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Oral Film Technology: Challenges and Future Scope for Pharmaceutical Industry

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ABSTRACT

The review is to enlighten the present and future prospective of oral film technology. Recent years, the research groups are focusing on this technology. Amongst Oral Drug Delivery System, Oral film Technology (OFT) is gaining much attention. The advantages of Oral film Technology are the administration to pediatric and geriatric population where the difficulty in swallowing and larger oral dosage forms is eliminated. It is an alternate platform for molecules that undergo first pass metabolism. Oral films are formulated using polymers, plasticizers, colours, flavors and sweeteners. The oral film is manufactured using solvent casting method, hot melt extrusion method, rolling method and solid dispersion method. The Oral film Technology is a good tool for product life cycle management for increasing the patent life of existing molecules or products.

INTRODUCTION

The most agreeable route for the patients is oral route preferred by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form [1]. Peroral dosage form can be distinguish as solid or liquid oral dosage form in which prior fall in the category of pills, capsules, granules and powders while the latter include solution, suspension or emulsions offering more advantages over monolithic dosage from [2].

Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking [3]. Apart from this solid dosage form shows lower bioavailability, long onset time and dysphagia. Patients turned the manufacturer to the parenterals and liquid orals [4].

While the liquid dosage form posses certain disadvantages such as finding non toxic excipients , and need preservative which might causes adverse effects in children, microbiological stability and also shows the problem with accurate dosing are, and pain associated with parentrals drug delivery. This has made the pharmaceutical industry look for alternative dosage form of drug delivery by oral route. 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, formulated the fast dissolving tablets by using superdisintigrants and hydrophilic ingredients which has the higher bioavailability, quick action and most patient compliance. Many FDTs are prepared by using the expensive lyophillisation process and sometimes difficult to carry, store and handle (fragility and friability) and also fear of chocking with fast dissolving tablet [5].

Therefore research in the oral drug delivery segment has led to evolution of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet and fast dissolving tablets. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times [4].

For the past one decade, an enhanced demand is seen to develop patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms [6].

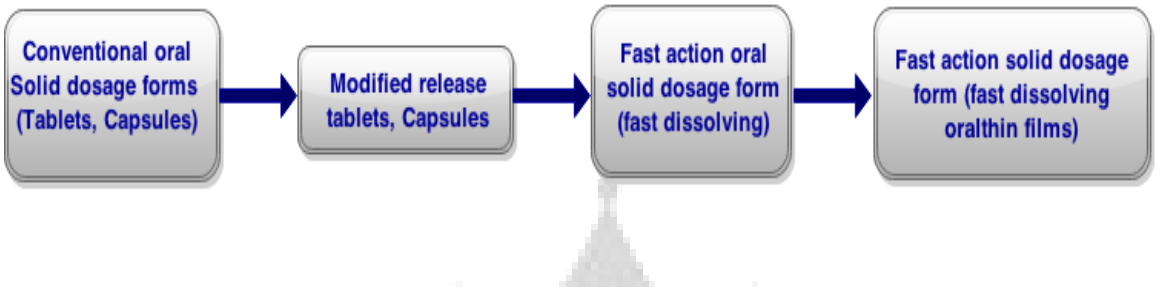

Figure 1: Stages in the development oral solid dosage forms

The Pharmaceutical industry is no stranger to the use of thin polymer film for the drug delivery as many prescription and OTC preparation comes in the form of transdermal patches [7]. However oral delivery route is preferred route for administering therapeutic agent, the idea of orally dissolving film as a drug delivery vehicle has attracted considerable attention in recent years.

Oral film originally been developed as novelty confection. The first of the kind of orally dissolving film was developed by the major pharmaceutical company Pfizer, who named it as Listerine® pocket packs™ and was used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films (OTF) which contained 7 benzocaine and were used for the treatment of sore throat and in some over the counter medication such as Flu Thin Strips®, Sudafed PE Quick Dissolving Films®, and Gas X Strips® [7-8].

