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ORAL THIN FILM TECHNOLOGY- CURRENT CHALLENGES AND FUTURE SCOPE

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Abstract: *Over the past few years, Oral Thin Films (OTFs) have intrigued scientists and researchers in the domain of pharmaceutical formulations and are being looked upon as a novel approach to designing efficient drug delivery systems. OTFs are currently speculated to be an alternative to the conventional solid and liquid oral dosage forms. Oral Thin Films are dissolving films or oral drug strips to administer drugs via their adsorption in the mouth, ensuring that the drug directly enters systemic circulation. The thin films enable the drug to bypass the first pass metabolism, have quick action, are more convenient for pediatric and geriatric patients where problems of swallowing or nausea are generally encountered, are easy to transport and package and have many such advantages over traditional dosage forms. However, the commercialization of these OTFs has been limited majorly to the American, Japanese and European Union markets only for a restricted number drugs. There is extensive research going on to enable different types of drugs to be formulated into these strips and to overcome certain challenges confronted during manufacture, scale up and the cost effectiveness of the OTFs. The presented review focuses primarily on the different manufacturing processes adopted for making the OTFs like Solvent Extraction, Hot Melt Extrusion, Semi-Solid Casting, Solid Dispersion Extrusion and innovative ones like Flexographic PrintingTechnologies and the technical and economic difficulties that manufacturers encounter during their large scale production. It also describes the current trends in the OTFs market and its future scope worldwide and in India and analyses the feasibility of this innovative approach in terms of the current knowledge and technological resources available.*

Keywords: *Oral Thin Films (OTFs), drug delivery, extrusion, first pass metabolism.*

1. INTRODUCTION

A pharmaceutical formulation is a system that comprises of the active drug, combined with other pharmaceutical ingredients to produce a complete and biocompatible medical product. Tablets, capsules, sprays, creams and syrups are all widely known and accepted pharmaceutical formulations. A drug delivery system has a significant impact on the therapeutic efficacy of the drug. Oral formulations are the most preferred form of drug delivery systems as they are convenient, cost effective and easy to administer. However the oral route may be problematic for pediatric and geriatric and choking where problems of swallowing are prevalent. As a result of this, Oral Thin Films (OTFs), also known as orodispersible film by the European Medicines Agency have attracted significant research and acceptance recently. The idea of OTFs was first presented in the 1970s [1] to overcome swallowing difficulties that the traditional dosage forms like capsules and tablets exhibited. Fast dissolving oral films were first introduced in the market as breath fresheners and personal care products such as dental strips and soap strips. 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[2]. However, the United

States and European markets have rapidly evolved them as efficient drug delivery platforms. An OTF is essentially a dissolving film or drug strip to administer drugs by adsorbing them in the mouth either buccally or sublingually. The films are essentially made using hydrophilic polymers that dissolve rapidly on the tongue or in the buccal cavity. Thus the drug is delivered directly to the systemic circulation thereby bypassing the first pass metabolism, where a major loss of drug generally occurs in the case of conventional dosage forms. Ease of administration, patient compliance and cost effectiveness in the development of formulations are some of the major advantages of these thin films. Various manufacturing processes are currently being employed while many new ones are being developed for the production of Oral thin Films. However the widespread consumer acceptance of any novel technology depends mainly on its cost effectiveness. The presented review paper focuses primarily on the different manufacturing processes adopted for making the OTFs like Solvent Extraction, Hot Melt Extrusion, Semi-Solid Casting, Solid Dispersion Extrusion and non-conventional ones like Flexographic Printing Technologies along with the technical and economic difficulties that manufacturers

encounter during their large scale production. It also describes the current trends in the OTF market and its future scope worldwide as well as in India and analyses the feasibility of this innovative approach in terms of the current knowledge and technological resources available.

