvent casting method. HPMC is used in the ratio (1:1 and 2:1) in combination with HPC. The formulation F4 have uniformity in weight with thickness of 0.930 mm, drug content of 98.3% and 100% drug release within 6 minutes. Hence this batch could be used for incessant drug release, enhanced rate of absorption, efficiency and increased bioavailability [62].

Buchi N. Nalluri et al in 2013, developed and evaluated mouth dissolving films (MDFs) of salbutamol sulfate using film former, hydroxypropylmethyl cellulose (HPMC) of different viscosity grades along with film modifier polyvinyl povidone K30 and sodium lauryl sulfate (SLS) by wet film applicator technique. MDFs with 13% w/w of HPMC E5 have shown better dissolution properties when compared to HPMC E15. MDFs with 0.04% w/w of SLS have shown superior dissolution properties as compared to MDFs without SLS. The film prepared using HPMC E5 and SLS showed

the highest dissolution rate, satisfactory in-vitro disintegration time and physico-mechanical properties [63].

Pamula Reddy B. et al in 2013, developed and formulated chlorpheniramine maleate mouth dissolving films using various water soluble polymers such as HPMC (3cps and 5cps), methyl cellulose (E-15) and kollicoat IR with suitable plasticizers such as PEG 400 and glycerine and citric acid as saliva stimulating agent by solvent evaporation technique. These films were evaluated for thickness, folding endurance, weight variation, pH and disintegration time. The formulation M15 containing drug and kollicoat IR was considered as an optimized formulation, which produced 100% release of drug in 5 minutes, with phosphate buffer of pH 6.8 as dissolution medium [64].

GS Khaja Nayub Rasool et al in 2014, formulated and evaluated oral films of Losartan potassium using different polymers such as PVA, PVP, HPMC, Carbopol, Pectin and Tragacanth by using solvent casting method. The in-vitro drug release was found to be 78-96% within 5 min. the disintegration and dissolution rates were increases with increased patient compliance by avoiding first pass metabolism and enhanced bioavailability [65]

Dr. D. Nagendrakumar et al im 2015, formulated and evaluated fast dissolving oral films of Metoprolol succinate by using HPMC E5 and HEC polymers by solvent casting method. The optimum formulation has diaintegration time of 7 seconds and showed 98% drug release within 5 minutes.[66]

Shaik Firoz et al in 2013 prepared and evaluated mucoadhesive buccal films of Pantoprazole using film forming p[olymer like HPMC-K100 and sodium alginate by solvent casting method. The drug release was found to be increased with increase in polymer concentration. Four formulation were prepared by this method out of which formulation 2 and 4 showed optimum drug release.[67]

Rakesh Patel et al in 2013, prepared Levocetirizine dihydrochloride by using PVA and HPMC E15 in combination as film forming polymer and PEG as plasticizer to get rapid release and onset of action in allergic conditions. This film is prepared by using solvent casting method at different concentration of PVA, HPMC E15 and PEG. Formulation with HPMC E15: PVA (3%) and PEG (10%) were found to be optimum for quick disintegration and dissolution [68].

Amit E. Birari et al in 2014, developed and evaluated fast dissolving films of Atenolol by using solvent casting method. These films are prepared by using PVA, glycerine, SLS and HPMC. In this all concentrations were kept constant by varing concentration of HPMC. Formulation 2 showed good results as compared to other formulations with release of 99.47 % at the end of 5 min. [69].

Govind Shankar Pandey et al in 2014, had studied the effect of Maltodextrin and Glycerine on oral thin films of Salbutamol sulfate by using solvent casting method. Mouth dissoving films prepared by 55% w/w Maltodextrin and 19.99% w/w Glycerine was found to be optimum. Prepared film showed good results for bioavailability, disintegration and dissolution with good flexibility and tensile strength [70].

Ramani Gade et al in 2014, designed and developed Pravastatin Sodium fast dissolving films from natural mucilage of Ocimum Bacilicum seeds. Films werw prepared by using glycerine, PEG 400 as plasticizer, aspartame as sweetner, eugenol as flavouring agent, Xylitol, Mannitol and sorbitol as film modifiers. Different formulations were propared but formulation with PVA and Ocimum Bacilum mucilage powder in the ratio of (1.5%: 0.5%) was found to be suitable in the form of fast dissolving oral films. This formulation showed less disintegration time and faster release of drug [71].

