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RECENT ADVANCES IN ORAL THIN FILM DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT: Several fast-dissolving drug delivery systems have been designed to address issues like accurate dosing in liquid dosage formulation (suspension, emulation, syrup *etc*.) and swelling problems in solid dosage form (capsule, Tablet *etc*.). To fill these gaps fast-dissolving drug delivery system have been designed to address these issues. Biggest advantage of having Oral thin Film is, it can be taken without water, Easy to tackle and carry. Oral thin film formulates with various polymers, plasticizers, active pharmaceutical ingredients, sweetening agents, flavoring agents, coloring agents, stabilizing saliva enhancing agents and thickening agents. The method of preparation for oral thin film were reported are solvent casting, Semisolid casting, Hot melt extrusion, Solid dispersion extrusion and rolling. The current evaluation gives an account of different formulations methods of preparation and quality control of the fast-dissolving oral thin film. Stable drug-type tablets and capsules are inconvenient to administered for many pediatric and geriatric patients.

INTRODUCTION: Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms. These systems consist of solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the need of water [1]. Fast dissolving drug delivery systems include orally disintegrating tablets (ODTs) and oral thin films (OTFs). The Centre for Drug Evaluation and Research (CDER) defines ODTs as, "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [2].

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USFDA defines OTFs as, "a thin, flexible, non-friable polymeric film strip containing one or more dispersed active pharmaceutical ingredients which is intended to be placed on the tongue for rapid disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract" [3]. OTFs are coming into their own as mainstream pharmaceutical products. The first approved prescription OTF was Zuplenz (Ondansetron hydrochloride- 4 mg, 8 mg) which was approved in 2010.

The second approval followed quickly Suboxone (Buprenorphine and Naloxone). Statistics have shown that four out of five patients prefer orally disintegrating dosage forms over conventional solid oral dosages [4]. These factors, coupled with convenience and compliance advantages, have been (and will continue to) pave the way for ODT and OTF drug product growth.

This review highlights the various types of polymers, the different types of manufacturing techniques and evaluation tests for the oral films.

Need for Preparing Fast Dissolving Oral Thin Films: Pediatric, geriatric, bedridden, emetic patients and those with Central Nervous System disorders, have difficulty in swallowing or chewing solid dosage forms. Many of these patients are non-compliant in administering solid dosage forms due to fear of choking. Even in the case of ODTs, fear of choking is associated, which can be hazardous. Fast dissolving oral thin film drug delivery system is a better alternative to ODTs. OTFs when placed on the tip or the floor of the tongue, instantly wet by saliva. As a result, OTFs rapidly hydrate and then disintegrate and/or dissolve to release the medication for local and/or systemic absorption. ODTs are friable and may break during transport and handling. Thus, fast dissolving oral thin film drug delivery systems are being developed.

Advantages of OTF:

1. Ease of administration for mentally ill and non-compliant patients.
2. Useful in situations where rapid onset of action is required such as in motion sickness, allergic attack, coughing or asthma.
3. Has wide range of applications in pharmaceuticals, Rx Prescriptions and OTC medications for treating pain, cough/cold, gastro-esophageal reflux disease, erectile dysfunction, sleep disorders, dietary supplements, etc [4].
4. No water is required for the administration and hence suitable during travelling.
5. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, enhancing bioavailability of drugs.
6. May offer improved bioavailability for poorly water-soluble drugs by offering large surface area as it disintegrates and dissolves rapidly.
7. Leaves minimal or no residue in the mouth after administration.
8. Has ability to provide advantages of liquid medication in the form of solid preparation.
9. Adaptable to existing processing and packaging machinery.
10. Cost-effective.
11. Gives accurate dosing as compared to liquids.
12. Provides good chemical stability.
13. Free of need of measuring, which is an essential drawback in liquids [5].
14. Offers market expansion and product differentiation
15. It can be developed and launched within 12-16 months, thus provides improved product development life-cycle time [4].

Disadvantages of OTF:

1. Dose uniformity is difficult to maintain
2. Only those active pharmaceutical ingredients having small dose can be incorporated [6]. Research has proven that concentration level of active pharmaceutical ingredient (API) can be improved up to 50% w/w. Novartis Consumer Health's Gas-X thin strip has 62.5 mg of Simethicone per strip [4].
3. Require expensive packaging.
4. Since OTFs dissolve quickly, dose termination is impossible.
5. OTFs are not official in any pharmacopoeia.

Formulation of Fast Dissolving Oral Thin Films: Formulation includes consideration regarding mechanical properties, taste masking, fast dissolving, physical appearance, mouth feel. Fast dissolving oral thin films are generally with an area of 5-20 cm^2. APIs can be incorporated up to 30 mg [7]. From the regulatory point of view, all the excipients used should be generally regarded as safe (GRAS) listed and should be used as per Inactive Ingredients Limit (IIG limit). Various components of fast dissolving oral thin films are shown in **Table 1.**

TABLE 1: COMPOSITION OF FAST DISSOLVING ORAL THIN FILMS [8]

Components	% w/w
Active pharmaceutical ingredient	5-30
Film forming polymers	Upto45
Plasticizers	0-20
Surfactants	q. s.
Sweetening agents	3-6
Saliva stimulating agents	2-6
Super disintegrants	up to 8
Coloring agents	up to 1
Flavoring agents	up to 10

Active Pharmaceutical Ingredients (APIs): Since, the size of the thin films has to be small enough to be conveniently placed on the tongue, those active pharmaceutical ingredients with high dose are not suitable candidates for incorporation into fast dissolving oral thin films [9].

Ideal Characteristics of APIs to be Incorporated into Fast Dissolving Oral Thin Films:

1. Low dose
2. Palatability
3. Small molecular weight
4. Solubility and stability in saliva

Some of the suitable candidates for incorporation into thin film formulation are given in **Table 2.**

TABLE 2: SUITABLE CANDIDATESFOR INCORPORATION INTO THIN FILM FORMULATION

Active pharmaceutical ingredients	Category	Dose (mg)
Levocetirizine, Loratadine	Anti-histaminic	5, 10, 10
Ketorolac, Indomethacin, Valdecoxib, Piroxicam	NSAIDs	10, 25, 10, 20, 10, 20
Zolmitriptan, Sumatriptan succinate	Anti-migraine	2.5, 5, 35, 70
Mirtazapine	Anti-depressant	15, 30, 45
Buspirone	Anxiolytic	5, 15, 30
Carvedilol	β-blocker	3.125, 6.25, 12.5, 25
Glipizide	Anti-diabetic	2.5, 5
Galantamine, Donepezil	Anti-Alzheimer	4, 8, 12, 5, 10
Nitroglycerine derivatives	Vasodilator	0.3, 0.6
Oxycodone	Opioid analgesic	2.5-10
Famotidine	Antacid	10
Ketoprofen	Anti-inflammatory	12.5, 25
Dextromethorphan	Anti-tussive	15, 30
Ondansetron	Anti-emetic	8-24
Loperamide	Anti-diarrheal	2
Buprenorphine-Naloxone	Opioid Dependence	1.4

Water soluble APIs exist in the dissolved state or as solid solution and there is no problem of uniformity of distribution. But water insoluble APIs have to be homogenously distributed so as to have an acceptable drug content uniformity. Water insoluble APIs can also be added as milled, micronized or in the form of nanocrystals or microcapsules [10] in order to maintain smooth texture of the film and also for fast dissolution.

