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Review Article

FAST DISSOLVING ORAL FILM: A MODERN DEVELOPMENT IN DRUG DELIVERY SYSTEM

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ABSTRACT

Patient conformity always remains the major concern of research for all researchers working in the ground of pharmacy and specially pharmaceutics. Over the last few decades, propensity toward innovative drug delivery systems have majorly enlarged attempts to make sure worth, safety and patient acceptability, thereby increasing the product patent life cycle. As innovation and expansion of new chemical agents is a complex, costly and time consuming process, so current trends are changing toward designing and developing novel drug delivery systems for existing drugs. The FDDFs includes the mouth dissolving tablets, mouth dissolving thin films. These fast disintegrating films have advantage over fast disintegrating tablets as the latter are connected with the risks of choking and friability. It is a robust form of DDS where the film is placed on the top or the bottom of the tongue. When place on the tongue, this film dissolves immediately, releasing the drug which dissolves in the saliva. Some drugs are engrossed from the mouth, pharynx and esophagus as the saliva passes down into the stomach as a result enhancing drug bioavailability, no peril of choking, providing fine mouth feel. Generally, hydrophilic polymers along with added excipients are used for preparing FDOFs. FDOFs have potential for business and market utilization because of their many of benefits over orally disintegrating tablets. So it's gaining the interest of large number of pharmaceutical industries. Additionally, the market view of this novel dosage form is also targeted. This present review attempts to discusses oral mucosa, focus on benefits, formulation ingredients, composition, approaches for formulation and evaluation, future prospects of FDOFs.

Key words: Fast dissolving oral film, Mouth dissolving thin films, Formulation, Future prospects.

INTRODUCTION

Fast dissolving oral films (FDOFs) were initial introduced in the market as breath fresheners and personal care products such as dental strips and soap strips. However, they are introduced in the United States and European pharmaceutical markets for therapeutic effect (Narayana et al., 2013). Almost 90% of the drugs are administered to the body via oral route for the treatment of a variety of disorders and illness as it is

regarded as the safest, ease of administration, acceptability, non-invasiveness, adaptability, most suitable and most inexpensive method of drug delivery and have the maximum patient compliance (Chaudhary et al., 2013; Bhowmik et al., 2009; Raju et al., 2011; Verma et al., 2010). Regarding oral route of drug administration, numerous alternates have constantly been presented by using new novel technologies for geriatrics, pediatrics, nauseous and non-compliance patients. Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are results of technological expansion. Among diverse dosage forms, the use of polymeric films for delivering medication into buccal cavity has developed great potential in current time (Arya et al., 2010). FDOFs when placed on tongue, immediately hydrates by soaking saliva subsequent disintegration and/or dissolution releasing API from the dosage form (Chauhan et al., 2012). FDOFs are type of formulations which are normally prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Fast dissolving oral tablets and fast dissolving oral films are the distinctive examples of the orally FDDD system. These systems were developed in late 1970 to provide as a choice to conventional dosage forms, for instance, fast dissolving tablets and capsules for geriatrics and pediatric patients having complexity in swallowing conventional dosage forms (Liew et al., 2012). Typical FDOFs is typically equal to the size of a postage stamp. In market place, the overture of FDOFs was strongly connected with counseling of patients about the suitable administration by giving instruction like do not chew/do not swallow. However, in malice of these instructions, incidents about chewing and swallowing were often reported. But, FDOFs untied the masses from these adverse events. The administration of FDOFs has many advantages and some of them are as follows:

i. Easy transportation.
ii. Ease of swallowing for geriatrics and pediatrics.
iii. Convenient and accurate dosing.
iv. No need of water for administration.
v. Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.
vi. Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability (Choudhary et al., 2012).