2. ADVANTAGES AND DISADVANTAGES

2.1 ADVANTAGES OF ORAL THIN FILMS

Oral Thin Films have the advantages [1, 2] listed below, which have made them potential alternatives to conventional dosage forms:

2.1.1 Advantages over Traditional Dosage Forms

i. OTFs have enhance the bioavailability of the drug which leads to quicker action
ii. Drugs bypass the first pass action unlike in the case of conventional dosage forms and hence the amount of drug required to be loaded is reduced.
iii. Thin Films have greater stability especially compared to liquid dosage forms that require various additives in order to extend their shelf life.
iv. They do not require special packaging as the drug is loaded into an abuse resistant matrix.
v. OTFs are less friable as compared to tablets [3, 4]
vi. Research has proven that, OTFs have lesser side-effects
vii. The higher surface area available in the oral cavity leads to faster disintegration and dissolution of the strip [5]
viii. Easily portable

2.1.2 Clinical Advantages

i. The administration is easy as it employs the oral route
ii. The patients do not risk choking or suffocation, especially in the case of pediatric and geriatric patients[6]
iii. The OTFs are a better alternative for patients with nausea
iv. OTFs are not required to be swallowed with water

2.1.3 Market Advantages:

i. This novel drug delivery `system presents pharmaceutical companies with patents on the verge of expiration to extend their revenue cycles.
ii. OTFs dissuade the misuse, tampering and abuse associated with some prescription drugs as the Film is loaded with a certain amount of drug [7]:

iii. The Thin Films market is currently in its embryonic stages and limited only to certain over the counter drugs available in the American, Japanese and EU Markets. Thus, researches and companies have a wide scope in formulating drugs that haven't been previously formulated into OTFs and developing newer and cheaper technologies.

iv. In India, according to Indian Demographics for 2017 roughly 13.39% of the population are senior citizens while 45.7% are children. Thus, Indian investors have a wide consumer range and whereas this technology is only inchoate in our country.

2.2 DISADVANTAGES OF ORAL THIN FILMS

i. A major manufacturing difficulty that confronts manufactures is the drying time required for the OTFs. Since thermo labile drugs prohibit the use of hot air ovens and high temperatures, it takes a day for the films to dry at room temperature thereby reducing the production rate.[7]

ii. The films are highly hygroscopic and tend to lose stability in environments having high RH

iii. It is difficult to achieve uniformity of dosage

iv. Drugs that are unstable at the buccal pH or irritate the mouth mucosa cannot be formulated into thin films.

v. The co-administration of multiple drugs remains to be a challenge as the dissolution time is affected.

3. COMPOSITION OF ORAL THIN FILMS

OTFs contain the following key ingredients [5]:

i. Drug or Active Pharmaceutical Ingredients (API)

Needless to explain, the drug is the core ingredient of these polymeric films and generally comprises of 5-30% (w/w) of the films.

Examples: antiallergic, antiemetic, antimigrant etc

ii. Film Forming Agents

Biocompatible and water soluble polymers are the backbone of the OTFs and carry the drug. Various natural and synthetic drugs are available for this purpose.

Multiple polymers can also be combined to achieve desired properties. The polymers must be non-toxic, no-irritant and devoid of any impurities.

Examples: HPMC E3, E5 and E15; K-3 Methyl Cellulose; A-3,A-6 and A-15 Pullulan; pectin, gelatine, Chitosan, cellulose, starch

iii. Plasticizers

Plasticizers improve the strength and flexibility of the polymeric matrix. They decrease the brittleness. Plasticizers are chosen based on the polymers involved and the method used for formulation.

Examples: Glycerol, Dibutyl phthalate, PE glycol

iv. Surfactants

Surfactants are essentially the solubility enhancers that also improve the wetting properties of the film to ensure rapid dissolution and drug release. Examples: Sodium Lauryl sulphate, Tween, Benzalkonium Chloride.

v. Sweetening and Flavouring Agents

Sweetening and flavouring agents are necessary for taste and odour masking of the drug and to increase the appeal of the film. This is an important factor for paediatric patients. Natural of artificial sweeteners and flavours can be incorporated.

Examples: Saccharin, Aspartame

vi. Saliva Stimulating Agents

The OTFs disintegrate on coming in contact with the liquid in the oral cavity which is essentially saliva. Saliva Stimulating Agents produce saliva that helps in quick disintegration and dissolution of the films.