Rajesh KAZA et al in 2014, designed fast dissolving oral films of Valsartan by solvent casting method using different grades of polymer HPMC (E5, E50 and K4M). They prepared six formulations and evaluated. The formulation which contains HPMC E5 and valsartan solid dispersion with guargum at weight ratio of 1:4 showed excellent film characteristics [72].

Saneha S. Chauhan et al in 2012, prepared and evaluated Nicitine hydrogen tartarate (NHT) fast dissolving films for smoking cessation. Films were prepared by using 2%, 3% and 4% HPMC by solvent casting method. The type and concentration of polymer used had minimal effect on release of NHT from the film but did not show any effect on disintegration time [73].

Vedhi Desai et al in 2014, formulated and evaluated Olmesartan Medoxomil mouth dissolving film by different polymers using solvent casting method. It can be concluded that solubility of these films was increased by using β- CD. Combination of polymer HPMC E15 and PVA was found to be optimum for final formulation [74].

Qingqing Chen et al in 2014, formulated and evaluated oral thin films containing the German cockroach Blatella germanica (Bla g2) allergen. In this a sublingual immunotherapy (SLIT) formulation of thin film has been developed for the treatment of hypersensitivity to the german cockroach, which could contain about 25 ug/ filmstrip of Bla g2 allergen, nearly 10 fold higher compared to the doses studied for liquid extracts. These films have good mechanical strength, consistent potency and high stability.[75]

Prasanna Kumar Desu et al in 2013, formulated and evaluated fast dissolving films of Rizatriptan using hydroxypropyl methyl cellulose (HPMC cps) by solvent evaporation method. Formulation study shows good mechanical properties, less disintegration time and the drug release from the formulation was found to be good.[76]

Venkata Anupama M et al in 2015, prepared and evaluated oral thin films of Desloratadine, 12 formulations were prepared by casting method using different concentration of polymers such as sodium alginate (1, 1.5, 2 w/v %) and Xanthum (0.4, 0.7 w/v %). As the concentration of polymer increased tensile strength and folding endurance were also improved with more dissolution time. Film formulations were also prepared using varying concentration of Gellan Gum (0.1, 0.3, 0.5 w/v %) and higher concentration of polymer showed good physical and rheological properties. Formulation with 1.5% sodium alginate was found to be optimum.[77]

Vijay Kuchana et al in 2014, prepared and evaluated oral thin films of Buclizine by using solvent casting method. The oral thin films of

buclizine were prepared by using drug and polymer ratio of 1:1 and 1:2. These films were prepared with an aim to have rapid onset of action and increased bioavailability in allergic conditions. During this study PVA and PEG were found to show good physiochemical properties as compared to other polymers.[78]

D. Kapoor et al in 2015, prepared oral thin thin films of Leukotrine receptor antagonist (LTRA) such as Montelukast sodium. Thin films were prepared by using various film forming agents like HPMC, PVP, PEG-400 and glycerol as plasticizer and mannitol as filler and sweetner by solvent casting method. The films prepared by HPMC were clear, transparent and had smooth surface with improved dissolution rate. The in-vitro dissolution time of films prepared by HPMC was in the range of 25.38 to 39.12 sec. [79]

Pradeep Kumar Jangra et al in 2014, developed fast dissolving oral thin films of Thiocolchicoside by using polymers such as HPMC (5cps and 15 cps) by solvent casting method. The formulation containing 300mg HPMC 15 cps was selected as best formulation as its disintegration and dissolution time was less and its released drug content was greater than other formulations. Dose of drug was reduced to from 4 mg to just 1 mg which was also helpful in reducing its adverse effect.[80]

Sayed H Auda et al in 2014, designed and formulated fast dissolving films of Dextromethorphan hydrobromide. In this study, HPMC E15 was used as film forming polymer and crosspovidone (CPV), microcrystalline cellulose (MCC) were used as superdisintegrants which had pronounced impact on the film physiochemical properties as well as drug dissolution rate. The presence of saccharin and menthol may increase patient palatability. [81]

Harsha Kathpalia et al in 2013, developed and evaluated oral films of Tramadol hydrochloride by using polymers like modified pea starch (Lycoat RS-720) and pullulan. Two plasticizers such as propylene glycol and sorbitol were evaluated which showed drug content above 98% and drug release within 15 minutes.[82]