Formulated Chlorpheniramine maleate microparticles by encapsulating Chlorpheniramine maleate into Eudragit EPO by spray drying of water-in-oil emulsion method. The optimized microparticles were incorporated into OTF with satisfactory weight and drug content uniformity and acceptable physical strength. OTFs disintegrated immediately (in less than 40 seconds) in simulated saliva solutions [11].

Formulated OTFs of hydroxypropyl methyl cellulose (HPMC) by incorporating API in the form of nanosuspension. They transformed nano-suspension produced from wet stirred media milling (WSMM) into polymer films containing drug loaded nanoparticles by mixing with HPMC E15 LV solution containing glycerin followed by film casting and drying [12].

As the thin film formulation is to be placed on tongue, those drugs having bitter and unpleasant taste may cause vomiting sensation and may be inacceptable by the patient. Hence, various taste masking technologies for the drug like coating with polymers, inclusion complexation with cyclodextrins, microencapsulation, complexation etcwith ion-exchange resinsare being practiced which are asshown in **Table 3.**

TABLE 3: TASTE MASKING TECHNOLOGIES FOR BITTER APIs

Active pharmaceutical ingredient	Taste masking technology	Material used
Famotidine [13], Terfenadine [14]	Coating with polymers	Hydroxypropyl methyl cellulose, Hydroxyl propyl cellulose, Sodium alginate, Carrageenan
Ibuprofen [15]	Inclusion complexation with β-cyclodextrins	Hydroxypropyl-β-cyclodextrin
Sulphathiazole [16]	Solid dispersion systems	Povidone
Beclamide [17]	Microencapsulation	Gelatin
Pseudoephedrine [18]	Ion-exchange resins	Amberlite CG 50
Chloroquine phosphate [19]	Liposomes	Egg phosphatidyl choline
Chloramphenicol, Clindamycin Triamcinolone [16]	Prodrugs	Palmitate ester, Diacetate ester

Film Forming Polymers: Since, the film formulation rapidly disintegrates and dissolves in oral cavity, the film forming polymers used must be water soluble. The polymers can be used alone or in combination with others in order to obtain the desired film which should be tough enough so that there won't be any damage while handling or during transportation and at the same time showing fast dissolution in the mouth. The robustness of the film depends on the type and amount of polymer used in the formulation. The disintegration time of the polymers is increased by increasing the molecular weight of polymer film bases [20]. Since, polymers are the major components of the film formulation along with the APIs, their proportion related to each other is governed by 2 factors:

A. Minimum % w/w concentration of polymer required to form matrix which incorporates APIs and other excipients with desirable mechanical and viscoelastic properties.

B. % w/v concentration of polymer in solution to be casted as film which is governed by the desired viscosity. Viscosity should be optimum enough to prevent suspended solids from settling and to form a smooth spreadable film [21].

Ideal Properties of Polymers:

1. Non-toxic

2. Non-irritant

3. Bland

4. Good mouth feel

5. Should be stable for a long period

6. Should not alter properties of the active pharmaceutical ingredient or other excipients of the formulation

7. Inexpensive

8. Should have good wettability and spread ability

9. Should not retard the disintegration time of the film

10. Should have optimum peel strength and tensile strength

Natural Polymers:

Gum Polysaccharides: Gum polysaccharides like gum Arabic, κ-carrageenan and sodium alginate are some of the potential polymers for film formation. They can be used in combination with others so as to provide primary film structure and rapid dissolving characteristics. Some examples are shown in Table 4.

Advantages:

- Addition of these can improve dissolution of films in mouth
- Reduces tensile strength only to a minimal extent

TABLE 4: FILM COMPOSITION AND THE RESULTING DISSOLUTION TIME [22]

Film composition	Dissolution time (Seconds)
Gum Arabic (1.25%) along with sodium alginate (2.5%) and low viscosity carboxy methyl cellulose (1.25%) and water	20
κ-carrageenan (1.25%) along with sodium alginate (2.5%) and low viscosity carboxy methyl cellulose (1.25%) and water	28
Polydextrose (1.25%) along with sodium alginate (2.5%) and low viscosity carboxy methyl cellulose (1.25%) and water	12.60

Gelatin: Gelatin consists of a mixture of purified protein fractions obtained either by partial acid hydrolysis which is called as type A gelatin or by partial alkaline hydrolysis which is called as type B gelatin of animal collagen. Gelatin is prepared by the thermal denaturation of collagen isolated from animal skin, bones and fish skins [23]. It is readily soluble in water above 40ºC, and it forms viscous solutions of randomly coiled polypeptide chains. Mammalian gelatins have better physical properties and thermostability than most of the fish gelatins due to their higher amino acid content. The properties and film forming ability of gelatin is directly related to the molecular weight of gelatin, i.e., the higher the average molecular weight, the better the quality of the film. The molecular weight distribution depends mainly on the degree of cross-linking of collagen fibers and the extraction procedure used. Gelatin films could be formed from 20-30% gelatin, 10-30% plasticizer (glycerin or sorbitol) and 40-70% water followed by drying the gelatin gel [24].

Advantages of Gelatin Films:

a) Dissolve rapidly

b) Films are excellent carriers for flavors

c) Films produce a smooth mouth feel [25]

- Formulated Montelukast sodium fast dissolving films using gelatin as a film base (3.54% w/w). It was observed that films had desired tensile strength and optimum *in-vitro* dissolution time [26].

Pullulan: Pullulan is a biopolymer. It is water soluble, neutral linear polysaccharide consisting of α (1→6) linked malt triose residues. It is a fungal exopolysaccharide produced from starch by black yeast *Aure basidiumpullulan* [27]. Bender and Wallenses discovered the enzyme pullulans, which specifically hydrolyzes α (1→6) linkage in pullulan and converts the polysaccharide to malt triose. Catley and co-workers established the occurrence of a minor percentage of randomly distributed maltodextrins subunits in pullulan [28]. The regular occurrence of α (1→6) linkage in pullulan interrupts a linear amylase chain. This unique pattern of linkage is responsible for the structural flexibility of pullulan, resulting in distinct film forming characteristics [29]. Pullulan PI-20 grade is the deionized form of pullulan having an average molecular weight of 2,00,000 Daltons and possess excellent film forming properties. Pullulan is used in the range 0.3-15% w/w [30].

Advantages of Pullulan:

a) It is non-hygroscopic

b) It is impermeable to oxygen

The impermeability of pullulan films to oxygen is suitable for protection of readily oxidized fats and vitamins in food. Pullulan films have a 300 times stronger oxygen barrier than HPMC films and 9 times stronger oxygen barrier than gelatin films of the same thickness [31].

c) No branching in structure in contrast to gum arabic, forming much stronger films [32]

d) It is easily soluble in cold and hot water to make clear and viscous solution

e) It also has high adhesion and film forming abilities

f) It is a nonionic polysaccharide and is blood compatible, biodegradable

g) It is non-toxic, non-immunogenic, non-mutagenic and non-carcinogenic [33]

h) Pullulan films are thermally stable and possess anti-static and elastic properties

i) Pullulan films can be developed into compression molding

j) Pullulan films are highly water soluble, colorless, tasteless, odorless, transparent and flexible

- Formulated rapidly dissolving films of Cetirizine hydrochloride using pullulan (15% w/w) as a film forming agent. They found that the amount of plasticizer was critical for film formation and separation properties. Acceptable mechanical properties and *in-vitro* disintegration time were obtained [34].