Examples: Citric acid, Lactic Acid, Ascorbic acid

vii. Colorants

Colouring Agents are used to increase the appeal of the film. Pigments are used as colouring agents. Titanium dioxide is most widely used colorant in ODFs and various other pharmaceutical preparations. Apart from titanium dioxide, a full range of colours are available including FD and C, natural and custom pantone-matched colours.

The following table summarizes the general composition of a typical OTF [1]:

Ingredients	Amount (w/w)%
Drug	5-30
Polymer	45
Plasticisers	0-20
Surfactants	*As Required*
Sweetening and Flavouring Agents	3-6
Saliva Stimulating Agents	2-6
Colorants	*As Required*

4. TYPES OF ORAL THIN FILMS

OTFs are classified into 3 types [1]:

i. Flash Release

ii. Mucoadhesive Melt Away Wafers

iii. Mucoadhesive Sustained Release Wafers

The following table presents the properties that differentiate the aforementioned types of OTFs:

Properties	Flash Release	MucoadhesiveMelt Away Wafers	Mucoadhesive Sustained Release Wafers
Area (cm^2)	2-8	2-7	2-4
Thickness	20-70	50-500	50-250
Structure	Single Layer	Single or Multilayer	Multilayer system
Excipients	Soluble 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	Gingival or buccal region	Gingival or other suitable region in the oral cavity
Dissolution	60 s	In few minutes forming Gel	Maximum 8-10 h
Site of Action	Systemic or Local	Systemic or Local	Systemic or Local

5. METHODS OF MANUFACTURE

5.1 CONVENTIONAL METHODS FOR THIN FILM MANUFACTURE

5.1.1 Solvent Casting: In this process Active Pharmaceutical Ingredient (API) is either suspended or dissolved in the selected plasticizer. The other ingredients are dissolved in volatile solvent. The resulting material is known as Film Dope.

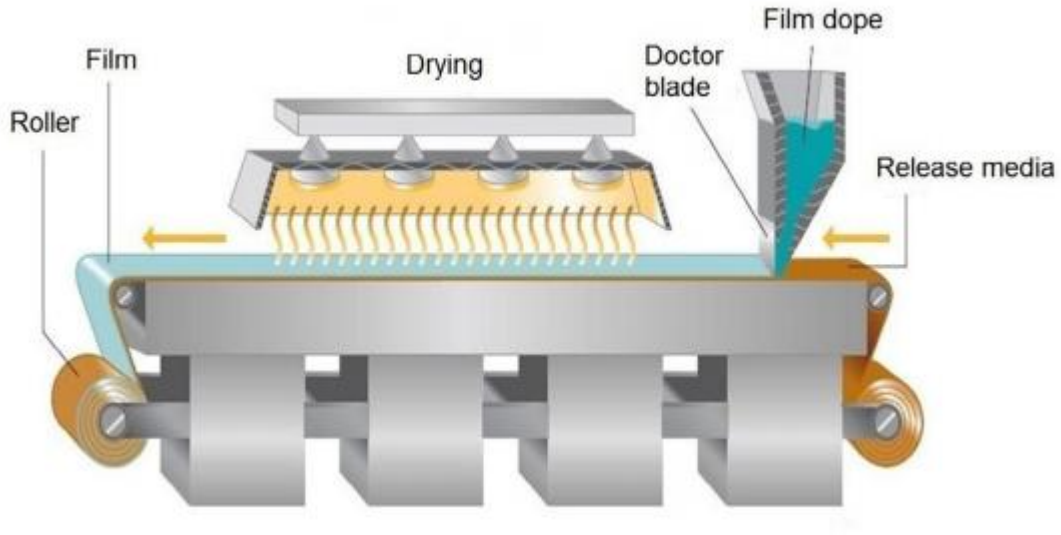

Figure 1: Commercial manufacturing of ODFs using solvent casting [1]

Using conventional solvent-cast film deposition method, the film dope is spread onto a continuous spread media like paper plasticizer. The solution is then dried to remove the solvents. Drying is performed in an oven or a convection chamber. The dried material is then die-cut in small pieces and packed in atmospherically resistant pouches.