Garima Bansal et al in 2013, developed oral thin films of Rizatriptan Benzoate by ternary complexation approach. In this complexation was done with β-cyclodextrin which masks the bitter taste of drug and HPMC E5 which enhance the stability of drug.[83]

Kamalesh Upreti et al in 2014, formulated and evaluated mouth dissolving film of Paracetamol by solvent casting method. These films were prepared by using varying concentration of polymer (HPMC) and plasticizer (glycerol). In-vitro dissolution studies were carried out in distilled water and simulated salivary fluid (Ph 6.8) and strips disintegrated completely within 4 minutes. The optimized formulation showed 92% drug release within 30 minutes.[87]

Evaluation parameters of fast dissolving oral films

Thickness

Thickness is essential to ascertain uniformity in the thickness of the film which is directly related to the dose accuracy in the film. It can be measured with the help of micrometer screw gauge or calibrated digital Vernier Calipers or dial gauge tester at different 5 locations of the film. It should be between the range of 5-200 micrometer [31, 85].

Tack test

Tack is the tenacity with which strip adheres to an accessory or a piece of paper that has been pressed into contact with the strip. There are eight stages of film drying process, they are: set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through, dry-to-recoat and dry print- free. Instruments are also available for this study [86].

Tensile Strength

It is the maximum stress applied to a point at which strip specimen break.

It is calculated by following formula: [32]

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

Tear Resistance

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically a very low rate of loading 51 mm (2 in)/min is employed and is designed to measure the force required to tear the specimen, is recorded as the tear resistance value in Newton's (pounds- force) [87] .

Folding Endurance Test

It is determined by repeated folding of the film at the same place till the film breaks. The number of times the film folded without breaking is computed as the folding endurance value [88, 89]

Moisture Uptake

This test was carried out to check the physical stability and integrety of the films at high humid conditions. Film was placed in the desiccator containing standard solution of aluminiun chloride, keeping the humidity inside the desiccator at 79.55% RH. After 3 days films were taken and weighed the percentage moisture absorption of the films was found [89].

$$\%\ \text{Moisture content} = ((\text{Initial weight} - \text{Final weight}) / (\text{Initial weight}) \times 100)$$

Percentage Elongation

when a stress is applied, a strip sample streches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. It increases as the plasticizer content increases [9].

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

In-Vitro Dissolution Studies

it is carried out in simulated saliva solution of 900 ml of pH 6.4 phosphate buffer using USP paddle apparatus at 37±0.5°C. Samples are withdrawn at regular intervals and analyzed by UV-Visible spectrophotometer. Many times difficulty can be seen in dissolution test due to tendency of a film to float on a surface of dissolution medium when the paddle apparatus is employed [3, 4, 90].

Disintegration test

Disintegration time will vary depending on the formulation but typically the disintegration time varies from 5-30 sec. Disintegration of films requires USP disintegration apparatus. Although no official guidance is available for oral fast disintegrating oral films. Both disintegration and dissolution test were performed in triplicate manner [4, 91, 92].

Stability Testing

Accelerated stability study is done under common stress conditions like temperature, humidity and light. A piece of film was stored in an aluminium package at 25°C with 50-60% humidity or at 40°C at 75% humidity for 4-24 weeks .then the content of drug was determined [9, 39, 93, 94].

Content uniformity

Content uniformity is determined by estimating the API content in an individual strip. Limit of content is 85-115% [9].

Elastic modulus

It indicates the measurement of stiffness of the film. It is also known as young's modulus. Higher the young's modulus with small elongation, hard and brittle will be the strip. It is represented as the [95]:

$$\text{Young's modulus} = \frac{\text{Force at corresponding strain}}{\text{cross sectional area}} \times \frac{1}{\text{Corresponding strain}}$$

Surface pH of film

This can be determined by placing the film on the surface of 1.5% w/v agar gel then again placed on Ph paper whose pH range is 1-11. The change in colour of pH paper was observed [96, 97].

