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A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents"

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Abstract: Fast dissolving oral films (FDOFs) 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. The FDOFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the oral film technology. However, for future growth point of view the oral thin film sector is well-positioned. In US market the OTC films of pain management and motion sickness are commercialized. More importantly, prescription OTFs have now been approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly.

Key words: Fast dissolving oral films · Oral mucosa · Permeability · Solvent casting and disintegration

INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance.

Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using superdisintigrant/s and hydrophilic ingredients. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.

Fast dissolving oral films (FDOFs) 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 saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [1]. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

OTFs also have an established shelf-life of 2-3years, depending on the API but are extremely sensitive to environmental moisture [2].

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion in near future according to Technology Catalysts [3].

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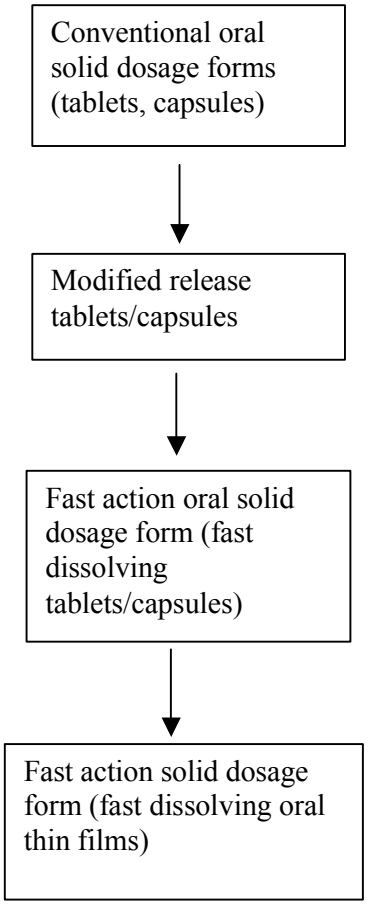
The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology [4].

In North America more than 80 oral thin film brands launched since 2003, the market remains limited when compared to ODTs. However, for future growth point of view the OTF sector is well-positioned. In US market the OTC films of pain management and motion sickness are commercialized. More importantly, prescription OTFs have now been approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly [5].

Flow Chart for the Development of Oral Solid Dosage Form



Advantages [6]: Fast dissolving film combines all the advantages of tablets (accurate dose, self administeration) with those of liquid dosage forms (easy swallowing, quick bioavailability). The administration of drugs by the oral route has several advantages over other route of administration such as;1,8

- No special set up required for the industry
- Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity and promote the systemic absorption of APIs
- No need of water or a spoon for administration and without chewing
- Dose accuracy in comparison to syrups
- Rapid onset of action
- The drug enters the systemic circulation with reduced hepatic first pass effect
- Lower doses
- Minimal side effects
- Destructive acidic environment of stomach can be avoided
- Delivery can also be terminated relatively easily if required.
- Site specific action and local action
- Noninvasive 13.Patent life extension

Disadvantage [7]

- The disadvantage of OTF is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip 7
- Expensive packaging of oral film

Limitations: Drugs with larger doses are difficult to formulate into FDT e.g. rifampin (600 mg), ethambutol (1000mg) etc. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip [16].

Most bitter drugs should be avoided or taste masking is required

Proteinaceous drugs should be avoided if used then co-administration of enzyme inhibitors such as aprotinin, bestatin, puromicin and bile salts required for the inhibition of proteolytic enzymes present in saliva

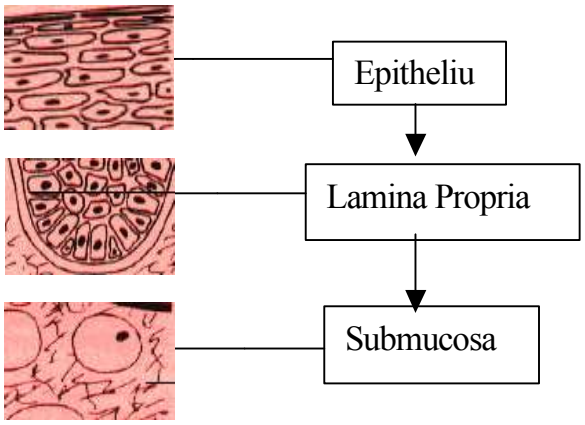


Fig. 1: Different layers of oral mucosa

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

Structural Features of Oral Mucosa

Structure: The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure 1). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [8].