This method is best for heat sensitive because the temperatures required for removing the solvent is low. The properties of API like compatibility, temperature sensitivity and polymorphic nature play an important role in selection of solvent. Various precautions need to be taken while producing ODFs like:

a. Effect of moisture: the strength is affected
b. Temperatures need to be maintained to ensure proper viscosity and temperature sensitivity.

Casting of the film, uniform thickness of the film and proper drying are important steps and need to be monitored properly. [2, 3] Also mixing step might lead to introduction of air into the mixture, hence proper de-aeration is required to ensure effective strength. [4]

5.1.2 Hot Melt extrusion: Major areas of production using HME are sustained-release tablets, transdermal and transmucosal systems. Using knowledge of polymers, formulators can extrude mixtures of plasticizers, drugs, polymers into various shapes and final forms for variation in drug release mechanism. In this process, the dry particles are heated by the action of extruder screw until they are molten and homogenized.

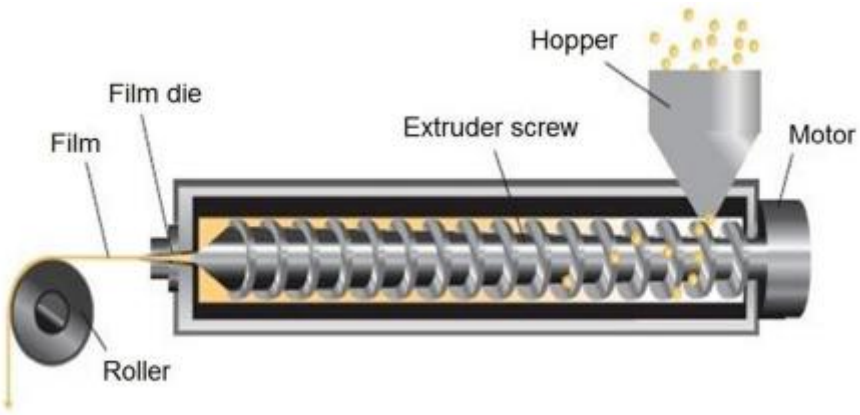

Figure 2: Manufacture of ODFs by Hot Melt Extrusion

The molten materials then passed through an extrusion die to get desired shape and size. The hot molten mass is passed over a roller to monitor the thickness and strength of the film. The extruded film is then cooled, cut and packed. Main advantages of this process include:

a) There is no need of using solvent or water
b) The operating parameters can be properly monitored.
c) Minimum waste
d) Fewer steps

However in HME, the substances are subjected to very high temperatures, which might lead to thermal degradation and loss of volatile substances. [2, 5, 6]

5.1.3 Rolling method: The drug is rolled along with the solvents in a carrier. The film is dried on the rollers and then cut and packed. The solvents used are generally water and volatile solvents. [7]

5.1.4 Semisolid casting: In this method, polymer is prepared which is water-insoluble. A separate solution of insoluble polymer is prepared in ammonia and sodium hydroxide. The two solutions are mixed together properly along with suitable amount of plasticizers to form a gel like solution. This gel like solution is passed over heat controlled drums to form thin films or ribbons. 1:4 is the ratio maintained between the amounts of acid insoluble polymer to the film forming polymer. Various acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate. [8]

5.1.5 Solid-dispersion extrusion: As the name suggests, the process involves the dispersion of one or more APIs in solid state in an inert carrier using methods like HME. The

immiscible components are extruded with the drug, which are further converted into solid dispersions. The dispersions are shaped into films using dies. [9]

5.2 NON-CONVENTIONAL METHODS FOR THIN FILM MANUFACTURE

The 3D printing technologies have gained tremendous impetus over the past few years and are emerging as platforms for manufacturing pharmaceutical products. These technologies have been adopted for production of OTFs and have the following advantages over the conventional methods of production:

i. Accuracy in drug loading, especially for potent drugs that are prescribed in small dosages
ii. Compatibility with different types of APIs including poorly water soluble, peptides and proteins.
iii. Homogeneity of the OTF which is challenging to achieve in the conventional methods
iv. Minimal wastage and efficient recycle leads to cost cutting.