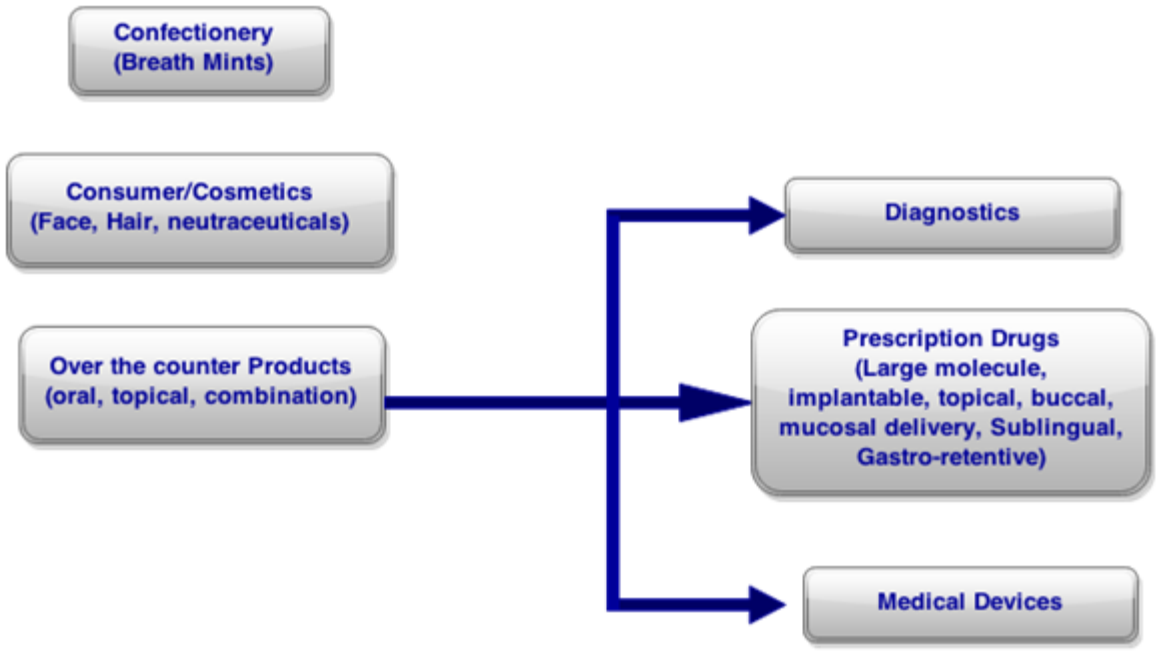

Figure 2: Evolution of oral thin films of oral

General Attributes of oral films

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Dissolving film delivery is vehicle, essentially just a thin flexible sheet of polymer in which active pharmaceutical ingredient (API) incorporated. Oral thin films are loaded with active substances. The thin films are taken orally and dissolve immediately in the mouth or applied to the mucosa. For transmucosal films, the active substance enters the bloodstream directly via the oral mucosa, without having first pass through the gastrointestinal tract.

Oral thin films (OTF) are thin, flexible films for drug delivery. They are placed on or under the tongue, where they dissolve. Transmucosal films are absorbed by the body directly via the oral mucosa. The excellent blood supply to the oral mucosa means the active substance enters the bloodstream immediately [9].

Depending on the nature and desired dosage that the film is to deliver the API either dissolved or suspended as crystal or amorphous particles in the polymer matrix of the film. Size and thickness of oral dissolving film product is largely depend on dosage of API that is intended to deliver but the physical attributes are also influenced by disintegrating characteristics that the film is

intended to have: a higher surface to mass ratio for a strip of film shows raid disintegration time than lower one. In general oral dissolving films tends to be few square centimeters in surface area and are typically 50 to 150 um (2-6 mils) thick. These dosage types are usually intended to dissolve as quickly as possible on the order of few seconds [7].

The thickness of a typical film ranges from 1 to 10 mm and its surface area can be 1 to 20 cm^2 for any geometry. At the same time, the rapid hydration rate facilitates an almost immediate softening of the film upon application in the oral cavity. The wet-tack and mucoadhesive properties of the system are designed to secure the film to the site of application.

The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for thickness of 2 mm. The drug is released from the dosage form upon disintegration and dissolution. The disintegration and dissolving times are prolonged as the film thickness increases [10]. Film texture is the primarily the matter of consumer preference. The physical feel applicability of the film can have an influence on patient compliance.