No expensive lyophilization, high mechanical strength, accessible in various size and shape, thin elegant film, un-obstructive, rapid disintegration and reduced choking risks are the quality attributes of FDOFs (Arya et al., 2010; Preis et al., 2012; Goel et al., 2008). FDOFs have attained notable consequence in pharmaceutical industry for the reason of possessing exclusive properties and fast disintegration time ranging from seconds to one minute (Choudhary et al., 2012). FDOFs design permits to integrate a range of drugs for their pharmacological effects e.g., anti-tussive, anti-epileptic, expectorant, anti-asthmatic, etc. (Arya et al., 2010). Elevated temperature and moisture sensitivity necessitating costly packaging and incapability of high dose loading are some disadvantages of FDOFs. Thin films have the possible to allow the expansion of sensitive drug targets that may otherwise not be possible in liquid or tablets formulations (Siddeshwar et al., 2014). Today, these are proven to be acceptable for OTC (Over the Counter) medications and are in the early to mid- development stages for prescription drug. Zulpenz is the initial oral soluble disintegrating film approved by the FDA as a prescriptions medication (Goel et al., 2008). 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 (TCIC, 2011).

Physiochemical properties of oral mucosa

Permeability coefficient of a drug is the measure of ease with which the drug can infuse a membrane. Arrange of permeability is intestine> buccal mucosa> skin. This permeability position is based upon the relative thickness and degree of keratinization Fig. 1. Permeability of buccal mucosa is 4-4000 times better than that of skin. Due to fewer permeability of buccal mucosa than the intestine some permeability enhancer has been widely developed in the buccal drug delivery system like (Jaiswal, 2014) 23-Lauryl ether, Aprotinin, Dextran sulphate, Benzalkonium chloride, Sodium taurodeoxy- cholate. Therefore buccal delivery serves as an exceptional platform for absorption of drug. Absorption of oral film takes place either through transcellular route and paracellular route. Oral mucosa consists of three layers: outermost layer (Stratified squamous epithelium), intermediate layer (Lamina propria), innermost layer (Submucosa) (Dodla and Velmurugan, 2013; Mitul et al., 2011). Epethelium of oral mucosa is 40-50 cell layers thick which are composed of intercellular ground substance called mucus which consists of proteins and carbohydrates. Mucosal thickness of hard and soft palates, the ventral tongue, the floor of the mouth and the gingival varies from 100-200 um. Submucosal layer secrets gel like secretion known as mucous which contain of 1-5% of water insoluble glycoprotein, 90-99% water and other components like enzymes, proteins, electrolytes and nucleic acids in very small quantities and this composition varies depending upon the origin of secretion in the body (Dodla and Velmurugan, 2013; Mitul et al., 2011). Function of mucous: sustains hydrating conditions of oral cavity, gives adequate lubrication, gives concentrated protective molecules such as secretory immunoglobulins and also reduces attachment of micro-organisms. Salivary gland consists of lobules of cell which exude saliva and parotid through the salivary duct near the teeth submandibular and the sublingual ducts. Minor salivary glands present in the lips, buccal mucosa and in lining of the mouth and the throat. Total quantity of saliva secreted per minute is 1-2 ml. Saliva consists of water, salivary amylase, mineral salts, lysozyme, immunoglobulins, mucus and blood clotting factors (Waugh and Grant, 1995). Saliva and salivary mucin give to the barrier properties of oral mucosa. Negative charge of mucin contains sulphydryl group and salic acid responsible for the muco-adhesive phenomenon.

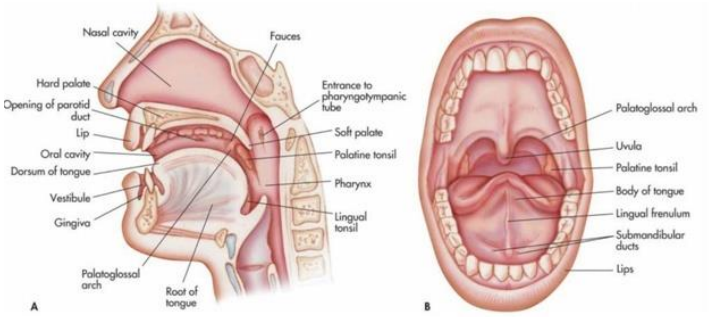

Fig. 1. Anatomy of the oral cavity (http://baldaivirtuves.info/human- anatomy-mouth/human-anatomy-mouth-anatomy-mouth-oral-cavity-human-anatomy-library-physiology/)

Formulation Consideration

FDOFs having a region ranging from 5 to 20 cm^2 in which drug is included in the form of matrix using hydrophilic polymer. API can be integrated up to 1-30 mg along with other excipients i.e., sweeteners, plasticizers, colorants, taste masking agents, etc. Plasticizer increases spreadability, workability and flexibility of films thereby

reducing the glass transition temperature of polymers (Arya et al., 2010). The general composition of FDOFs is shown in Table 1.