Two of the major printing techniques, currently being looked upon by many manufacturers and researchers have been described below:

5.2.1 INKJET PRINTING

Inkjet Printing is a computer printing technology that creates digital images fed to the computer into 3D items by propelling drops of ink onto desired surfaces. [8]

Considering its applications in the pharmaceutical industry, Inkjet Printing can be divided into two main categories

i. Continuous Inkjet Printing (CIP)
ii. Drop on Demand Printing (DoD)

In CIP technique, there is consistent ejection of ink from a nozzle. Before reaching the nozzle, the ink stream is broken down into droplets by applying suitable acoustic waves. The drops are then deflected to reach their suitable position by subjecting them to an electric field. The degree of deflection depends on the amount of electric field to which the drop is subjected and thus the necessary pattern is generated. [9] The solvent used is volatile and vaporizes almost instantly after the drop falls, leaving behind our desired compositions

In DoD Printing, the drops are generated in multiple nozzles when voltages are applied, due to the change in shape of a piezo-electric material in the ink chamber that generated a pressure wave in the ink. [2]d

The major drawbacks of Inkjet printing are the high cost of equipment and maintenance and requirement of extremely skilled labour to handle these machines. Hence for industrial use, Flexographic Printing Technologies are better candidates.

5.2.2 FLEXOGRAPHIC PRINTING

This is a unique orienting technique that works on the principle of contact printing. [10] It consists of a Fountain roller that transfers the ink, containing the active ingredient in solution or suspension that transfers the ink further to an Anilox Roller. This roller accurately measures the amount of ink required for uniform thickness to the plate cylinder which holds the polymeric strip. Pressure is applied to print the ink onto the polymer. This process is advantageous as the film on which the drug is printed is already manufactured and dried. Thus the loss of activity of API due to heat drying is avoided. The production efficiency is high, considering an average of 530 oral films per minute. The drawbacks of this process are the manufacture of a large print roller and high risk of contamination.

These techniques, though highly innovative are confronted by certain challenges like the optimization and improvement of soft wares for a wide range of drugs and excipients, clinical survey to assess the efficacy, stability and safety in terms of long and short term side effects on the patients. [2] Also it must be ensured, that the usage of these techniques does not, in any way, alter the physicochemical or therapeutic properties of the API. It can be anticipated that a faster way to broaden areas of application of these techniques and to commercialize them is to combine them with conventional processes and then optimize, which will lead to a great increase in the OTF market.

Other than these there are a few patented technologies to manufacture OTFs. These include Xgel, Soluleaves, Wafertab, Foamburst and MiCap.

6. ECONOMIC ASPECTS

Due to the ease of application and high effectiveness, there is no surprise that the thin film drugs have recorded a high market acceptance. The technology has gained attention from both established and start- up pharmaceutical firms. The sale has been picked up significantly in economies such as U.S. and the countries in Europe. The drug products market in oral thin film formulations was predicted to be valued at$500 million in 2007 and could reach $2 billion by 2010. Further according to a research report, the global thin film drug manufacturing market is expected to be worth US$15,984.3 mn by the end of 2024

from US$7,337.8 mn in 2015, thus estimating an increase of 117% over 10 years. However, in 2015 there existed around 10 prescription products only and around 29 such thin film products under clinical trials. Thus, it can be anticipated that the manufacturing market is going to increase considerably in the coming years.

In the overall market of the thin films, oral thin films will remain the most promising due to the maximum advantages it has over others. The oral thin film segment is likely to surge at a significant CAGR of 18.3% between 2016 and 2024. Currently North America is emerging as the largest manufacturer of the OTFs with a share of 85.3%. Among the key players in the manufacturing are Pfizer, Inc., Novartis AG, Wolters Kluwer, Solvay, Allergan plc. Sumitomo Dainippon Pharma Co., Ltd., IntelGenx Corp. Some of the startups such as FFT Medicals and Cynapsus Therapeutics are also emerging. Around 38% of the products are based on the MonoSol's PharmFilm technology or Applied Pharma Research / Labtec'sRapidFilm technology.