The turnover time for the buccal epithelium has been estimated at 5-6 days [9] and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 µm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of the gingivae and hard palate are keratinized similar to the epidermis which containe ceramides and acylceramides (neutral lipids)which have been associated with the barrier function. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized [9] which are relatively impermeable to water and only have small amounts of ceramide [10-12]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. The nonkeratinized epithelia have been found to be considerably more permeable to water than keratinized epithelia [9-11].

The figure1 given below shows the layer of oral mucosa from outside to innermost.

Permeability: The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin[13]. There are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa [9].

For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer. Some example of permeation enhancer given;

- Aprotinin [14]
- 23-lauryl ether [15]
- Azone [16-18]
- Benzalkonium chloride [19]
- Cetylpyridinium chloride [20-23]
- Cyclodextrin [24]
- Dextran sulfate [25]
- Menthol [15]
- Sodium glycodeoxycholate [26-31]
- Sodium taurodeoxycholate [32]

Composition of Oromucosal Region

Oromucosal Cells: Are made up of proteins and carbohydrates. It is adhesive in nature and acts as a lubricant, allowing cells to move relative to one another with less friction [33]. The mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems [34]. In other part of body mucus is synthesized and secreted by the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands [33, 35].

Another feature of the oral cavity is the presence of saliva (digestive secretion) produced by three pairs of salivary glands(parotid, submandibular and sublingual glands). Saliva is mostly water with 1% organic and inorganic materials. The digestive enzyme present in

saliva is salivary amylase, which breaks down starch molecules to shorter chains of glucose molecules. Saliva is made from blood plasma and thus contains many of the chemicals that are found in plasma. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation [33, 35]. The salivary pH ranges from 5.5 to 7. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Composition of the Formulation [34-36]: Oral dissolving film is a thin film with an area of 1-20 cm^2 (depend on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30mg. Formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films.

A typical composition contains the following

- Drug 5% to30%w/w
- Water soluble polymer 45%w/w
- Plasticizers 0-20%w/w
- Surfactants q.s.
- Sweetening agent 3 to 6 %w/w
- Saliva stimulating agent 2 to 6%w/w
- Fillers, colors, flavors etc. q.s.

Drugs [37]: Several classes of drugs can be formulated as oral dissolving films including antiulcer (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. paracetamol, meloxicam, valdecoxib). Less bitter, potent and highly lipophilic drug should be preferred for OTF as in case of fast dissolving tablets. Most advanced research has proven that the concentration level of API per dose can extend up to 50% per dose weight. Novartis Consumer Health's Gas-X thin film has proven this by loading 62.5 mg of simethicone per thin film.

Water Soluble Polymers [39, 40]: Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water soluble polymers used as film former are HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and Eudragit RD108,9,10,11,12 Eudragit RL100. Polymerized rosin is a novel film forming polymer.

Plasticizers: By addition of plasticizers, the mechanical properties of formulation (tensile strength and elongation) can be improved. Mechanical property is plasticizers

Table 1: [38]

Category of drugs	Examples
Selective serotonin reuptake inhibitors	Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram and alaproclate.
Anti-emetics	Ondansetron, granisetron, palonosetron, dronabinol, aprepitant, ramosetron, metopimazine, nabilone, tropisetron, metoclopramide, prochlorperazine, trimethobenzamide, dimenhydrinate, prochlorperazine and dolasetron.
5HT3 antagonists	Alosetron, ondansetron, granisetron, palonosetron, ramosetron and tropisetron.
Anti-epileptics	Carbamazepine, clonazepam, diazepam, divalproex sodium, fosphenyloin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenyloin, pregabalin, primidone, tiagabine, topiramate, valproate sodium, vigabatrin and zonisamide.
Anti-migraines	Almotriptan, dihydroergotamine mesylate, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan.
Dopamine D1 and D2 antagonists	Amisulpride, bromperidol, cabergoline, domperidone, fenoldopam, haloperidol, metoclopramide, metopimazine, pergolide mesylate, prochlorperazine, quetiapine, ropinirole hydrochloride, sulpiride, tiapride and zotepine.
Nootropics	Almitrine dimesylate and raubasine, cevimeline hydrochloride, codergocrine mesylate, donepezil, galantamine, ginkgo biloba extract (EGb 761), memantine, nicergoline, piracetam, rivastigmine, sulbutiamine, tacrine and vinpocetine.
Statins	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

concentration dependent property. The commonly used plasticizers are glycerol, di-butylpthallate and polyethylene glycols etc. [41].