Table 1 Composition of FDOFs

Name of the excipient	Quantity
Active pharmaceutical ingredient	5-30%
Hydrophilic polymer	40-50%
Plasticizer	0-20%
Filler, Color, flavor	0-40%

Active pharmaceutical ingredient

Forever use low dose API because high dose of drug is tricky to integrate in fast dissolving film micronized API is useful become it improve the texture of film and provide better dissolution and uniformity in the fast dissolving film (Thakur et al., 2013). Drugs should have the pleasant taste, having smaller or moderate molecular weight, good stability in water as well as in saliva, should partially unionized at the pH of oral cavity and should permeate oral mucosal tissues (Muhammad et al., 2015). A variety of drugs can be incorporated into FDOFs e.g., anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc. Dimenhydrinate can also be integrated into FDOFs for taste masking. Frequent examples of drugs integrated into FDOFs are verapamil, ondansetron, dexamethasone, rofecoxib, salbutamol sulfate, rizatriptan benzoate, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc. FDOFs of anti-emetic agent like prochlorperazine were also formulated by using microcrystalline cellulose and other film forming polymers (Nishimura et al., 2009).

Hydrophilic polymers

The victorious development of FDOFs is a function of acceptable selection and concentration of polymers as the mechanical strength of films is strongly connected with these factors. They can be used either alone or in combination with added polymers to modify film properties. The concentration of used polymers is also significant factor while developing FDOFs. The integrity of FDOFs is dependent upon vigilant selection of polymer nature and concentration. Generally, polymer concentration used in preparing FDOFs is around 45% w/w of total weight of dry thin film; however, it can be increased up to 60–65% w/w in order to attain the film of preferred attributes and characteristics. Polymer used as a film forming agent in formulation of thin strips should possess confident properties; Non-irritant, should not delay with the disintegration time of ODF, reasonable, should possess good spreadability, should possess sufficient shelf-life, should have good mechanical properties, should exhibit sufficient tensile strength, non-toxic, non-irritant. In current time, both natural and artificial polymers are used for making FDOFs formulation (Table 2). Diverse polymers are employed to adjust diverse properties of films. Pullulan has increased solubility, enhancing flexibility and films incorporating pullulan have elevated tensile strength and stability over a wide range of temperature. Molecular weights of gelatins influence the properties of prepared films and a considerably appealing film can be attained by using polymers with higher average molecular weight. The combination of chitosan and high methoxy pectin or low methoxy pectin provides brilliant quality of film. Cellulose derived film forming polymers give films with fewer water vapor barriers due to their hydrophilic nature. Polyethylene glycol also has a excellent film forming properties either alone or in combination with other polymers (Pathare et al., 2013).

Table 2 List of polymers used in oral thin films

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

Plasticizers

Mechanical properties such as tensile strength and percent elongation are enhanced by adding plasticizer to the formulations by dropping the glass transition temperature of the polymer. It also reduces brittleness of the strip as a result improves its flexibility. Selection of plasticizer depends upon type of solvent used and its compatibility with the polymer. The concentration of plasticizer usually ranges from 0% to 20% w/w. Frequent examples of plasticizers are glycerol, diethyl phthalate, triethyl citrate, PEG, tributyl citrate, etc. (Bala et al., 2013). Inappropriate use of plasticizer may lead to film cracking, blooming, splitting and peeling of the film.

Surfactants

Surfactants play a very important role as wetting, dispersing and solubilizing agent thus enabling films to disintegrate within seconds releasing the integrated drug, quickly. Frequently used surfactants are tweens, polaxamer 407, benzalkonium chloride and sodium lauryl sulfate (Siddiqui et al., 2011).