Classification of Oral Films [4,11]

There are three different subtypes

1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained-release wafers

Sub type	Flash release wafer	Mucoadhesive melt-away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4
Thickness (μm)	20-7	50-500	50-250
Structure	Film: single layer	Single or multilayer System	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid Solution
Application	Tongue(upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds Maximum 8-10 hours	Disintegration in a few Minutes forming, gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Advantages of oral films [4,7, 11]

- Dissolving film, as drug dosage form encompass many of the benefits of both liquid and solid dosage form. Little tablet, a film physical structure and its low moisture content make it inhospitable environment for microbial growth, which minimizes the need to incorporate preservatives and affords greater stability and shelf life.
- Unlike traditional solid dosage forms, however, thin, flexible sheet of polymer are not friable, allowing them to resist the kind of physical degradation that would damage normal tablet and capsule.
- Greater stability also afforded by the packaging of the films: film strips can be individually wrapped in flat, seal packages practically devoid of air. Therefore they are exposed to atmospheric moisture and oxygen only at the time of administration.

- Dissolving films are portable dosage forms, single doses of medicine can be carried individually without need of secondary container.
- In contrast with the traditional dosage form like tablet and capsule, a strip that is administered orally, dissolved rapidly in the ambient mucosal moisture and the resultant hydrated material function with the same rapid release characteristic as like typical liquid suspension or hydogel formulation.
- Accessibility of larger surface area leads to quick disintegration and dissolution in the oral cavity within seconds due to rapid wetting by saliva.
- One of the primary benefits of oral dissolving film is ease of administration to pediatric, geriatrics, bedridden patients and psychiatric patients who refuse to swallow tablets.
- Taste-masking technique is used to avoid the bitter taste of drugs. So these are used for paediatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improved clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Useful in cases where a rapid onset of action required such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma.
- Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.

Manufacturing of Film

Formulation of Oral Film involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc. From the regulatory perspectives, all excipients used in the formulation of Oral Film should be

Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms [4].

There are different types of ingredients required for the formulation of oral films.

a. Film forming agent

These ODFs contain film-forming polymers such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), pullulan, carboxymethyl cellulose (CMC), pectin, starch, polyvinyl acetate (PVA), and sodium alginate [12]. These polymers are water soluble and can be used alone or in combination to obtain the desired strip properties. They comprise the physical structure of the films, affording their integrity. The robustness of the strip depends on the type of polymer and the amount in the formulation [13]. Polymers are selected not only for the physical characteristics that the impart to the films but also for the rate at which they dissolves. The dissolution rate of dissolving polymer is inversely related to the molecular weight of the polymer, and will in turn dictate the rate at which medicine deliver [7]. As the film forming polymer (which forms the platform for the Oral Film) is the most essential and major component of the Oral Film, at least 45% w/w of polymer should generally be present based on the total weight of dry Oral Film [14].

b. Plasticizers

It improves the flexibility of film and decrease the brittleness of the polymer film. The selection of plasticizers depends on the compatibility with polymer, method of formulation and the nature of solvent.

Plasticizers such as glycerin, sorbitol Propylene Glycol, Glycerol, castor oil, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters, can be added to the formulation to alter mechanical properties of final film. By lowering the glass transition temperature of the polymers more structurally pleasant, stronger and a flexible film can be prepared [7, 16]

c. Flavoring and sweetening agent:

The flavors enhance the acceptance of the formulation and enhance the elegance properties of film. Flavoring agents can be selected from the synthetic flavor oil, oleo resins, extracts derived from various parts of the plant like leaves, fruits, and flowers. Any flavor can be added such as essential oil or water soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary. Flavors are such as vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple.

Sweeteners use to mask the bad odour and bitter taste of the drugs. Both type of sweeteners are used, natural and synthetic sweeteners i.e. monosaccharide's, disaccharides and polysaccharides such as galactose, glucose, mannose, fructose, xylose, ribose, dextrose, maltose, sucrose, sugar, sorbitol, xylitol, mannitol and soluble saccharin salts, saccharin, cyclamate salts, acesulfam-K, Aspartame, Neotame respectively [11,17-18].

d. Surfactant

These are used to enhance the solubility and wetting property of film to release within minute the drug. There are many surfactants which are used i.e. benzalkonium chloride, sodium lauryl sulfate, benzathonium chloride, tween and polaxamer.

e. Thickener and Stabilizers

These stabilize and enhance the viscosity i.e. xanthan gum, carrageenan and derivatives of cellulose [16].

f. Saliva stimulating agent

These activate the salivary gland to produce the saliva which helps in rapid disintegration of the film. These agents are used alone or in combination between 2-6% w/w of the strip. Some acids are used as saliva stimulating agent i.e citric acid, ascorbic acid, lactic acid, tartaric acid [11,16].

g. Coloring agents

Coloring agents may include FD & C coloring agents, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc oxide. These agents are added to lower quantities than would be needed in liquid formulation because dissolve film hydrated with trace amount of moisture, is highly concentrated.