Swelling properties

Swelling property is determined by weighing each film sample and placing it in pre-weighed stainless steel wire mesh. The mesh containing film is submerged into 15 ml medium in a plastic container. Increase in the weight of film is determined at different time interval until a constant weight is observed. The degree of swelling was calculated by using following equation [4, 96, 97]:

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

Where: wt= Weight of film at time t
wo= Weight of film at time zero

Transparency

The transparency of the film can be determined by using a simple UV spectrophotometer. Cut the film sample into rectangles and placed on the internal side of the spectrophotometer of the cell. The transmittance of the film is determined at 600 nm [4].

$$\text{Transparency} = (\log T600)/b = -€c$$

Where: T_{600}= Transmittance at 600 nm
b= Film thickness (mm)
c= Concentration

Contact angle

Contact is measured by Goniometer at room temperature. Place a drop of distilled water on the surface of dry film. Images of water droplet were recorded within 10 sec. of deposition by means of digital camera. The contact angle was measured on both side of drop and average is taken [11].

Drug content

The film of area 2 2 was cut and dissolved in distilled water. Then solvent ethanol and dichloromethane were added to solublize the polymer and remaining volume is made with distilled water upto 100 ml in 100 ml volumetric flask. Then 1ml was withdrawn from the solution and diluted to 10 ml. The absorbance was observed at relevant wavelength and concentration was calculated. By correcting dilution factor, the drug content was calculated [88].

Table 9: Marketed formulations of oral thin films

S.NO.	Product	Manufacturer
1	Triaminic	Novartis Consumer Health [98]
2	Zuplenz	MonoSol Rx [99]
3	Suboxone	MonoSol Rx
4	Ondissolve	Labtec Pharma [100]
5	Setofilm	Labtec Pharma
6	Sudafed	Pfizer [101]
7	Caffeine	Hughes Medical Cooporation [102]
8	Loratidine strips	Hughes Medical Cooporation [103]
9	Chloaseptic	Prestige [104]
10	Suppress	InnoZen [105]

Packaging of fast dissolving oral films

There are number of packaging varities available for oral thin films, it should be selected adequately to preserve the integrity of the product. Criteria that must be taken into consideration during packaging includes need for unit dose packaging, barcode labeling, the content in instructions for use, child-resistant seals and senior friendly packaging. Material selected for packaging must have following characteristics: [106, 48]

They must be non-toxic
They must protect the preparation from environmental conditions
They must be FDA approved
They must be non-reactive with the product
They must not impart to the product taste and odours
They must meet applicable temper resistant requirement
Various type of packaging

Foil, paper and plastic pouches

It provides packaging which is temper-resistant
It provides high degree of environmental protection
During product filling operation a flexible pouch is formed by either vertical or horizontal forming, filling and sealing equipment [107]

Single pouch or aluminum pouch

Soluble drug delivery pouch is a peelable pouch for "quick dissolve" soluble films with high barrier properties
Using a 2 structure combination allows for one side to be clear and other to use a cost effective foil lamination which has zero transmission of both gas and moisture
The single dose pouch provides both product and dosage protection [107]

Blister card with multiple units

Blister container consists of two components: first, the blister (plastic), which is the formed cavity which holds the product and second, the lid stock (aluminium), which is the material that seals the blister [108].
The blister package is formed by heat softening by following method:
A sheet of thermoplastic resin is softened by heating
Softened sheet is vaccum dried into a countered mold
Sheet is released from the mold after cooling
Proceed to the packing station of filling machine
Previously formed semi rigid blister is filled with the product and lidded with the heat sealable backing material

Conclusion

From above, this can be concluded that fast dissolving oral films have proved to be an innovative drug delivery system for all groups of population or patients with problem of swallowing. Fast dissolving oral films have proved to be beneficial whenever rapid onset of action is required like incase of asthmatic attack, cardiac heart failure and in epilepsy. Oral thin films are used as a good tool to increase the life cycle of the existing product by getting patent of same product as fast dissolving oral films. So this technology is growing in fast pace challenging most of the pharmaceutical companies to develop oral films for a wide range of active pharmaceutical ingredients. A lot of research work is going on and will be started in near future on fast dissolving oral film. However, for future growth point of view the fast dissolving oral films sector is well-positioned. It seems that the value of the overall oral thin film market will grow significantly.

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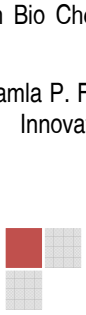

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