- Orally disintegrating film formulation of Nicotine is shown in **Table 5.**

TABLE 5: NICOTINE ORALLY DISINTEGRATING FILM

Ingredients	Amount per film (mg)
Nicotine base	1.00
Alginic acid	0.50
Pullulan	29.48
Purified water	0.0038
Sucralose	0.48
Solutol H15	1.00
Sucrose fatty acid esters D-1811	1.00
Alcohol	0.00
Glycerin	3.20
Triethyl citrate	2.00
Tween 80	0.60
Span 80	0.10
Peppermint oil	0.40
Menthol	0.20
FD & C Yellow #6	0.04
Total	31.40

In the above formulation, hydroalchoholic vehicle was used [35].

Starch: Starch is the major carbohydrate reserve in plant tubers and seed endosperm where it is found as granules. Each granule contains millions of amylopectin molecules accompanied by smaller amylase molecules. Amylose is responsible for the film forming capacity of starch [36].

Advantages of Starch

a) Starch films are biodegradable

b) Starch films are transparent or translucent

c) Starch films are flavorless, tasteless and colorless [37].

Disadvantages of Starch:

a) Starch films have poor mechanical strength

b) Film forming conditions have an effect on crystallinity of the starch films and their properties.

Films of high-amylose corn starch or potato starch were more stable during aging, lost little of their elongation and had slight or no increase in tensile strength [38]. Films from Cassava starch had good flexibility and low water permeability, indicating the potential application as edible film former [39].

Modified starch, due to its low cost, is being widely used in combination with pullulan.

Lycoat: Lycoat is a novel granular hydroxypropyl starch polymer obtained from pea starch that has been designed especially for fast dissolving oral thin films. It is manufactured by Roquette Pharma.

Advantages of Lycoat:

a) Lycoat disperses easily in cold water without formation of lumps

b) It can be used alone as a film forming polymer to formulate fast dissolving oral thin films with excellent functionality without the need of additional film forming agent [40]

c) It is neutral in taste

d) It forms films without the use of organic solvents

e) APIs can be loaded in crystalline form, or they can be solubilized in an organic solvent

- Formulated oral disintegrating films of Benzocaine using Lycoat RS 720 as a film forming polymer. They concluded that Lycoat RS 720 alone was capable of producing oral disintegrating films. It also offered dose homogeneity and fast dissolution [41].

- Formulated Tianeptine sodium or dispersible films using Lycoat NG 73 as a film forming polymer. They concluded that the films made up of Lycoat NG 73 showed the highest dissolution rate, suitable *in-vitro* disintegration time and satisfactory physical-mechanical properties as compared to those made up of other polymers [42].

Maltodextrin: Maltodextrin is a non- sweet nutritive saccharide polymer. It is produced by partial hydrolysis of starch. Maltodextrin consists of D-glucose units connected in chains of variable length. The glucose units are primarily linked with α (1→4) glycosidic bond. Maltodextrin is typically composed of a mixture of chains that vary from 3-19 glucose units [43]. Maltodextrins are classified by DE (dextrose equivalent) and have DE between 3-20. Higher the DE value, shorter the glucose chains, higher the sweetness and higher the solubility [21]. Maltodextrin is used in the range of 2-10% w/w [44].

- Formulated Nicotine fast dissolving films made of maltodextrin. They found that on decreasing the DE value of maltodextrin, the tenacity of the film improved [45].

Synthetic Polymers:

Hydroxypropyl Methyl Cellulose (HPMC): HPMC or Hypromellose is partly O-methylated and O-(2-hydroxypropylated) cellulose [46]. Depending upon the viscosity grades, concentrations of 2-20% w/w are used for film forming solutions [47]. Lower grades of HPMC like HPMC E3, HPMC E5and HPMC E15 are particularly used for film formation because of their low viscosity [48]. Lower grades are used with aqueous solvent [41]. Additives are incorporated to improve specific properties of films. Several studies have been carried out to investigate the influence of additives on physical-chemical properties of HPMC films. Lipids such as waxes, triglycerides (tristearin), fatty acids (stearic acid, palmitic acid) result in decreased water affinity and moisture transfer due to their high hydrophobic properties [26].

Advantages of HPMC:

a) It has good film forming properties and excellent acceptability

b) HPMC forms transparent, tough and flexible films in aqueous solutions [46]

- Formulated Prochlorperazine oral disintegrating film using HPMC (7.4% w/w) in combination with low substituted HPC (1.3% w/w). Films showed excellent stability and desired dissolution profile [48].

- Prepared fast dissolving oral thin films containing Dexamethasone using HPMC (7.4% w/w) in combination with low substituted HPC (1.3% w/w). 90% of Dexamethasone was found to be dissolved within 5 minutes [49].

- Formulated and evaluated flash release oral films of Metoclopramide hydrochloride. The formulation released 99.40% of drug within 30 seconds [50].

- Formulated and evaluated mouth dissolving films of Domperidone. The film was prepared by solvent casting technique utilizing HPMC E15 as film forming agent and PEG 400 as plasticizer. The film containing HPMC E15 (500 mg) showed greater dissolution (more than 75% within 15 minutes), satisfactory *in-vitro* disintegration time (45 seconds) and suitable physical-mechanical properties [51].

- Orally disintegrating film formulation of Diclofenac is shown in **Table 6.**

TABLE 6: DICLOFENAC ORALLY DISINTEGRATING FILM [52]

Ingredients	Amount per film (mg)
Diclofenac free acid	11.08
Methocel E5 (HPMC E5)	3.20
Methocel E50 (HPMC E50)	4.80
Glycerol	0.70
α-Tocopherol	0.0064
Spearmint flavor 501495 T	0.70
Masking flavor 501483 T	2.75
Sodium chloride	0.75
Levomenthol	1.50
Acesulfame-K	0.75
Water	37.00
Total	63.23

Polyvinyl Alcohol (PVA): Poly (vinyl alcohol) (PVA), a polyhydroxy polymer, is the synthetic, water-soluble polymer which is produced commercially by the hydrolysis of poly (vinyl acetate) (PVAc). To improve its deformability, PVA is usually plasticized by low molecular compounds mostly containing polar groups, which are associated with hydroxyl groups of PVA chain (with or without water assistance) developing hydrogen bonds.

Advantages of PVA:

1. PVA has excellent film forming and emulsifying properties

2. It is resistant to oil and grease

3. PVA is odorless and nontoxic

4. PVA has high oxygen and aroma barrier properties

5. PVA has high enough tensile strength and satisfactory flexibility

6. High biodegradability [53]

- Formulated mouth dissolving films containing Rofecoxib where, PVA (4%w/w) was used to as film forming polymer. They found that, with increasing the concentration of PVA, mechanicalproperties of the film increased elasticity of the polymer and release of the drug occurred within 1 minute [54].