Manufacturing Methods

The manufacturing of orally dissolving films is done by various methods such as:

1. Solvent casting method
2. Hot melt extrusion method
3. Semisolid casting method
4. Rolling method
5. Solid dispersion extrusion

One or a combination of the following process can be used in the manufacturing of ODFs.

1. Solvent casting method

Solvent casting is the centaury-old film making process. For pharmaceutical application, API either suspended or dissolved in solution of polymers plasticizers and other ingredients dissolved in volatile solvent like water and ethanol. This material, referred to as the film dope, is spread out, using classical solvent-cast film deposition methods, onto a continuous roll of release media, like plastic-impregnated paper. The coated media is passed through a drying apparatus, such as an oven or a convection chamber, to drive off the solvents. The dried film is then die-cut into strips and packaged individually in sealed, atmospherically resistant pouches. Solvent-casting is ideal for manufacturing films containing heat-sensitive API's because the temperatures required to remove the solvents are relatively low compared to those needed for a hot-melt extrusion process. However, the dried solvent-cast films may contain trace amounts of residual solvents, which have present issues with compendial compliance.

The properties of the API play a critical role in the selection of a suitable solvent. The physicochemical properties of the API should be considered. These properties include compatibility of the API with other film-forming excipients, compatibility with solvents, the

polymorphic nature of the API selected, and temperature sensitivity. Manufacturing and packaging ODFs requires special precaution to be taken to control the effect of moisture. Figure 3 indicates critical factors involved in ODF manufacturing using the solvent-casting method. Stability of the film and its mechanical properties are significantly affected by the presence of moisture. Another factor requiring strict control is temperature. Controlled temperature conditions are required for maintaining the viscosity of the solution and temperature sensitivity of the API.

Specific types of equipment such as rollers are required for pouring the solution on an inert base. The clearance between the roller and the substrate determines the required thickness of the film. The final step, drying the film, removes the solvent and helps to obtain the finished product. Usually, glass, plastic, or teflon plates are used as an inert base for film casting. When the manufacturing technology is transferred from laboratory scale to production scale, several problems can be encountered. These problems include the casting of the film, obtaining uniform thickness of the film, and proper drying of the sample. The selection of the proper type of dryer is needed in the final step of drying.

Figure 3. Crucial factors involved in manufacturing orally disintegrating films using the solvent-casting method

Once the films are dried, cutting, stripping, and packaging is done. Suitable size and shapes of films can be cut. The commonly available sizes of films are 3 x 2 cm^2 and 2 x 2 cm^2. Selection of the packaging container is an equally important parameter for the ODF. The packaging container should provide sufficient mechanical strength to protect the film during shipping and from external factors such as temperature and humidity. Depending upon the characteristics of the film, single-unit containers and multiple-unit dispensers can be selected. The packaged films are inspected before being packed into a secondary packaging container [7,13].

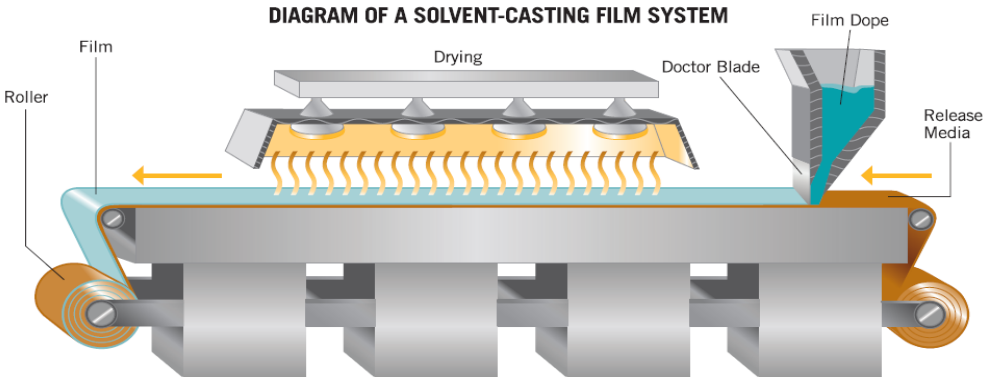

Figure: 4 Diagram of a Solvent-Casting Film System

Advantages

- Solvent-casting is ideal for manufacturing films containing heat-sensitive API's because the temperatures required to remove the solvents are relatively low compared to those needed for a hot-melt extrusion process.
- Better uniformity of thickness and bitter clarity than extrusion.
- Film has fine gloss and freedom from defects such as lines.
- Film has more flexibility and better physical properties.