Surfactants: Surfactants act as solubilizing or wetting or dispersing agent in formulation so that the film is getting dissolved within seconds and release active agent quickly. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent [42].

Sweetening Agents [43]

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

Artificial Sweeteners: The artificial sweeteners have gained more popularity in food and pharmaceutical preparations. The artificial sweeteners can be classified in I generation and II generation sweeteners which are given below in table. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200 - 300 time sweetness [44].

Saliva Stimulating Agent [45]: More saliva production helps in the faster disintegration of the fast dissoving film formulations so the formulations may contain acids which are used in the preparation of food as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

Flavor [46]: Any flavor (US-FDA approved) can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors15. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

Table 2:

First Generation	Second Generation
Saccharin	Acesulfame-K
Cyclamate	Sucralose
Aspartame	Alitame
	Neotame

Color [47]: Pigments such as titanium dioxide or a full range of colors are available, including FDandC colors, EU Colours, Natural Colours and custom Pantone-matched colours.

Manufacturing Methods [48, 49]: There are five methods for manufacturing purpose i.e.

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

But the most commonly used industrial methods are solvent-casting method and Hot melt extrusion

Solvent-casting method

The OTF is preferably formulated using the solvent-casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

Ex;A. Mahesh *etal.* [50] formulated levocetirizine.2HCl oral film with pullulan polymer by using solvent casting method. The optimized films of levocetirizine dihydrochloride were obtained.

Advantages:

- Better uniformity of thickness and better clarity than extrusion.
- Film has fine gloss and freedom from defects such as die lines.
- Film has more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 µm, although various thicknesses are possible to meet API loading and dissolution needs.

Disadvantages:

- The polymer must be soluble in a volatile solvent or water.

- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

Hot Melt Extrusion: In present method the mass is prepared first under the control of temperature and steering speed. Afterwards, the film is coated and dried in a drying tunnel, once again the temperature, air circulation and line speed are controlled. Then follows a slitting and in the last step the films are punched, pouched and sealed. Ex. F. Cilurzo *etal*.[51] formulated Piroxicam film with Maltodextrin plasticized by glycerin by using Hot-melt extrusion method.

Advantages:

- Without use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages:

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

Semisolid Casting: In this method solution of water soluble film forming polymer are mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate, cellulose acetate butyrate).After sonication it is coated on non-treated casting film. On drying

The thickness of the film is about 0.381-1.27 cm. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Solid Dispersion Extrusion: Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method: In this method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and gives desired shape and size [52].

Various Technologies Used in Oral Film Formulation [53] XGel: XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

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

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

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

Micap: Micap plc signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the BioProgress water-soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs).

Evaluations

Thickness: The thickness of film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations) . This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

Dryness Test/Tack Tests: About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print free. Although these tests are primarily used for paint films, most of the studies can be adapted intricately to evaluate pharmaceutical OS as well [54]. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.

Tensile Strength: Tensile strength is the maximum stress applied to a point at which the film specimen breaks [55]. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{film width}}$$

Percent Elongation: When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increases [56].

Percent Elongation:

$$= \frac{L \times 100}{L_o}$$

L = Increase in length of film
L_0 = Initial length of film

Tear Resistance: The maximum stress or force (that is generally found near the onset of tearing) required to tear the film is recorded as the tear resistance value in Newton (or pounds-force) [57].

Young's Modulus: Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

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

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation.

Folding Endurance: Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value [58].

Stickiness Determination: It is evaluated by texture method usually used for measurement of the tack of pressure sensitive adhesives.

Swelling Index [59]: It is useful in case of film formulation having gelling property and measured by 2methods.

Linear Expansion Coefficient in Water: Film is immersed in water. Specimen is taken 2,4,6,8,10,15,30 and 60 seconds and the size of side length is measured. It is calculated as

$$L\% = \frac{(L_1 - L_0)}{L_0} * 100$$

Where
L_1 = Side length after immersion
L_0 = Side length before immersion

Amount Absorbed in Purified Water: The film is weighed (W_1) and put into the stainless steel mesh basket. The weight after immersion in water is measured(W_2).Similarly weight after immersion of basket without film(W_3).The amount absorbed(W) is determined by following equation;

$$W\ (g/g) = \frac{(W_2 - W_1 - W_3)}{W_1}$$

Contact Angle Measurement [60]: Time dependent contact angle is measured by an optical contact angle meter. The Contact angle measured by different methods like the two tangential methods, a height width ratio, the circle fitting and sessile drop fitting. It's prediction for wetting behavior, disintegration and dissolution of oral films.