Ondansetron Rapid Film formulation is shown in **Table 7.**

TABLE 7: ONDANSETRON RAPID FILM FORMULATION

Ingredients	Amount per film (mg)
Ondansetron base	8.00
Mowiol (Poly vinyl alcohol)	2211.00
Polyethylene glycol	6.00
Glycerol anhydrous	2.00
Rice starch	10.00
Acesulfame-K	0.20
Titanium dioxide	0.30
Menthol	1.00
Polysorbate	1.00
Total	50.50

Dissolution profiles of Ondansetron film coated tablet, oral dissolving tablet (Zofran 8 mg and 4 mg) and Rapid Film (8 mg and 4 mg) were compared.

Dissolution studies were carried out in USP apparatus Type I (paddle), using 900 ml of 0.1 N HCl buffered water at pH 1.0 at 100 rpm and 37^{o}C. The results of the dissolution study can be summarized as follows:

- Ondansetron film coated tablet showed 0.8% drug release in one minute while at the time point of 10 minutes; it showed 103.3% drug release.

- Oral dissolving tablet (8 mg) showed 100.30% drug release in one minute while Rapid Film (8 mg) showed 97.10% drug release in one minute. At the time point of 10 minutes, both the formulations showed 100.80% drug release.

- Oral dissolving tablet (4 mg) showed 102.30% drug release in one minute while Rapid Film (4 mg) showed 71.80% drug release in one minute. At the time point of 10 minutes, Oral dissolving tablet (4 mg) showed 101.80% drug release in one minute while Rapid Film (4 mg) showed 105.20% drug release.

From the above data, it can be concluded that though the drug release from oral dissolving tablet is faster than Rapid Film initially, at the time point of 10 minutes, drug release from both the formulations is comparable and both are better formulations as compared to Ondansetron film coated tablet [55].

Polyethylene Oxide (PEO): Polyethylene oxide is a synthetic polyether. It is available in a wide range of molecular weights. Usually 3-5% w/w solution is used for film formation [56].

Advantages of PEO:

a) PEO has a high melting point

b) It has good structural integrity

c) It has low glass transition temperature

d) It has low toxicity and biocompatibility

e) It is highly hydrophilic with a good film forming capacity [21].

- Sumitha *et al.* formulated rapid disintegrating films of Ondansetron using PEO N10 and HPMC E15. It was observed that the incorporation of PEO helped in faster disintegration and provided good elegance to the film [57].

- Representative formulation of Donepezil hydrochloride orally disintegrating film is shown in **Table 8.**

TABLE 8: REPRESENTATIVE FORMULATION OF DONEPEZIL HYDROCHLORIDE ORALLY DISINTEGRATING FILM [55]

Ingredients	Amount per film (mg)
Donepezil hydrochloride	10.00
Polyethyleneoxide	50.00
Tween 80	1.00
Glycerol anhydrous	12.00
Citric acid anhydrous	1.00
Titanium dioxide	0.50
Acesulfame-K	1.50
Anise flavor	1.65
Peppermint flavor	3.84
Total	81.49

Polyvinyl Pyrrolidone (PVP): Soluble polyvinyl pyrrolidoneis synthesized by radical polymerization of N-vinyl pyrrolidone in 2-propanol. The soluble

PVP products of pharmaceutical quality are designated as Povidone in the USP. Soluble PVP products are marketed under bran name Kollidon®. PVP range comprises of products of different K-values. The K-value is associated with the mean molecular weight. It is included as part of the trade name and is calculated from the relative viscosity in water. Different grades of PVP and their mean molecular weight is shown in **Table 9.**

TABLE 9: DIFFERENT GRADES OF PVP AND THEIR MEAN MOLECULAR WEIGHT

Grades of PVP	Mean molecular weight
Povidone K 12	2000-3000
Povidone K 25	28000-34000
Povidone K 30	44000-54000
Povidone K 90	1000000-1500000

Advantages of PVP:

a) PVP is readily soluble in water and most other solvents

b) PVP has a very good film forming capacity

c) It has the ability to form a water-soluble complex with insoluble APIs which can improve their release rate and solubility

d) It is temperature resistant, pH-stable and colorless [58]

e) Films are clear, glossy and hard [59].

- Formulated PVP films containing Indomathacin to evaluate the potential of isothermal calorimetry to monitor and characterize crystallization in drug-loaded fast dissolving oral films [60].

Formulated mouth dissolving film of Carbamazepine using PVP K30 as film forming polymer. They found that crystallization of Carbamazepine occurred due to hygroscopicity of PVP [61].

Ali *et al*. formulated Diphenhydramine and Ibuprofen strips with Kolli don K-90. Diphenhydramine films showed a disintegration time of 50 seconds while that of Ibuprofens trips was 5-6 times higher [62].

Major manufacturing companies of polymers are shown in **Table 10.**

TABLE 10: POLYMERS AND THEIR MANUFACTURERS

Polymers	Manufacturer
Gelatin	GELITA, Rousselot, PB Leiner, Weishardt
Pullulan	Hayashibara, Tsukioka
Lycoat	Roquette
Maltodextrin	Cargill
Hydroxypropyl methyl cellulose	Dow
Polyvinyl alcohol	Sigma-Adrich
Polyethylene oxide	Sigma-Adrich
Polyvinylpyrrolidone (Kollidon)	BASF

Plasticizers: Plasticizers aid in improving the flexibility and reduce the brittleness of the film by reducing the glass transition temperature of the polymer. Plasticizers also improve the tensile strength and reduce brittleness. The plasticizer should be compatible with the polymer and the solvent used. Plasticizers also enhance the tensile strength of the polymers [63, 64]. Glycerol, propyleneglycol, low molecular weight polyethylene glycols, citrate derivatives such as tributyl citrate, triethyl citrate, triacetin and castor oil are some of the commonly used plasticizers [65-71]. Inappropriate or extensive use of plasticizer can cause film cracking, splitting and peeling of the film. Some plasticizers also affect the absorption rate of drug [54]. The plasticizer should impart permanent flexibility to the film**.** Plasticization takes place by two mechanisms: internal plasticization which involves chemical interaction of molecular groups of the polymer itself and external plasticization where, a physically active plasticizer is externally added. External plasticization does not involve chemical interactions in the product and hence, it is the preferred mechanism of plasticization [71]. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like polyethylene glycol, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid [72]. Glycerol is a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both hydroxypropyl methyl cellulose as well as polyvinyl alcohol films [73].

Plasticizers used in different thin film formulations are shown in **Table 11.**

TABLE 11: PLASTICIZERS AND THEIR CONCENTRATIONS USED IN DIFFERENT THIN FILM FORMULATIONS

Drug	Polymer	Plasticizer	Concentration (% w/w)
Rofecoxib [54], Nicotine [45]	HPMC, PVA, Maltodextrin	Glycerin	15, 14-15
Tianeptine sodium [42]	Lycoat NG 73, PVA, HPMC	Propylene glycol	7-8
Cetirizine hydrochloride [34], Rizatriptan benzoate [74]	Pullulan, HPMC E5 LV	Polyethylene glycol 400	25, 7-8
Ambroxol hydrochloride [75]	HPMC 5 cps	Polyethylene glycol 4000	20-25

Surfactants: Surfactants act as wetting or dispersing agents so that the film gets dissolved within seconds and releases API quickly. Sodium lauryl sulfate and polysorbates are the commonly used surfactants. One of the most important surfactants is Poloxamer 407 which can be used as wetting, solubilizing and dispersing agent [7]. Formulated and evaluated fast dissolving films for the delivery of Triclosan to the oral cavity. Film forming agents like HPMC, xanthan gum, xylitol was used. The potential of Poloxamer 407 and hydroxypropyl-β-cyclodextrin (HPβCD) to improve the solubility of Triclosan was investigated. The films were evaluated for *in-vitro* dissolution profile and *in-vitro* antimicrobial activity. Films containing Poloxamer 407 exhibited better *in-vitro* dissolution profile and *in-vitro* antimicrobial activity as compared to the films containing HP-β-CD. Also, the effect of incorporation of eugenol on the *in-vivo* performance of Poloxamer 407 containing films was evaluated in human volunteers. Films containing eugenols improved the acceptability of films with respect to taste masking and mouth freshening without compromising the *in-vivo* dissolution time [76].