Flavor: Flavoring agents are required to cover the bitter or nauseating taste of integrated drug. Amount of flavor depends upon its nature and strength. Any US-FDA accepted flavor can be used such as sweet, sour or mint flavor (Siddiqui et al., 2011). Research work verified that mint, licorice and sucralose mixture flavors suitably mask the bitter taste of diclofenac sodium. Electronic tongues are used to distinguish the effect of various taste masking agents (Cilurzo et al., 2011).

Sweetening agents

Sweetening agents are considered to disintegrate or dissolve in oral cavity. Both artificial and natural sweeteners are used in making FDOFs Natural- Glucose, dextrose, fructose, sucrose and isomaltose, Artificial- Acesulfame-K, sucralose and neotame. Neotame and Alitame are 2000–8000 times sweeter than sucrose [Siddiqui et al., 2011]. Fructose has more sweetening power compared to sorbitol and mannitol (Desu et al., 2013). Sucralose was found to be 600–1000 times sweeter than sucrose when oral disintegrating films of donepezil were evaluated for taste, after taste mouth feel. Aspartame and saccharin sodium are likely to be 200 and 300–500 times sweeter comparedto sucrose, respectively. It was also reported that sweeteners and flavors have slight effect on flexibility of film.

Saliva stimulating agent

Salivary stimulants are normally acidic in nature exciting the production of saliva in buccal cavity and promoting the disintegrating of FDOFs. Some normally used saliva stimulating agents are tartaric acid, citric acid, malic acid, lactic acid and ascorbic acid (Siddiqui et al., 2011).

Coloring agents

Pigments are used as coloring agents. Titanium dioxide is most broadly used colorant in FDOFs and a variety of other pharmaceutical preparations. Apart from titanium dioxide, a full range of colors are available including FD and C, natural and custom pantone-matched colors (Siddiqui et al., 2011).

Methods used for the formulation of fast dissolving films

Conventional approaches

- Solvent casting method
- Hot-melt extrusion
- Semisolid casting
- Solid dispersion extrusion
- Rolling.
- Spray technique

Solvent casting method

Solvent casting is the most frequently used method for the preparation of FDOFs. In this method, initially the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is integrated with the API dissolved in suitable solvent. 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 preferred size Fig. 2.

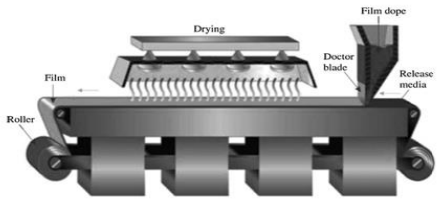

Fig.2 Explanation of solvent casting technique.

Hot-melt extrusion

In hot melt extrusion method, the initial mass is formed with the assist of carriers. To form initial mass, the drug is mixed with carriers and a solid mass is obtained and dried. Then dried granular material is introduced into the extruder. The extruder is divided into four zones having following degrees of temperature: 800 (zone 1), 1150 (zone 2), 1000 (zone 3), and 650°C (zone 4). The speed of extruder screw should be set at 15 rpm in order to process the granules within the barrel of extruder for about 3-4 min so that mass should be properly melted. The extrudate (T = 650°C) obtained is then pressed into a cylindrical calendar in order to obtain a film. There are certain profits of hot melt extrusion: less operation units, least product wastage, opportunity to scale up, an anhydrous process, lack of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix and improved content uniformity (Thakur et al., 2013).

Semi-solid casting

This method is mostly preferred when film ingredient involves acid insoluble polymer. In this firstly, the water soluble polymers are dissolved in water. The obtained solution is added to the acid insoluble polymer solution which is separately formed. Both the solutions are mixed properly. After mixing the two solutions, appropriate amount of plasticizer is added to the obtained final solution so that gel's mass can be obtained. At last, the gel mass is casted onto the films or ribbons using heat controlled drums. The

thickness of the film should be about 0.015-0.05". The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Examples of acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate.

Solid dispersion extrusion

This involves the solid dispersion of drug integrated in melted polymer solution so that drug can be loaded. The drug is dissolved in suitable liquid solvent and obtained solution is added to the melt of suitable polymer, accessible below 70°C without removing the liquid solvent to obtain the solid dispersion. Lastly the obtained solid dispersions are shaped into films by means of dyes.