2. Hot melt extrusion [7,13,17]

HME is commonly used to prepare granules, sustained-release tablets, and transdermal and transmucosal drug-delivery systems. The HME process recently has gained popularity in the pharmaceutical industry. Based on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers, and plasticizers into various final forms to achieve desired drug-release profiles.

In hot-melt extrusion, the dry ingredients for the film are heated and homogenized by the action of an extruder screw until they are molten and mixed. The melted material is forced through a flat extrusion die that presses extrudate into the desired film shape. The thickness and strength of the film can further be affected by elongation rollers while the material is still hot and pliable. The extruded film is then cooled, cut and packaged

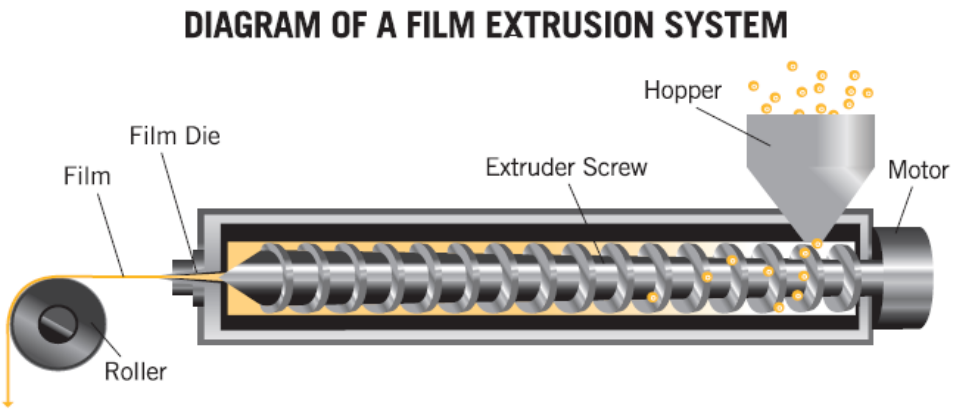

Figure 5: Diagram of a Film Extrusion System

Advantages of HME for film formation include the following

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.
- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high-shear methods.
- Minimum product waste.
- Possibility of scale-up.
- Good control of operating parameters.

Table 1: Comparison of the solvent-casting and hot-melt extrusion method for manufacturing orally disintegrating films

Manufacturing technique	Solvent Casting	Hot-melt extrusion
API selected	Thermolabile, thermostable	Thermostable
Solvent required	Yes	No
Process	Hydrous	Anhydrous
Equipment required	Rollers, coaters	Hot-melt extruder
Scale-up	May create problems	May not be difficult
Change of air entrapment	High chance	Low chance

The primary drawback of hot-melt extrusion is that it subjects the film ingredients to high temperatures, which can cause thermal degradation. All the ingredients that are used in a hot-melt film must also be devoid of water or any other volatile solvents. The heat of processing will cause such contaminants to boil and create voids in the film, affecting its uniformity, strength and appearance.

3. Semisolid casting

In semisolid casting method firstly solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4 [18].

4. Solid dispersion extrusion

The term solid dispersion refers to the dispersion of one or more APIs in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers using methods such as HME. In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies [19].

5. Rolling method

In rolling 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 cut into desired shapes and sizes [5].

Future Scope

Oral drug delivery technologies form an integral part of the pharmaceutical industry. From the conventional tablets/capsules to modern-day fast disintegrating and rapidly acting tablets / films, the market has come a long way. Lower bioavailability of oral solid drugs, inconvenience of administering injections, inaccurate dosing by liquid formulations have turned the focus of pharmaceutical companies to develop novel oral dosage forms that eliminate several known limitations. Oral thin films are able to meet most of these challenges. The concept isn't new and several over the counter oral thin films are readily available. Good acceptance from the users and an increasing demand of over the counter oral film products has led to the development of prescription drugs into oral thin films. These films not only offer a range of benefits to specific patient population segments but also provide a number of additional benefits to other stakeholders in the industry. The emerging area has gained attention from both established and start up pharmaceutical firms. Companies are utilizing their oral thin film technologies to develop different types of oral thin films (e.g. oral dispersible, sublingual, buccal). In addition to the drugs, several hormones and vaccines are also being formulated into oral thin films with the aim of providing improved patient compliance. Some of the key players in this area include MonoSol Rx, Applied Pharma Research/Labtec GmbH, BioDelivery Sciences and NAL Pharma. Many companies are collaborating with these technology providers and utilizing oral thin films as a life cycle management tool for their branded drugs that have lost patent in other dosage forms.