Sweetening agents: Natural as well as artificial sweeteners are used to improve the palatability of the fast-dissolving oral thin films. Sweeteners include sucrose, dextrose, fructose, glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus, it is widely used. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth feel and cooling sensation. Polyhydric alcohols are also less carcinogenic and do not have bitter after taste. The sweetness imparting property of most of the polyols is less than half of that of sucrose except xylitol and maltitol (both have sweetness similar to sucrose). The use of natural sugars in such preparations needs to be restricted in the case of diabetic patients [77, 78]. Due to this reason, artificial sweeteners are more popular in food and pharmaceutical preparations. Saccharin and aspartame are the first generation of artificial sweeteners. These are found to be carcinogenic and are banned in some countries. Research is being carried out in order to prove find out the extent of carcinogenicity. Acesulfame-K, sucralose, alitame and neotameare are the second-generation artificial sweeteners. Acesulfame-K and sucralose have more than 200- and 600-time sweetness respectively. Neotame and alitame have more than 2000- and 8000-time sweetening power as compared to sucrose. Robainais the herbal sweetener which is derived from plant Stevia rebaudiana. It has more than 200–300-time sweetness [79].

The disadvantage of the artificial sweeteners is that they have after taste. This disadvantage of artificial sweeteners can be reduced by mixing or blending natural and artificial sweeteners. The blending of sweeteners may lead to synergism and improve the taste of the formulations. In formulation of 8 mg film composition incorporating Ondansetron, sucralose (7% w/w) was used along with Magna sweet® (0.5% w/w) [80]. Magna sweet® is monoammonium-glycyrrhizinate and is available from Mafco, New Jersey. Magna sweet® has a tendency to build in intensity over time. It produces sweetness that extends over the time till the product is being experienced in the mouth [81]. Different roles of Magna sweet® and concentration for each are shown in **Table 12.**

TABLE 12: ROLE OF MAGNA SWEET® AND ITS CONCENTRATION [82]

Role	Concentration (% w/w)
Sweetness modulation	0.002-0.010
Masking aftertaste	0.002-0.05
Flavor enhancement	0.002-0.01

Magna sweet®Plus is manufactured by blending of Rebaudioside A (97%) and Magna sweet®. It adds to sweetness without adding sugar or leaving aftertaste [83]. Various sweetening agents used in the thin film formulation are shown in **Table 13.**

TABLE 13: SWEETENING AGENTS, THEIR BRAND NAME, MANUFACTURER AND CONCENTRATION

Sweetening agent	Brand name	Manufacturer	Acceptable daily intake (mg/ kg body weight)
Aspartame 84	NutraSweet, Ajinomoto, Holland Sweetener Company	NutraSweet, AminoSweet Sancta	40- 50 85
Acesulfame-K 86	Sunette	Celanese	9 [87]
Sucralose 88	Splenda	Johnson & Johnson subsidiary McNeil Nutritional's LLC	5
Robaina 89	Stevia	Stevia Corp.	4
Monoammonium glycyrrhizinate 81	Magna sweet®	Mafco	0.015- 0.2 [90]

Saliva Stimulating agents: Saliva stimulating agents increase the rate of production of saliva and help in the faster disintegration of the formulations. Generally, food grade acids can be used as saliva stimulating agents. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are some of the saliva stimulating agents. Among them, citric acid is the most preferred one and is most widely used. These can be used alone or in combination. The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow at equal time under same conditions [91].

Prepared Montelukast sodium fast dissolving films using citric acid (3-4% w/w) as saliva stimulating agent [26]. Prepared oral thin films of Rizatriptan benzoate using citric acid (11-12% w/w) as saliva stimulating agent [74].

Super Disintegrants [92]: Super disintegrants provide quick disintegration as a result of combined effect of both swelling and water absorption, when they are added in the formulation. Super disintegrants absorb water and swell which promotes the dispersibility of the system, thereby enhancing disintegration and dissolution. Strong interaction with water is essential for disintegration. Mechanisms of disintegration includes swelling, wicking, deformation or combinations of any of these. **Table 14** shows some of the widely used super disintegrants and their concentrations.

TABLE 14: SUPER DISINTEGRANTS AND THEIR CONCENTRATION

Super disintegrants	Brand name	Concentration (% w/w)	Mechanism of disintegration
Sodium starch glycolate	Primogel, Explotab	2-8	Rapid water uptake followed by raid swelling
Crosspointe	Polyplasdone XL10	2-5	Combination of swelling and wicking
Polacrilin potassium	Indion 294, Amberlite IRP 88	0.5-5	Rapid water uptake followed by raid swelling

Prepared and evaluated fast dissolving films of Montelukast sodium using HPMC as film forming polymer along with different concentrations of super disintegrants like microcrystalline cellulose (MCC) and crospovidone. The formulations with crospovidone (4% w/w) and MCC (10% w/w) respectively showed maximum cumulative percentage drug release of 97.42% and 94.64% respectively at the end of 30 minutes [26].

Coloring agents: FD&C approved coloring agents, EU colors, natural coloring agents or pigments can be incorporated up to 1% w/w [93, 94]. In Nicotine orally disintegrating film formulation, FD&C Yellow #6 was used as coloring agent [35]. In Ondansetron RapidFilm formulation, titanium dioxide was used as coloring agent [55].

Flavoring agents: The selection of flavor depends on the type of drug to be incorporated. The acceptance of the oral disintegrating or dissolving formulation by an individual depends on the initial flavor which is perceived in first few seconds after the dosage form is consumed and the after taste of

the formulation, which lasts for at least about 10 minutes [95].

Flavors can be used alone or in combination. Upto10%w/w flavors are preferably added in the formulation. Menthol, chloroform and some salts are used as flavor adjuncts. They impart flavor and odor of their own and have mild anesthetic effect on sensory receptors associated with taste. Flavors used for taste masking of different tastes are given in **Table 15.**

TABLE 15: FLAVORS USED FOR TASTE MASKING OF DIFFERENT TASTES [96]

Basic taste	Flavors used for taste masking
Bitter	Wild cherry, mint, anise, walnut, chocolate
Sweet	Vanilla, fruit, berry
Salty	Butterscotch, peach, vanilla, wintergreen mint, maple, apricot
Sour	Raspberry, citrus, licorice root

Manufacturing Methods:

Solvent Casting: This is the most widely used method for manufacturing fast dissolving oral thin films. **Fig. 1** indicates equipment used for solvent casting method.