Rolling method

In this method, both the drug and film forming polymer solution are mixed carefully and the resulting solution or suspension is subjected to the roller. The solution or suspension should have precise rheological consideration. The film is dried on rollers and cut into preferred shapes and sizes (Bala et al., 2013).

Spray technique

API, polymers and all other excipients are dissolved in an appropriate solvent to form a clear solution. This clear solution is then sprayed onto suitable material such as glass, polyethylene film of non-siliconized Kraft paper or Teflon sheet (Panda et al., 2013).

Characterization and evaluation

Organoleptic evaluation

Particular controlled human taste panels are used for such purpose. This in vivo taste evaluation is carried out on human volunteers. In-vitro taste evaluation of FDOFs is performed by using taste sensors for screening. In vitro taste assessing methods and technologies are suitable and enough for high-throughput taste sensing of such dosage forms. Both in vivo and in vitro procedures analyze the taste masking skill and sweetness level of taste masking agents.

Thickness

The thickness of film is deliberate by micrometer screw gauge or calibrated digital Vernier Calipers. The thickness of film should be in range 5-200 µm. (Sani et al., 2011) The thickness should be evaluated at five different locations (four corners and one at center) and it is necessary to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose division in the film.

Dryness/tack test

In all there have been 8 stages identified for film drying and these 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. Tack is the tenacity with which the strip adheres to an accessory that has been pressed into contact with film. Instruments are also available for this study (Okabe et al., 2008).

Tensile strength

It is the maximum stress applied to a point at which the film sample breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of film as given in the equation below:

Tensile strength = Load at failure × 100/ film thickness × film width

Percent elongation

When stress is applied on a film (2×2 cm^2) sample it gets stretched, this is referred to strain. Strain is basically the deformation of film before it gets broken due to stress. It is measured by using houns field universal testing machine (30). Generally, elongation of strip increases as the plasticizer content increases. It is calculated by the formula:

% Elongation = Increase in length of film × 100/Initial length of film

Tear resistance

It is the resistance which a film offers when some load or force is applied on the film specimen. The load mainly applied is of very low rate 51 mm/min. The unit of tear resistance is Newton or pounds-force. In

other words it is the maximum force required to tear the sample (Ali et al., 2007).

Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of film (Mashru et al., 2005). It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's modulus = Slope × 100/ film thickness × Cross head speed

Hard and brittle films demonstrate a high tensile strength and Young's modulus with small elongation.

Folding endurance

It gives the brittleness of a film. The method used to determine endurance value is that the film specimen ($2\times2cm^2$) is repeatedly folded at the same place until it breaks or a visible crack is observed. The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value (Kalyan and Bansal, 2012).

Swelling property

Simulated saliva solution is used to ensure the swelling studies of films. Initial weight of film is determined and is placed in pre-weighed stainless steel wire mesh. This mesh containing film is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant pre-determined time intervals until no more increase in weight. Degree of swelling is determined by these parameters:

Degree of swelling =final weight-initial weight/initial weight

***In vitro* disintegration test**

It is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time. In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates (Dahiya et al., 2009; Vishwkarma et al., 2011).

***In vitro* dissolution studies**

It is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent concentration. The standard basket or paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing. The selection of dissolution medium will essentially depend as per the sink conditions and highest dose of API. The temperature of dissolution medium should be maintained at 37±0.5°C and rpm at 50. When the paddle apparatus is used, it has a disadvantage that oral films have a tendency to float over the dissolution medium (Dinge et al., 2008).

Drug content uniformity

Content uniformity is determined by estimating the API content in individual films by any standard assay method of the standard pharmacopoeia. Limit of content uniformity is 85-115% (Sharma et al., 2007).

Surface pH test

The surface pH of fast dissolving film can cause side effects to the oral mucosa. The surface pH of film should be 7 or close to neutral. For this, a combined pH electrode can be used with the help of water, OS was made slightly wet and the pH was measured by bringing electrode in contact with surface of oral film (Parmar et al., 2012). In another method the films are placed on the 1.5%w/v agar gel and then the pH paper are placed on the film, change in color of pH paper gives surface pH of the film.