There are not many prescriptions for oral thin films currently available in the market; however, the pipeline holds a wider promise. Despite the uncertainties related to the development, approval and penetration rate, the market is likely to witness stable growth in the coming decade**.**

Many patients primarily pediatrics, geriatric and dysphasia find it difficult to swallow traditional tablets and capsules. Moreover, some diseases require rapid onset of action. This is possible through injections; some patients, though, find it inconvenient and painful to administer injections. Oral thin films provide the best alternative dosage form for administering drug for such patients. It is important to highlight that less prescriptions of oral thin film products are commercially available yet. Several companies are developing innovative technologies to formulate oral thin films, which provide the advantage of rapid dissolution without the need of water and rapid onset of action when delivered through mucosa.

Clinical and regulatory aspects

In the US Food and Drug Administration (US FDA), if the product is bioequivalent to that of the existing oral product the drug, an Abbreviated New Drug Application (ANDA) route is followed. There is no clinical studies associated on this generic approval processes (section 505 (j) of the Food, Drug, and Cosmetic Act). The example of such case would be a comparative bioequivalence between an orally disintegrating tablet (ODT) formulation and orally dissolving film (ODF) product. However, developed oral film product may exhibit different pharmacokinetic profile compared to the existing marketed product. The ODF 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 new clinical study is that it would award 3 years of marketing exclusivity to the product. Preclinical toxicity studies are not required if the molecule is the same as that of the approved product. Safety, tolerability, and efficacy features are to be demonstrated in such trials. Oral mucosa-irritation testing is carried out in both animal models and humans. In Europe, marketing authorization approval is essential as per the European Medicine Evaluation Agency guidelines. Either of the two modes, that is, decentralization procedure or mutual recognition process can be adopted.

Applications of OTF in Drug Delivery Systems

- Oral mucosal delivery via sublingual, buccal, and mucosal routes by use of oral thin film could become preferential delivery method for therapies requiring rapid drug absorption, including those used to manage pain, allergies, sleep, and central nervous system disorders.

- Topical applications: The use of dissolvable films may be feasible in delivery of active agents such as analgesic or antimicrobial agents in the wound care and other applications.
- Gastrorententive delivery system: Dissolvable films are being considered in the dosage form for which water soluble and poorly soluble molecules of various molecular weight are contained in film format. Dissolution of film could be triggered by pH or enzyme secretion of gastrointestinal tract (GIT) and could potentially be used for treatment of gastrointestinal disorder [8].
- Diagnostic devices: Dissolvable films may be loaded with sensitive reagent to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device [22].
- Vaginal drug delivery system: Films that are intended for vaginal administration can be applied manually, without mess or inconvenience of gel or cream applicator. Upon contact with vaginal fluid, the film forming ingredients hydrates to form an ad hoc hydrogel that functions as a normal vaginal product. [7]

Challenges in Formulation Development of Fast Dissolving Oral Films

Technology catalysts give an idea of the market for drug products of oral thin film formulation which is valued at $ 500 million in 2007 and will be reached to $ 2 billion in future. Now a day, oral film is an alternative in the market due to patient's preference to tablets and capsules. Oral thin film technology is still in the beginning stages and will be the first preference of patient in future. Since 2003, North America is having more than 80 oral thin films brands but, the market remained limited when compared to oral dissolving tablets. In US market, the OTC films of pain management and motion sickness are commercialized. Now, prescription oral films have been approved in three major countries i.e. US, EU and Japan. These approved films have a potential to dominate over other dosage forms of same drugs. It seems that value of oral film market will grow significantly [5].

Today, huge literature is available on formulation, development and evaluation of oral fast dissolving or fast disintegrating tablets and films. However, formulator comes across with some challenges while development of such dosage forms. There is need to address such challenges which may help in future to explore the particular area in research and that may help in overall

formulation and development. These challenges are directly related to patient compliance. Hence, preference should be given to them in formulation and development.