Steps:

- Water soluble polymers are dissolved in water
- Other excipients and APIs are dissolved in aqueous solution under high shear
- Both the mixtures are combined to give viscous homogenous solutions.
- The solution is deaerated and transferred to the casting station where solution is cast into film on a release liner of thickness 30-120 cm

Film coating techniques include knife-over-roll, reverse roll, slot-die, gravure cylinder and Mayer rod coating [4].

1. Casted film is dried in oven
2. Dried films are cut into desired shape 97
3. Film products are investigated for desired qualities
4. Final inspection is done
5. Product is sent for packaging

The preferred finished film thickness is 12-100 μm, although various thicknesses are possible to meet API loading and dissolution needs. Solvents used for manufacturing oral thin films should be selected from ICH Class III solvents list [98].

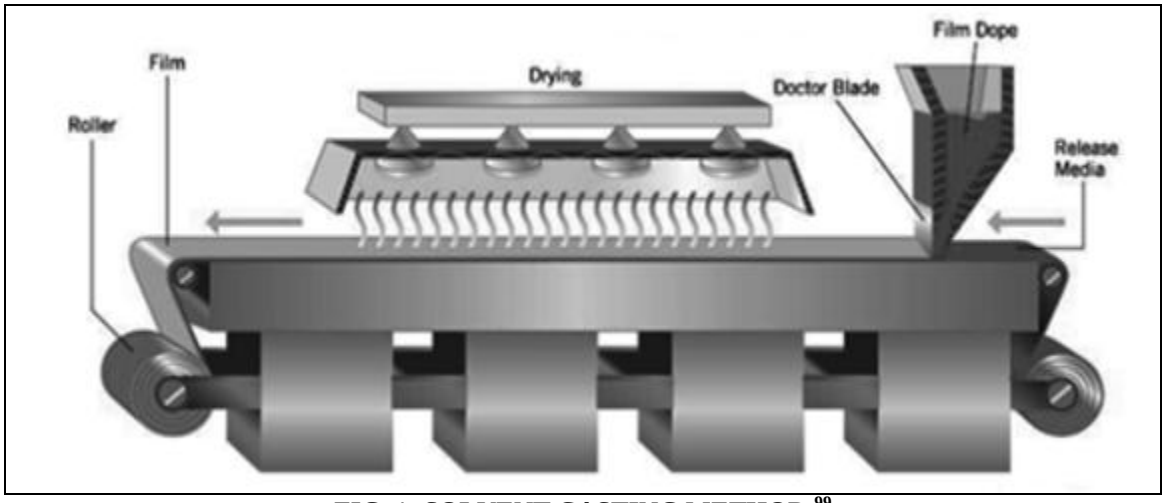

FIG. 1: SOLVENT CASTING METHOD [99]

Process Parameters [10]:

a) Mixing temperature: 20- 90^{o}C

b) Agitation time: 40-120 minutes

c) Rotating speed: 1000-2000 RPM

d) Flow rate while defoaming: 80 liters/hour

e) Passage time during casting: 2-8 minutes

f) Drying temperature: 50-130^{o}C

Advantages:

a) The method is cost-effective

b) Preferred over hot melt extrusion as it involves no exposure of API to elevated temperature, which may cause degradation of heat-sensitive APIs

c) Films have better uniformity of thickness and better clarity

d) Films have fine gloss

e) Films are free from defects such as die lines

f) Films have flexibility and better physical properties

Disadvantages:

a) The polymer must be soluble in a volatile solvent or water

b) A stable solution with a reasonable viscosity should be formed

c) Formation of a homogeneous film and release from the casting support must be possible [100]

- Formulated Tianeptine sodium Oro dispersible films by solvent casting method [42].
- Formulated fast dissolving films of Nicotine by solvent casting method [45].

Hot Melt Extrusion: Fig. 2 indicates hot melt extruder.

Steps:

a) The mass is prepared under controlled temperature and steering speed by mixing API with excipients

b) Mixture is melted in the extruder

c) The film is coated and dried in a drying tunnel

d) Then slitting is done

The films are punched, pouched and sealed [7].

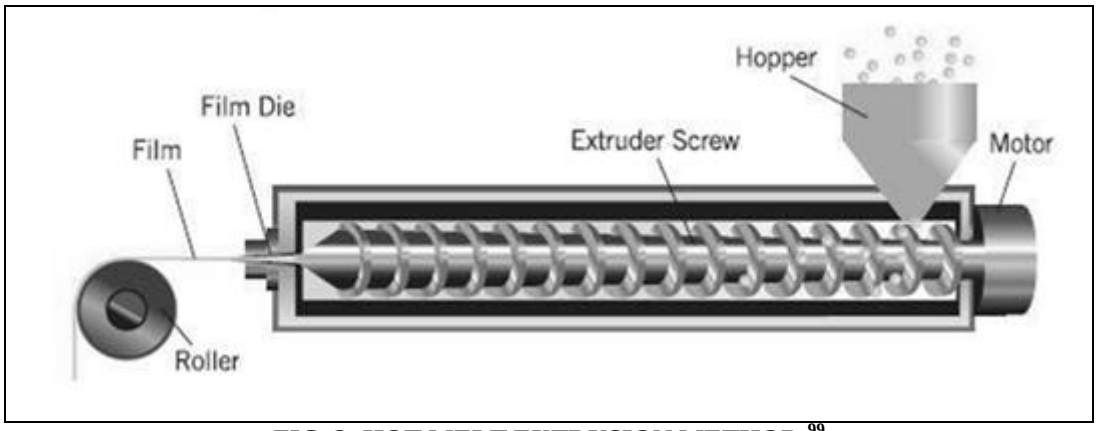

FIG. 2: HOT MELT EXTRUSION METHOD [99]

Process Parameters [1]:

a) Screw speed: 15 rpm

b) Processing temperature: 650-1150^{o}C

c) Extrudate temperature: 650^{o}C

d) Final film thickness: 200 μm

Advantages:

a) No use of solvent or water

b) Fewer processing steps

c) Better alternative for poorly soluble drugs

d) Less energy required compared with high shear methods

e) More uniform dispersion because of intense mixing and agitation

Disadvantages:

a) Thermal degradation due to the use of high temperature can take place

b) Flow properties of the polymer are essential for processing

Repka *et al.* formulated oral films containing Lidocaine using hot melt extrusion as manufacturing process where they used polymers HPC and HPMC in the ratio 80:20 [101]. Semisolid casting, Solid dispersion extrusion and rolling [7] are some other methods which can also be practiced for manufacturing purposes.

Some Recent Technologies:

Electrospinning: Electrospinning (ES) technology is mainly applied in the textile or filtration industry. The ES technology involves impact of high electric field on polymer solutions, thereby generating polymer fibers of submicron size when the surface tension of polymers is overcome by electric forces. The setup consists of a solution feeder and a high voltage power supply which is connected to a spinneret and a collector electrode. The solution on the spinneret electrode forms a droplet which can interact with electrostatic field. The droplet gains a cone shape and thin jet can emerge from the tip of the cone. Fibers are drawn by electrostatic forces between the two electrodes and the solvent evaporates, resulting in solid nanofibers. The prepared non-woven web is removable from the grounded collector as a sheet. Immediate release from nonwoven system of electrospun nanofibers is also known as mat or web [102]. The method involves mixing API with the liquefied polymer and electrospinning the solution onto a collecting element.