However, Asia Pacific is expected to grow at the fast rate during the forecast period with major contribution of countries such as India, Japan and China. In view of this, Indian Investors are looking OTF as an excellent opportunity for business. New companies such as Aavishkar Oral strips Pvt. Ltd, Hyderabad; NU Therapeutics, Hyderabad; and ZYM Laboratories, Nagpur have been extensively concentrating on this technology. Bigger manufacturers like Cipla, Mankind and Dr. Reddy's laboratory are also working for the development of this technology.

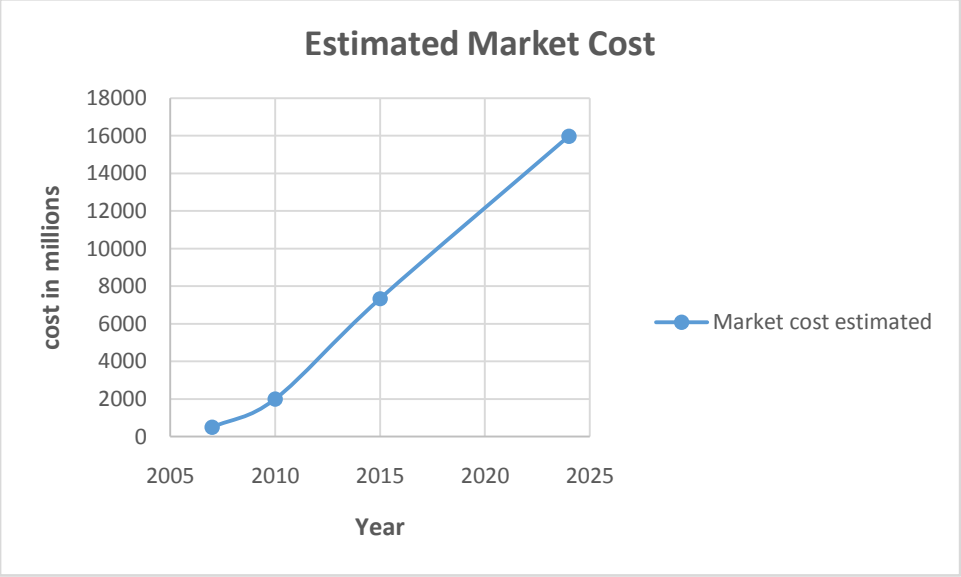

Figure 3: Estimated market cost of Oral Thin Films

Apart from drugs, hormones as well as vaccines are being formulated with OTFs with the aim of providing improved patient compliance. However it is important to note that the proscriptions available for the OTFs are less currently.

In general, OTFs are more expensive to develop and manufacture than the conventional ways of drug delivery. Currently they are considered only as an alternative for the patients with pediatric, geriatric and dysphasia disorders who find it difficult to swallow. Due to the established nature of the manufacture of the conventional tablets, the costs are cheaper than the OTFs.

7. CONCLUSION

Oral Thin Films are beyond doubt emerging as platforms for drug delivery. They have many advantages the major ones being their ease of administration in the case of pediatric and geriatric patients as also patients with swallowing difficulties and have accurate dosing and quick action. This being said, currently oral thin films target only a limited section of the consumer market. OTFs are currently more costly to develop and manufacture as compared to tablets. The OTFs currently available in the market are for a limited number of drugs manufactured by the major companies involved in research and production of these OTFs, which has led to monopoly and consolidation in the thin film market. Tablets have been around for a lot longer and hence their market is well established. OTFs could be alternatives to the convenient dosage forms. However there needs to be extensive research put into their manufacture and clinical studies. Though at present the OTF technology is confronted by many challenges, optimizing the research, formulation and manufacture shows a promising picture and huge scope for OTFs in the future.

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