Following are some of the challenges in formulating fast dissolving oral film and trying to elaborate and solve these problems. These challenges are directly related to patient compliance.

These include

1) Insolubility of drug

2) Taste masking of bitter and obnoxious drug

3) Reduction in drying time of film

4) High dose incorporation in film

5) Co-administration of drugs

6) Stability of film against humidity and temperature

7) Need special packaging

8) Dose uniformity

1. Insolubility of drug: Solubility plays a rate limiting parameter to get desired concentration of drug of orally administered formulation in systemic circulation. Problem of solubility is a main challenge for formulation of oral film of BCS class II drugs having low solubility and high permeability [20].

2. Taste masking of bitter and obnoxious drug:

Taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the paediatric and geriatric population. Taste is an important parameter in case of fast dissolving oral film. Oral film has to remain in contact with oral mucosa until it completely dissolves in saliva in oral cavity. For this, taste of bitter drugs should be masked. So, taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the paediatric and geriatric population [21].

3. Reduction in drying time of film

Drying time plays an important role in oral film formulation and also in case of rate of production of oral film in industries. Generally, hot air oven is not used for drying of oral film of

thermo labile drugs. So, oral film is dried at room temperature. But, it takes more time to dry (about one day).

Panchal M. S.et.al. (2012) has reported that time taken by formulation for drying was found to be 24 hours at room temperature for the formulation of mouth dissolving film of Ropinirole hydrochloride prepared by using Pullulan polymers [26]. 35°C temperature for 12 hours was used by Jadhav S. D. et.al. (2012) for drying fast dissolving oral film of Levocetirizine Dihydrochloride [22].

4. Dose incorporation in film

Dose of drug in oral film formulation can be increased by increasing area of container. Only area should be increased keeping thickness of formulation solution constant so that volume of solution needed for formulation is also increased which help in incorporation of high dose and reduction in drying time also. [23]

5. Co-administration of drugs

Use of more than one drug i.e. co-administration of drugs is a very difficult task in oral film formulation. Because, it may affect disintegration time as well as dissolution rate of formulation [23].

6. Stability of film against humidity and temperature

Fast dissolving oral film consists of about 45% of polymer which is hydrophilic in nature. In the humid atmosphere, film will absorb water and get liquefied due to dissolution of film in water. So, the stability of film against humidity is very difficult and challenging task. Amorphous drugs often have higher dissolution rates than their crystalline forms, but lower physical stability during storage. Addition of crystallisation inhibitors such as hydrophilic polymers to the amorphous drug to form a film formulation is the best method to prevent drug crystallization [24].

7. Need of special packaging

In the pharmaceutical industry, it is vital that the package selected adequately preserve the integrity of the product. A variety of packaging options are available for fast dissolving films. An aluminium pouch is the most commonly used packaging material. APR- Labtec developed the

Rapid card, patented packaging system designed for the Rapid films. The rapid card has same size as a credit card and holds three rapid films on each side. Every dose can be taken out individually [25].

8. Dose uniformity

Film which is to be made in a container has to cut into desired area containing required dose of drug. So, to get a uniform dose in all films which cut into desired area is a challenging task.

CONCLUSION

Oral dosage forms remain the primary delivery route for pharmaceuticals because of ease of administration and beneficial release characteristics. A number of pharmaceutical dosage forms are available in the market. A number of pharmaceutical dosage forms are available in the market. There are problem of tablets and painful parenteral dosage forms. Fast dissolving oral film has many advantages related to disintegration, dissolution and bioavailability over these existing dosage forms. In addition to this, film avoids first pass metabolism due to pre-gastric absorption and fast onset of action. Patient compliance is high in all age groups patients especially paediatrics and geriatrics. However, the pharmaceutical industry's interest has increased in this delivery forms that administer medicines directly through vehicles, like transdermal patches, and drug-impregnated medical devices, like intravaginal rings. The rapidly dissolving film drug delivery vehicle bridges the gap between the two ideas, incorporating positive elements from both solid and liquid dosage forms into an elegant, stable, and effective delivery vehicle. But, this film dosage form has come across some obstacles during its formulation and development. So, there is need to address such challenges which may help in future to explore the particular area in research and that may help in overall formulation and development and large scale manufacturing.

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