Advantages:

a) Electrospun polymer is capable of disintegrating aqueous medium within less than a minute due to its large surface area [103]

b) Wide versatility for application to different polymers

Formulated electrospun water soluble polymer (PVA) mat for ultrafast release of Donepezil hydrochloride. The disappearance time of the samples was 13±6 seconds, 11±4 seconds, 6±3 seconds for electrospunPVA placebo, electrospun PVA: Donepezil hydrochloride (5:1) and electrospun PVA: Donepezil hydrochloride (2:1) respectively [102].

Electro Spraying 104: Electro spraying is a recent method which can be adopted for the preparation of OTFs. It involves spraying a solvent under the influence of a high electric field. Here, the polymer is dissolved in a liquid, and it is subsequently electro sprayed; the polymer will be dispersed inside small droplets. Polymer particles can then be deposited on a substrate to form a continuous film. The deposition of polymer depends on the surface energy of the substrate and the polymer, the droplet or particle size at deposition and the viscosity of the polymer/liquid mixture at deposition. In the case that the solvent and other parameters are chosen such that a stable electrospray is obtained, the viscosity and the size of the particle/droplet are the two major parameters to control film characteristics. The droplet size of the spray can be controlled with liquid flow, surface tension and conductivity. Since liquid flow is also an important parameter to control spray stability, the conductivity is the most convenient parameter to influence the droplet size. The viscosity of a droplets at deposition depends on the polymer itself, but also on the quantity of liquid still present with the depositing polymer. The liquid content depends on the initial concentration of polymer and solvent and on the evaporation before deposition on the substrate. If the concentration of polymer becomes too high, electrospray will change into electrospinning. This will result in completely different film morphologies.

Drying of Films: Drying helps to maintain overall low temperature inside the film. Even if the film surfaces are exposed to a temperature above which the API degrades, the film interior may not reach this temperature. Due to this temperature difference, the API does not degrade. The films are dried for 10 minutes or less. Drying the films at 80°C for 10 minutes produces a temperature difference between the atmosphere and the film matrix of about 5°C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5°C less than the outside exposure temperature. In many cases, drying times of4-6 minutes are sufficient. Due to this temperature difference between the atmosphere and the film matrix, the films may be dried at high air temperatures without causing heat sensitive APIs to degrade.

Once a sufficient amount of the volatile liquid has evaporated, further exposure to heat leads to uniform heat diffusion throughout the film. The components desirably are locked into a uniform distribution throughout the film, and the final shape of the film is established. It may be desired to form a viscoelastic solid rapidly. Although minor amounts of water may remain subsequent to formation of the viscoelastic film, the film may be dried further without affecting the desired heterogeneity of the film. Further drying forms the final film wherein, solvent is further removed so that only less than 6% of the solvent remains in the final film formulation [105].

Various Technologies Used in the Formulation of Fast Dissolving Oral Thin Films: Bio Progress has developed a platform technology like as Soluleaves™, XGEL™, Wafer Tab™ for formulating fast dissolving oral thin films.

Soluleaves:
Features of Soluleaves™:

a) A vegetable-based polymer film that carries low levels of active ingredients and flavoring

b) Fast dissolution in the mouth

c) Enhanced taste masking

d) Enhanced convenience, portability and discreet format

e) Sugar free variant suitable for diabetics

f) Aqueous based and solvent free

g) Application in a range of vitamins, flavorings, and APIs

h) The Soluleaves™ system is patented [106].

Foam Burst: This is a variant of the Soluleaves™ technology 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 [7].

XGEL: The XGEL™ film systems can be made to encapsulate any oral dosage form and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimized for the intended use. All of the XGEL^{TM} ingredients are well known and generally regarded as safe (GRAS) [106].

Wafer Tab: The Wafer Tab™ filmstrip can be flavored for additionally improved taste masking. The API is precisely dosed and integrated into the body of a pre- manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture, potentially enhancing product stability. The Wafer Tab™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. Wafer Tab™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty swallowing [97].

Packaging: Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the fast-dissolving dosage forms. Single packaging is mandatory. An aluminum pouch is the most commonly used packaging material. APR-Labtech has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for Rapid films. The Rapid card has same size as a credit card and holds three films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics

1. It must not be reactive with the product

2. It must protect the preparation from environmental conditions

3. It must be FDA approved

4. It must be tamper-resistant

5. It must be non-toxic

Packaging Materials:
Foil, Paper or Plastic Pouches: The flexible pouch can provide sufficient tamper resistance and high degree of environmental protection. A flexible pouch is formed during the product filling by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

Single Pouch and Aluminum Pouch: Fast dissolving oral thin film drug delivery pouch is a peelable pouch for fast dissolving soluble films with high barrier properties. The pouch is transparent for product display. Using a two structure combination allows one side to be clear and the other to use cost-effective foil lamination. The foil lamination has essentially zero rate of transmission for both gas and moisture. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

Blister Card with Multiple Units

The blister container consists of two components

a) Blister, which is the formed cavity that holds the product

b) Lid stock, which seals the blister

The blister package is formed by heat softening a sheet of thermoplastic resin and then vacuums drawing the softened sheet of plastic into a contoured mold. After cooling, the sheet is released from the mold. Then it proceeds to the filling station of the packaging machine. The previously formed semi rigid blister is filled with the product and lidded with the heat sealable backing material. Generally, the lid stock is made up of aluminum foil. The material used to form the cavity is plastic, which can be designed to protect the dosage form from moisture.

Barrier Films: Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. Several materials may be used to provide moisture protection such as polychlorotrifluoroethylene film, polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent barrier to gas and vapor. But the drawback is lack of clarity [107].

Evaluation Tests for Fast Dissolving Oral Thin Films:

Differential Scanning Calorimetry: Differential Scanning Calorimetry is performed to indicate compatibility of drug with other excipients. Differential Scanning Calorimetry of plain drug and other excipients in the formulations can also be performed. Film samples weighing approximately 5 mg are cut, sealed in aluminum pans, and analyzed in an atmosphere of nitrogen at flow rate of 25 ml/min. A temperature range of 0°C to 200°C is used, and the heating rate 10°C/min is used [108].

Morphology Studies (Appearance): Surface morphology is studied by using Scanning Electron Microscopy (SEM). The presence of pores, surface uniformity, and particle dispersion can be seen [34]. A small piece of film is placed on carbon tape with the help of sputter coater for analysis.

Near Infrared (NIR) Chemical Imaging: NIR chemical imaging method complements SEM analysis. It is more quantitative in nature as it aids in evaluating drug distribution in a larger surface area.

X-ray Diffraction and Raman Spectroscopy: X-ray diffraction patterns and Raman spectra assist in determining the crystalline or amorphous nature of the unprocessed APIs and APIs incorporated in films [12].

Thickness Measurements: The thickness of each film is measured at five different locations (center and four corners) using Vernier caliper micrometer. Data is represented as a Mean±Standard deviation of five replicate determinations [7].

Palatability Study: This study is conducted on the basis of taste. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grades then it would be considered as good and the one with all three A grades, it would be the very good formulation.

Grades: A= Very good, B= Good, C= Poor [109]

Weight Variation: One cm^2 samples representing five different regions is cut. The weight of each film strip is taken, and the weight variation is calculated.

