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CURRENT REVEIW ON ORAL THIN FLIM- ALTERNATE FOR CONVENTIONAL DOSAGE FORM

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ABSTRACT

In the field of pharmaceutical formulations, oral thin films, or OTFs, have piqued the interest of scientists and researchers in recent years and are being considered as a cutting-edge method of creating effective drug delivery systems. At the moment, OTFs are being considered as a potential substitute for the traditional solid and liquid oral dose forms. Drugs are administered by oral thin films, which are dissolving films or oral drug strips that adsorb in the mouth and guarantee that the drug enters the bloodstream immediately. Thin films give the medication the ability to avoid first-pass metabolism, act quickly, are more practical for elderly and pediatric patients who frequently experience nausea or difficulty swallowing, are simple to package and transport, and offer numerous other benefits over conventional dosage forms. However, only a small number of medications have seen commercialization of these OTFs, primarily in the US, Japan, and EU markets. Numerous studies are being conducted to enable the formulation of various medication types into these strips and to address some of the issues encountered during production, scale-up, and the cost-effectiveness of the OTFs. The main focus of the review is on the various manufacturing techniques used to create OTFs, such as solvent extraction, hot melt extrusion, solid dispersion extrusion, and semi-solid casting, as well as cutting-edge techniques like flexographic printing technologies, and the financial and technical challenges that producers face when producing them on a large scale. Additionally, it outlines the present and projected global and Indian OTF market trends and evaluates the viability of this novel strategy in light of the available information and technology resources.

KEYWORDS: Oral thin flim, first -pass metabolism, conventional dosage forms.

INTRODUCTION

A pharmaceutical formulation is a system that consists of the active medication together with other pharmaceutical components to create a comprehensive and biocompatible medicinal product. Pharmaceutical formulations that are commonly recognized and accepted include tablets, capsules, sprays, creams, and syrups. The therapeutic effectiveness of a medicine is greatly influenced by its distribution method. Because oral formulations are practical, affordable, and simple to use, they are the most used type of drug delivery mechanism. However, in pediatric and geriatric settings where swallowing issues are common, the oral route may provide challenges. Because of this, oral thin films (OTFs), which the European Medicines Agency refers to as orodispersible film, have recently drawn a lot of attention and approval. OTFs were initially proposed in the 1970s[1] as a solution to the swallowing issues that conventional dosage forms, such as tablets and capsules, displayed. In the beginning, fast-dissolving oral films were sold as breath fresheners and personal hygiene items like soap and dental strips. The well-known pharmaceutical corporation Pfizer created the first oral dissolving film of its sort, which they called Listerine® pocket packs ™ and used to refresh mouths.[2]

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.

For the creation of oral thin films, a number of manufacturing techniques are already in use, and several new ones are being developed. Nonetheless, the cost-effectiveness of every new technology is the primary determinant of its broad market acceptability. Difference between OTF and ODT are mentioned in table1.

The main focus of the review paper is on the various manufacturing techniques used to create OTFs, such as solvent extraction, hot melt extrusion, solid dispersion extrusion, and semi-

solid casting, as well as unconventional techniques like flexographic printing technologies. It also discusses the financial and technical challenges that manufacturers face when producing these products on a large scale. Along with describing the OTF market's present patterns and potential future growth both globally and in India, it also evaluates the viability of this novel strategy in light of the available knowledge and technology resources.

Ideal properties of Oral Thin Flim

- It need to be able to pass through the oral mucosa.
- It ought to have an immediate impact.
- The pH of the oral cavity should ionize it.
- Medication should be soluble in saliva and extremely resistant to moisture.[3]

Marketed Advantage of Oral Thin Flim

- Pharmaceutical companies can extend their revenue cycles by using this innovative drug delivery method to extend their patents that are about to expire.
- The market for thin films is still in its infancy and is now restricted to a few over-the-counter medications that are sold in the US, Japan, and the EU. As a result, researchers and businesses can create new and less expensive technologies as well as medications that haven't been created into OTFs before.
- According to Indian Demographics for 2017, children make up 45.7% of the population while seniors make up 13.39%. As a result, Indian investors have a diverse client base, while this technology is still in its infancy in our nation.