Disintegration Time: The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral film [61]. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for film is 5-30 s [62].

Dissolution Test: Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API [63]. Many times the dissolution test can be difficult due to tendency of the film to float onto the dissolution medium when the paddle apparatus is employed. So mostly we use the basket apparatus for evaluation.

Dissolution Rate via Conductivity [64]: The fast-dissolving oral films completely dissolve within one minute. Mostly marketed oral films today contain ionizable components. For high resolution monitoring of the dissolution of fast dissolve oral films by measuring conductivity of the dissolution medium.

Assay/Drug Content and Content Uniformity: This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual film. Limit of content uniformity is 85-115%.

Organoleptic Evaluation: This is essential step in case of most oral formulation due to more residence time in the oral cavity. The product should possess the desired features of sweetness and flavor which is acceptable to a large mass of population. For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose [65]. Experiments using electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste-masking formulation [66].

Morphology Studies [60]: Scanning electron microscopy (SEM) study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API.

Near-infrared chemical imaging (NIR-CI) study helps in determining the difference between drug distributions in drug loaded films and recrystallization.

Clinical and Regulatory Aspects: In the US Food and Drug Administration, if the product is bioequivalent to that of the existing oral product of the drug, an Abbreviated New Drug Application (ANDA) route is followed.

There are no clinical studies associated in this generic approval process (section 505(j) of the Food, Drug and Cosmetics Act). The example of such a case would be a comparative bioequivalence between and ODT formulation and OTF product. However, developed oral film product may also exhibit a different target pharmacokinetic profile compared to the existing marketed product. The OTF product is categorized as 'new dosage form' and the section 505(b) (2) approval process needs to be followed. In this case, a new clinical study would be required. The advantage of a new clinical study is that it would award three years of marketing exclusivity to the product. In Europe, Marketing Authorization approval (Abridged Application) is essential as per the European Medicines Evaluation Agency guidelines. Either of the two modes i.e. the decentralized procedure or the mutual recognition route can be adopted. The Ministry of Health, Labor and Welfare is primarily responsible for product approvals in Japan. [67].

Measurement of Disintegration in the Oral Cavity: Films are randomly selected and administered to six healthy male volunteers at one hour intervals. The time required for complete disintegration of film in oral cavity is recorded.

Some Approved Marketed Products of Fast Dissolving Oral Films: There are some approved marketed products of fast dissolving oral films given in table 3;

Some under Developed Fast Dissolving Oral Film Formulations: It is given in Table 4.

Packaging: The Fast dissolving system can be packaged using various options, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roll dispenser. There are some patented packaging systems for oral film given in table 6.

Various Patents on Fast Dissolving Oral Films/Strips: Various patents in United States on fast dissolving oral films/strips are given in detail in Table 7.

Table 3:

Formulations	Brand name	Types	Manufacturer/marketed	Country
Fast dissolving oral film	Zolmitriptan Rapidfilm®	prescription product	Labtec's production site in Hamburg, Germany.	Europe
Ondansetron ODF	Setofilm®	prescription product	BioAlliance Pharma	Europe
Ondansetron ODF	Zuplenz(R)	prescription product	MonoSol Rx Marketed by Strativa Pharmaceuticals United	States
Oral films of ✓Methylcobalamin ✓Diphemhydramine HCl ✓Dextromethorphan ✓Folic Acid ✓Loratidine ✓Caffeine	--	OTC	Hughes Medical Corp.	--
d-Amphetamine film	KP106	prescription product	MonoSol Rx and KemPharm	--
Listerine PocketPaks			MonoSol Rx	--
Buprenorphine/ Naloxone film	Suboxone	prescription product	MonoSol Rx Marketing partner Reckitt Benckiser	--
Donepezil film	Donepezil Rapidfilm®	prescription product	Labtec	Marketed in Europe as well as in the US
Vitamins, hormones, nutraceuticals films		OTC	Paladin Labs	Canada and the United States.
Midazolam Maleate		Oral FilmAoxing	Pharmaceutical	CompanyChina

Table 4:

Drugs	Category
Rizatriptan	Migraine/Fast onset
Epinephrine	Severe allergic reaction
Insulin	Diabetes
Montelukast sodium	Asthma/allergic
Meloxicam	Antiinflammatory drug