Folding Endurance: The folding endurance of the film is determined by repeatedly folding one film at the same place till it breaks. The number of times of film could be folded at the same place without breaking is noted, which gives the value of the folding endurance [110].

Determination of Moisture uptake: Films are cut in particular shape. The moisture uptake by the films is determined by exposing them to an environment of definite relative humidity and temperature for one week [111]. The uptake of moisture by the films is measured and calculated as % increase in weight by formula

% increase in weight = (Final weight- Initial weight) / Initial weight x 100

Drug Content Determination: The drug content is determined by any official assay method described for the particular API in any of the standard pharmacopoeias.

Content Uniformity: The content uniformity is determined using 20 films and estimating the API content in individual film spectrophotometrically. Content uniformity should be within 85-115% and relative standard deviation should be not more than 6% [112].

Tensile Strength: The tensile strength is determined by the apparatus which has two clamps, the upper one is fixed and the lower is movable. The film sample (0.5×3 cm) is clamped between the two clamps. The force at tearing and elongation is determined.

The percentage elongation (%E) is calculated using the following equation

$$\% E = \{(L_s-L_o) / L_o\} \times 100$$

Where, L_o = Original length

L_s = Length of the film after elongation

The modulus of elasticity of films was calculated from the equation

$$F/A = EM \{(L_s-L_o) / L_o\}$$

Where F = Breaking load (N),

A = Cross- sectional area of the film

EM = Modulus of elasticity [42]

Water Vapor Transmission Rate: For water vapor transmission rate study, vials of equal diameter can be used as transmission cells. Cells are washed thoroughly and dried in an oven. One gm of calcium chloride is taken in the cell and the polymeric films (two cm^2 area) are fixed over the brim with the help of an adhesive. The cells are accurately weighed, and the initial weight is recorded. Films are then kept in a closed desiccator containing saturated solution of potassium chloride (80-90 % RH). The cells are taken out and weighed after 18, 36, 54 and 72 hours. From increase in weights, the amount of water vapor transmitted and the rate at which water vapor transmitted can be calculated by using the following formula

Water vapor transmission rate = WL/S

Where, W = Water vapor transmitted in mg

L = Thickness of the film in mm,

S = Exposed surface area in cm^2 [113]

Contact Angle Measurement: Contact angle is measured by a goniometer. A drop of distilled water is placed on the surface of the dry film and images are recorded with the help of digital camera within 10 seconds [114].

Surface pH of Films: Films are left to swell for 2 hours on the surface of an agar plate, prepared by dissolving 2% w/v agar in warmed isotonic solution of desired qualities under stirring and then pouring the solution into a petri dish till gelling at room temperature. The surface pH can be measured by means of a pH paper placed on the surface of the swollen film.

***In-vitro* Disintegration Time:** *In-vitro* disintegration time is determined visually in a glass dish with 10 ml distilled water with swirling every 10 seconds. The disintegration time is the time when the film starts to break or disintegrate [42].

***In-vitro* Dissolution Study:** The drug release studies are performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus is thermostatic at the temperature of 37 ±1^oC and stirred at rate of 50 revolutions per minute. Each film is fixed on a glass slide. Then the slide is immersed in the vessel containing 500 ml of phosphate buffer pH 6.8. The aliquots of one ml are withdrawn at the time interval of 2, 4, 6, 8, 10 minutes and replaced with equal volume of dissolution medium. The sink conditions are maintained throughout the study.

The absorbance is checked by selected analytical method [42, 97].

Marketed Products: Large number of OTF formulations is available in market. First, breath freshener films were introduced into market. Then, over the counter (OTC) and nutraceutical film formulations which incorporated active ingredients such as vitamins, herbal extracts and non-herbal extracts. Pfizer introduced Listerine®pocketpaks® in 2001 for as breath freshner. The brand augmentation started after this was fairly successful for several popular OTF products from Novartis and J&J Consumer (Triaminic®, TheraFlu®, Benadryl®, and Sudafed™). Biofilm is utilizing OTF for the brand extension of the existing products in pharmaceuticals as well as nutraceuticals with a range of aphrodisiac, energy boosters, vitamins and appetite suppressors. Some marketed OTC products of OTFs are shown in **Table 16.**

TABLE 16: MARKETED OTC PRODUCTS OF OTFS

Product	Active ingredient	Manufacturer
Eclipse Flash Strips	Mint	Wringleys
Neocitran®Thin Strips™ Nexcede® Gas-X	Dextromethorphan Ketoprofen Simethicone	Novartis
Health strips	Soluble vitamins	Mattel/Momentus Solutions, LLC™
Benadryl	Diphenyhdramine hydrochloride	Pfizer
TheraFlu Thin Strips	Dextromethorphan	Novartis
Ora film	Benzocaine	Apothecus Pharmacetutical Corp.
Sudafed PE™	Phenylephrine	Pfizer/Johnson & Johnson
Orajel	Menthol/pectin	Del
Chloraseptic® Relief Suppress™ Cough strips	Benzociane Dextromethorphan hydrobromide	InnozenInc.
Zentrip	Meclizine hydrochloride	Sato
Melatonin PM	Melatonin	-
-	Methylcarbylamine Diphenhydramine hydrochloride Dextromethorphan Folic Acid Loratadine Caffeine	Hughes Medical Corp.
Bioenvelop	Nicotine	Paladin Labs Inc.
Listerine®pocketpaks®	Mint	Pfizer Inc.

Some marketed prescription products of OTFs are shown in **Table 17.**

TABLE 17: MARKETED PRESCRIPTION PRODUCTS OF OTFS

Product	Ingredients	Manufacturer
Triaminic Thin Strips®	Diphenhydramine	Hughes Medical Corporation
OndansetronRapid Film® Donepezil Rapid film®	Ondansetron Donepezil	Labtec GmbH
Zolmitriptan rapid film®	Zolmitriptan	
Suboxone®	Buprenorphine/Naloxone	MonoSol Rx, Reckitt Benckiser
Setofilm®	Ondansetron	BioAlliance Pharma
Zuplenz	Ondansetron	MonoSol Rx
KP106	d-Amphetamine	MonoSol Rx and Kem Pharm
Klonopin Wafers	Clonazepam	Solvay Pharmaceuticals

CONCLUSION: Many pharmaceutical companies are switching their products from tablets to fast dissolving oral thin films. Films have all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability). OTFs are new emerging novel drug delivery system of great importance during the emergency situations whenever immediate onset of action is desired and that allows children, elderly and the general population to take their medications discretely wherever and whenever needed, satisfying an unmet need. This technology provides a good platform for patent non- infringing product development and for increasing the patent lifecycle of the existing products. The application of fast dissolving oral thin films is not only limited to buccal fast dissolving system but also expands to other applications like gastro-retentive, sublingual delivery systems. Future applications include

incorporation of incompatible active pharmaceutical ingredients in the single formulation using multilayer films laminated together. An inactive film layer separating the incompatible active pharmaceutical ingredients can be introduced in between. Active pharmaceutical ingredients with significant transmucosal flux rates can be incorporated into thin films for disolving slowly into buccal or sublingual regions. Drugs coated with controlled release polymers can also be incorporated. This technology is being studied extensively and there is wide scope for further research in this field.

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CONFLICTS OF INTEREST: Nil

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