Disadvantage of Oral Thin Films

- One of the biggest challenges manufacturers face is the drying time needed for OTFs. The manufacturing pace is decreased since it takes a day for the films to dry at room temperature because thermolabile medications restrict the use of hot air ovens and high temperatures.
- Achieving dose consistency is challenging.
- It is not possible to synthesize medications into thin films that irritate the oral mucosa or are unstable at the buccal pH.
- Multiple drug co-administration is still difficult since it affects the dissolving time.[4]

Composition of Oral Thin Flim

Active ingredients used in Oral Thin Flim

Absorption requires the dissolution of the API. A highly lipophilic active ingredient is insoluble in aqueous solution and may not be absorbed to the appropriate degree. Consequently, the drug's lipophilicity and solubility are delicately balanced. The main way that drugs are absorbed is by passive diffusion. Therefore, the degree of ionization, molecular weight, and partition coefficient all significantly affect how well medications pass through oral mucosal membranes. Bioavailability requires consideration of the degree of ionization at ambient pH and the pKa of the API. The lipophilicity or partition coefficient of the API typically determines the extent of absorption, although the drug's solubility is also important. The drug's non ionized form diffuses through cellular membranes because it exhibits more lipid-soluble qualities. There are no issues with uniformity in the way water soluble APIs are distributed. But for water-insoluble APIs to have a suitable level of content homogeneity, they must be dispersed evenly.[5][6]

How to use API in OTF

- It must be taken in little doses.
- It contains low molecular weight.
- It should be stable and soluble in saliva.[3]

Table no. 1: Difference between OTF and ODT Film Forming Agents.

S.NO	ORAL THIN FLIM	ORAL DISSOLUTION TABLET
1	Greater disintegration as a result of the greater surface area	Less surface area means less disintegration.
2	In comparison to ODTs, it is far more durable.	It is less durable than OTFs
3	High patient compliance	Low patient compliance

The core of the Oral Thin flim is water-soluble and biocompatible polymers that transport the medication. There are numerous synthetic and natural medications available for this use. The desired qualities can also be obtained by combining several polymers. Non-toxic, non-irritating, and impurity-free polymers are required. Example of flim forming agents are listed in [table no:2].

Table no 2: Flim forming agent.

EXAMPLE OF FLIM FORMING AGENTS	HPMC, Methyl Cellulose, Chitosan, cellulose, starch

Plasticizers

Plasticizers increase the polymeric matrix's pliability and strength. The brittleness is reduced by them. The selection of plasticizers is determined by the polymers and formulation technique. Examples are mentioned in [table no:3].

Table no 3: Plasticizers.

EXAMPLE OF PLASTICIZER	Glycerol Di butyl phthalate Poly Ethylene glycol

Surfactants

Surfactants basically act as solubility enhancers, improving the film's wetting qualities to guarantee quick medication release and dissolution. example of surfactants Sodium Lauryl sulphate.

Sweeteners

OTFs are sweetened with both natural and artificial sweeteners. The most often used polyhydric alcohols are mannitol, sorbitol, maltitol, and isomalt. Furthermore, polyhydric alcohols can be combined to give the mouth a pleasant, cool sensation. Additionally, polyhydric alcohols are less carcinogenic and do not leave a harsh aftertaste in the mouth. With the exception of xylitol and maltitol, which are both similarly sweet to sucrose, most polyols have a sweetening effect that is less than half that of sucrose. In diabetic individuals, the use of natural sugars in these formulations is limited. Artificial sweeteners are therefore most commonly used in food and pharmaceutical products. Aspartame and saccharin are frequently utilized as artificial sweeteners in OTFs.[7]

Coloring Agents

Formulations may contain up to 1% by weight of natural coloring agents, pigments, FD and C approved colorants, or EU approved colorants.

Flavoring Agents

The type of API to be utilized determines which flavor is preferred. The patient's decision to accept the dose form as a result of oral disintegration or dissolution is based on how the OTF tastes in the first few seconds after intake and then for atleast 10mins after that. Thus,

selecting a flavoring ingredient is crucial.[8]

Preparation of oral thin flim

Solvent and semisolid casting method

The solvent casting method is the most widely used technique for creating Oral thin flim due to its straightforward application, inexpensive processing costs, and ease of preparation. The process involves combining water-soluble ingredients in a heated magnetic stirrer. The combination is then mixed with the medicine and additional excipients to create a viscous solution. The solvents are allowed to evaporate once the solution made using this approach is transferred into a petri plate. These are stored at room temperature for 20–25 or 24-48 hours, or for a shorter duration at 40°C–50°C in the oven, depending on the solvent system used. The films, which are 15-20 mm in diameter and 0.2-0.3 mm thick, are carefully removed from the petri plates once the solvents have evaporated. They are divided into pieces of the appropriate size based on the quantity of active ingredient they contain. Using gel- forming polymers, the semisolid gel mass is dried after being poured into appropriate molds in the semisolid process. Next, they are sliced into the appropriate sizes to get them ready.[4][9]

Hot melt extrusion method

Transmucosal, transdermal, granule, and sustained-release tablet drug delivery methods are all often made using the hot melt extrusion technique. Using an extruder with heaters, the mixture including the formulation ingredients is combined and melted. Consequently, the liquid combination is formed into a film using molds.[9][10]