Contact angle

It calculates the wetting behavior, disintegration time and dissolution of oral film. These measurements are performed with help of goniometer at RT (Meathrel and Moritz, 2007). A drop of double distilled water is placed on the surface of dry film.

Images of water droplet are recorded within 10s of deposition by means of digital camera. Digital pictures can be analyzed by image J 1.28v software for angle determination.

Transparency

A simple ultraviolet (UV) spectrophotometer can be used to determine it. The film sample is placed on the internal side of spectrophotometer cell. The transparency of films is calculated as follows:

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

Where T_{600} is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

Scanning electron microscopy

To study the surface morphology of film between different excipients and drug scanning, electron microscopy can be used.

Permeation studies

Modified Franz diffusion cell can be used along with porcine buccal mucosa. The Franz diffusion cell consists of a donor and a receptor compartment. In between the two compartments, mucosa is mounted and the size of the mucosa should be of the same size as that of the head of receptor compartment. The receptor compartment is filled with buffer and maintained at 37± 0.2°C and to keep thermodynamics a magnetic bead stirring at a speed of 50 rpm is used. A film specimen moistened with a few drops of simulated saliva should be kept in contact with mucosal surface. The donor compartment should consist of 1 ml simulated saliva fluid of pH 6.8. At particular interval, samples are withdrawn and replaced by same amount of fresh medium. By suitable analytical method, percentage of drug permeated can be determined.

Stability study

According to ICH guidelines it determined. The prepared formulation was wrapped in a butter paper then above it an aluminum foil was wrapped and the packing should be placed in an aluminum pouch and make it heat sealed. The storage conditions at which formulations are kept should be 30°C/60% relative humidity (RH) and 40°C/75% RH. After 3 months, the films were evaluated for drug content, disintegration time and physical appearance observation (Bala et al., 2013).

Packaging of orally disintegrating films

Packing deliberations are serious for storage, protection and stability of films. Packaging it includes foil paper or plastic pouches, single pouch, aluminum pouch, blister packaging with multiple units and barrier films. Barrier films are most commonly used for those drugs which are very moisture sensitive (Patil et al., 2014). Rapid film technology developed by Lab tec GmbH describes primary packaging made of a sealing pouch affords enough space for logos, codes, instructions or other information. The films are manufactured by a laminating process and packaging costs are comparable to tablets (Bhasin et al., 2011).

Patented technologies of fast dissolving oral films

XGel

XGel film technology is urbanized by BioProgress which causes a revolution in the product offerings and manufacturing methods which is now available to the pharmaceutical industry. These films may be coloured or printed during manufacture for branding and coding which is quite helpful in product identification and also developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare pouches (Gauri and Kumar, 2012). These films enhance the stability of product (Anupama et al., 2014).

Soluleaves

In this technology, the film on coming in contact with saliva releases its API, during this film adhere to the mucous membrane in order to release the drug slowly in 15 min (Gauri and Kumar, 2012). This technology is applied to flavoured products such as mouth

fresheners, confectionery and vitamins (Anupama et al., 2014).

Wafertab

Wafertab is a DDS which incorporates API into an ingestible film strip. When film came in contact with saliva it provides rapid dissolution and release of active ingredient (Patel et al., 2013). The Wafertab film strip can also be flavoured for additionally improved taste masking. The active ingredient is integrated into the body of a fused.

Foamburst

Foamburst is a novel patent granted in September 2004 which is for capsules made of formed film. During manufacture an inert gas is blown into the film, results in a film with honeycomb structure as a capsule which dissolve rapidly and causing a melt-in-the mouth sensation. The void in the film may be gas-filled, empty or filled with other materials to produce specific taste burst characteristics or deliver active drugs (Patel et al., 2013).

Micap

In 2004 Micap plc signed a harmony to combine its expertise in micro encapsulation technology with the BioProgress water soluble films. Their main aim is to provide new delivery mechanisms for the $1.4bn global market for smoking cessation products (Anupama et al., 2014).