Table 6:

Packaging	Company
RapidCard	Labtec
Core-Peel®	Amcor Flexibles

Table 7:

Title	United States Patent	Issued	Inventors	Assignee	Appl. No.	Filed
Fast dissolving orally consumable films containing a taste masking agent	7,648,712	January 19, 2010	Bess; William S. (Edison, NJ), Kulkarni; Neema (Randolph, NJ), Ambike; Suhas H. (West Hill, CA), Ramsay; Michael P. (Ajax, CA)	McNeil-PPC, Inc. (Skillman, NJ)	11/429,547	May 5, 2006

Table 7: Continued

Title	United States Patent	Issued	Inventors	Assignee	Appl. No.	Filed
Process for manufacturing thin film strip	6,824,829	Nov.30, 2004	Craig j.berry Walter klauser	Aupac packaging,inc.	10/226,451	Aug.23,2002
Fast dissolving orally consumable film	7,025,983	Apr.11,2006	Sau Hung Spence Leung,Robert S. Leone,Lori D. Kumar, Neema Kulkarni, Albert F. Sorg	Warner Lambert Company LLC.	09/836,474	Apr.18,2001
Fast dissolving orally consumable film containing sweetener	2003/0211136	Nov. 13, 2003	Lori D. Kumar, Neema Kulkarni, Albert F. Sorg	Warner Lambert Company LLC.	10/423,398	Apr.25,2003
Fast dissolving film for oral administration of drugs	2004/0208931	Oct.21,2004	David R.Friend, Aaron W. Levine, Kerrie L. Ziegler, Emmanuel Manna	William Squire,Esq.	10/744,479	Dec. 23, 2003
Fast dissolving orally consumable film containing a modified starch for improved heat and moisture resistance	2004/0247648	Dec. 9,2004	David John Fadden Neema Kulkarni, Albert F. Sorg	Pfizer, Inc.	10/838,045	May 3, 2003
Oral fast dissolving film for erectile dysfunction bioactive agents	2009/0047330	Feb. 19,2009	Ramesh bangalore	---	12/228702	Oct.9,2008
Water soluble film for oral administration with instant wettability	5,948,430	Sep.7,1999	Horst George Zerbe, Jian Hwa Guo, Anthony Serino	LTS Lohman Therapie- systeme GmbH	08/904,607	Aug.1, 1997
Water soluble sheet composition	6,800,295	Oct. 5,2004	Priscilla S. Fox	The Dial Corporation	10/267,235	Oct. 9,2002
Method for producing film type dosage	6,800,329	Oct. 5,2004	Michael Horstmann, Wolfgang Laux, Horst Dzekan,Katja Zinndorf	LTS Lohman Therapie- systeme AG	10/314,549	Dec. 9,2002
Process for manufacturing thin film strips	6,824,829	Nov. 30,2004	Craig J. Berry, Walter klauser	Acupac packaging,Inc.	10/226,451	Aug. 23,2002
Flavored film	7,132,113	Nov.7,2006	Horst G. Zerbe, Fadia Al- Khalil	Intelgenx Corp.	10/123,142	Apr.16,2002
Thin film strips	7,241,411	Jul.10,2007	Craig J. Berry, Walter klauser	Acupac packaging,Inc.	10/922,502	Aug.20,2004
Disintegratable films for diagnostic devices	7,470,397	Dec.30,2008	William G.Meathrel, Nathan A. Meyer,Scott D.Barnhart,Cathy M.Moritz,Andrew P.Full,Susan R.Newsom, Mary Robertson	Adhesives Research, Inc.	10/970,383	Oct.22,2004
Film comprising nitroglycerin	20100215774	August 26, 2010	Maibach, Todd	---	---	February8,2008
Pullulan film composition	7,267,718	Sep.11,2007	Robert Scott, Dominique Cade	Warner Lambert Company LLC.	10/941,182	Sep.15,2004

CONCLUSION

The present review conclude that fast dissolving oral film is most acceptable and accurate oral dosage form which bypass the hepatic system and show more therapeutic response. The pharmaceutical companies prefer this dosage form due to both patient compliance (especially pediatric and geriatric) as well as industrial acceptability. . Oral films can replace the over-the-counter (OTC) drugs, generic and name brand from market due to lower cost and consumer‘s preference. This technology is a good tool for product life cycle management for increasing the patent life of existing products.

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