Soild dispersion method

This technique creates the solid dispersion by extruding the medicine and formulation ingredients, followed by molds to create a thin film.[9]

Rolling Method

This procedure often uses water or water/alcohol combinations as solvents. The active ingredient and additional ingredients are dissolved in a little volume of aqueous solution using a high shear processor. Once on the carrier roller, the viscous mixture is rolled. To create the final films, the films are cut to the appropriate sizes and then carefully dried.[9] [10]

Evaluation of Oral Thin Flim

Morphological and organoleptic control

The Oral Thin Flim color, consistency, transparency, scent, and texture are all investigated both visually and perceptually. In particular, their flavor and taste qualities should be assessed.[11] [12]

Moisture absorption capacity

High humidity levels are used during this test to regulate the films' physical stability and integrity. The samples are weighed separately, then put in desiccators with an aluminum chloride solution and left to dry for three days. The films are then weighed, and using the formula below, the percentage of moisture absorption capabilities is determined.[13]

$$\% \text{ Moisture absorption capacities} = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Initial Weight}} \times 100$$

Tensile strength[14]

Tensile strength refers to the highest tensile force that can be applied before breaking a thin-film specimen. It is calculated by multiplying the applied force by 100 and dividing the result by the film's cross-sectional area.

$$\% \text{ Tensile Strength} = \frac{(\text{Load at Failure})}{(\text{Film Thickness} \times \text{Film Width})} \times 100$$

Weight variability

Each formulation's 1x1-cm2 films are cut, and their unique weights on a sensitive scale are used to determine the weight variability.[11]

Folding endurance

A film is folded repeatedly at the same location at a 180° angle until it breaks to test the flexibility of thin films. It is documented how many folds are made before breaking. A film is regarded as having exceptional flexibility if it can fold 300 times or more.[15] [6] [4]

Content Uniformity

The drug content in each film is determined using the proper quantification technique after each film has been screened for content uniformity and dissolved in an acceptable solvent. A relative standard deviation percentage of no more than 6% is anticipated.[6][4]

Disintegration Test

The weight and thickness of the film are important factors in determining the physical characteristics of water-soluble films. The disintegration time is defined as the amount of time (seconds) that a film disperses when it comes into contact with water or the saliva.[16]

The disintegration periods of OTFs can also be ascertained using the disintegration test equipment listed in pharmacopoeias. The disintegration time of the film composition typically ranges from 5 to 30 seconds, albeit this phenomena varies depending on the formulation content. There is no official manual for determining how long it takes for films that degrade quickly to dissolve.[17]

Dissolution Rate Test

Many research in the literature tested drug release from polymeric films using Franz diffusion cells, although some devices for dissolution rate testing were modified. Location of film specimens is the biggest challenge in the dissolving rate experiment. The literature has also used a variety of techniques where a double-sided adhesive band is used to adhere the film's rate of dissolving to the bottom of the glass container or the mixing device. [mentioned in figure no:1]

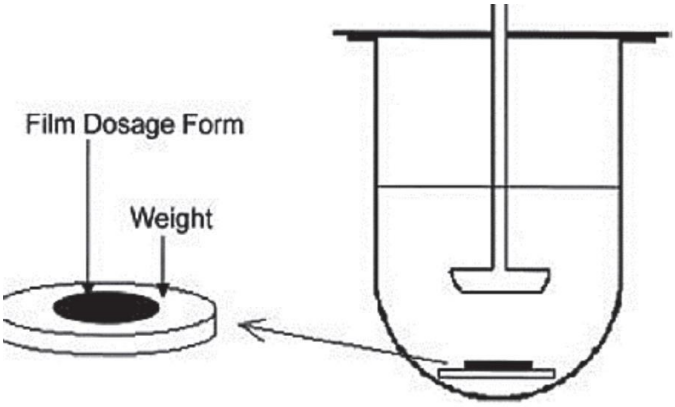

Figure no. 1: Modified Dissolution Apparatus.[6]

Oral Thin Flim stability

Guidelines from the International Council on Harmonization state that OTF stability must be preserved for a full year at controlled temperatures of 25°C and 60% relative humidity and 40°C and 75% relative humidity, respectively. OTFs need to be monitored for weight consistency, morphological characteristics, film thickness, tensile characteristics, water content, and dissolution tests at specific intervals while being stored.[19][20]

CONCLUSION

Tablets have a well-established market because they have been around for a lot longer. OTFs may serve as substitutes for the practical dose forms. However, clinical studies and their manufacturing require a great deal of research. Even though OTF technology is currently facing numerous obstacles, maximizing research, formulation, and manufacturing presents a positive outlook and enormous potential for OTFs in the future.

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