Rapid film™

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

Table 3 Recent patents on fast dissolving strips/films (Sharma et al., 2015)

Country	Patent No.	Title	Inventors
US	5,948,430	Water soluble film for oral administration with instant wettability	Zerbe et al.
US	6159498	Bioerodable films for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al.
US	2003/0211136	Fast dissolving orally consumable films containing sweetner	Lori et al.
US	2004/0208931	Fast dissolving films for oral administration of drug	Friend et al.
US	2004/0247648	Fast dissolving consumable films containing a modified starch for improved heat and moisture resistance	David et al.
US	7,025,983	Fast dissolving orally consumable films	Leung et al.
US	7182964B2	Dissolving thin film xanthone supplement	Kupper et al.
US	7,241,411 B2	Thin film strips	Berry et al.
US	6824829B2	Process for manufacturing Thin film strips	Berry et al.
US	7,470,397	Disintegratable films for diagnostic devices	Meathrel et al.
US	7579019B2	Pharmaceutical carrier devices suitable for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al.

US	20100215774	Film comprising nitroglycerin	Maibach and Todd
US	7946296B2	Dissolvable tobacco film strips and method of making the same	Wern et al.
US	20110305768A1	Quick dissolving oral thin film for targeted delivery of therapeutic agents	Hai-Quan Mao et al
WO	2012103464A2	Oral thin film vaccine preparation	Brian Pulliam
WO	2013085224A1	Bitter taste masked oral thin film formulation of Sildenafil citrate	Dae Kun Song et al.
EP	1680079A2	Rapidly disintegrating films for delivery of pharmaceutical and cosmetic agents.	Scott D Bamhart et al.
EP	2509631A4	Ph sensitive compounds in taste masking within oral thin film strips	Mark Schobel et al.
WO	2012053006A2	Improved oral fast dissolving films comprising combination of polymers and method of preparation thereof	Rajesh Jain et al.
WO	2014183054A1	Thin film with high load of active ingredient	Eric Allen et al.
US	7132113B2	Flavored films	Zerbe et al.
US	4136145	Medicament carriers in the form of film having active substance incorporated there in	Fuchs et al.
US	7267718B2	Pullulan filmcomposition	Scott et al.
US	7347985B2	Breath freshening and oral cleaning product with magnolia bark extract	Maxwell et al.

Table 4 List of some marketed products available as fast dissolving films

Product	Manufacturer	API	Uses
Listerine	Pfizer	Cool mint	Mouth fresheners
Triaminic	Novartis	Dextromethorphan	Cough suppressants
Suppress®	InnoZen®, Inc	Menthol	Cough suppressants
Gas-X	Novartis	Simethicone	Anti Flatuating
Theraflu	Novartis	Dextromethorphan	Cough suppressants
Ondansetron ODF	Setofilm	Ondansetron	Anti emitic
Donepezil film	Labtec	Donepezil Hcl	Alzheimer's disease
Klonopin Wafer	Solvay Pharm	Clonazepam	Anti anxiety
Benadryl	Pfizer	Diphenyhydramine	Antiallergic
Orajel	Del	Menthol/pectin	Mouth f fresheners
Chloraseptic	Prestige	Benzocain/menthol	Sore throat
Sudafed PE	Wolters KH Inc.	Phenylepinephrine	Congestion

Marketed products of oral films

A review of marketed products of FDF is compiled in the Table 4.

Future scope of development and conclusion

The formulation of a drug into various films has been popular in recent years. Several undesirable disadvantages associated with conventional dosage forms such as inconvenience of administration; lower bioavailability and patient non-compliance have pushed the development of novel polymeric thin films as a drug delivery platform. This drug delivery platform is being under observation from both start-up and recognized pharmaceutical companies. The companies endeavor to design a broad range of thin films for oral, buccal, sublingual, ocular and transdermal routes. Consequently, as an alternative to conventional dosage forms, polymeric thin films are predictable to stand out as a dosage form to conquer the limitations posed by existing dosage forms. The film dosage form meets several challenges during the phases of formulation development and manufacture. Such issues should be addressed to optimize the overall formulation even after transferring to large-scale manufacturing. The future looks very promising for the film technology in the time to come as new technologies are quickly introduced to prepare thin films.

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