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Oral Dissolving Films: A Review

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ABSTRACT

Oral dissolving films (ODFs) are thin, flexible, and fast-dissolving sheets that can deliver active substances to the oral cavity. They offer several advantages over conventional oral dosage forms, such as ease of swallowing, precise dosing, improved patient compliance, and rapid onset of action. ODFs can be used for various therapeutic applications, such as anti-ulcer, anti-asthmatic, antihistamine, and analgesic drugs. This review article presents a comprehensive analysis of recent advancements in ODF formulation, manufacturing techniques, and their diverse applications in pharmaceutical, nutraceutical, and biomedical fields. The formulation of ODFs involves the selection of suitable polymers, plasticizers, surfactants, flavours, and sweeteners. The polymers are the main component that determines the mechanical properties, disintegration time, and drug release profile of the films. The plasticizers are added to improve the flexibility and elasticity of the films. The surfactants are used to enhance the solubility and permeability of the drugs. The flavours and sweeteners are used to mask the unpleasant taste of the drugs and improve the palatability of the films. The production methods of ODFs include solvent casting, hot melt extrusion, and roll casting. These methods differ in terms of the equipment, process parameters, and film quality. Each technique's advantages, limitations, and potential for scalability are outlined, providing insight into the critical factors influencing ODF development. In summary, this review article provides a comprehensive overview of the recent progress in ODF technology, encompassing formulation optimization, manufacturing advancements, and innovative applications. As the field of oral dissolving films continues to evolve, this article offers valuable insights for researchers, clinicians, and pharmaceutical industry stakeholders seeking to harness the full potential of this versatile drug delivery platform.

Keywords: Oral dissolving films, Plasticizer, Solvent casting method, Hot melt extrusion, Roll casting

INTRODUCTION

Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients. Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are outcomes of technological development. Among various dosage forms, the use of polymeric films for delivering medication into buccal cavity has developed great potential in recent area. Orally disintegrating films (ODFs), when placed on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form. ODFs are kind of formulations which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are the typical examples of orally disintegrating drug

delivery systems. These systems were developed in late 1970 to serve as an alternative to conventional dosage forms, for instance, fast disintegrating tablets and capsules for geriatrics and pediatric patients having difficulty in swallowing conventional dosage forms. A typical ODF is usually equal to the size of a postage stamp **[1].** In market place, the introduction of ODT was strongly associated with counseling of patients about the appropriate administration by giving instruction like ‘‘do not chew/do not swallow’’. However, in spite of these instructions, incidents regarding chewing and swallowing were often reported. But, ODFs untied the masses from these adverse events. The administration of ODFs has numerous 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

No expensive lyophilization, high mechanical strength, rapid disintegration, and reduced choking risks are the quality attributes of ODFs21a have attained remarkable significance in pharmaceutical industry for the reason of possessing unique properties and fast disintegration time ranging from seconds to one-minute ODFs design permits to incorporate a variety of drugs for their pharmacological effects e.g., anti-tussive, anti-epileptic, anti-asthmatic, expectorant, etc.[2]

Anatomy of oral cavity

The structure and anatomy of oral cavity is studied for understanding the environment provided for delivering drugs [Fig. 1]. The oral mucosa allows direct access of drug to the systemic circulation and avoids first pass metabolism. The epithelium of the oral cavity is quite similar to that of the skin, with slight differences with regard to keratinization, protective and lubricant mucous which is spread across its surface [3]. The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral cavity is divided into two regions: outer being the oral vestibule bounded by the lips and cheeks; the hard and soft
Palates, the floor of the mouth and tonsils [4]. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. [5]

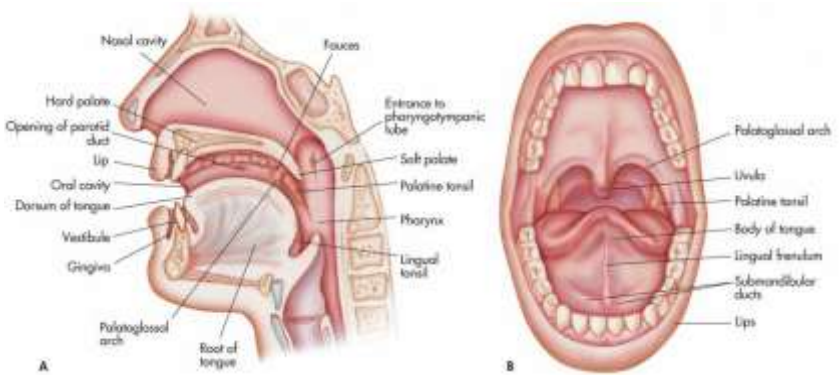

Fig:1 Anatomy of the oral cavity (http://baldaivirtuves.info/human-anatomymouth/ Human-anatomy-mouth-anatomy-mouth-oral-cavity-human-anatomy-libraryphysiology/)

Fast dissolving drug delivery system (FDDS)

Fast dissolving drug delivery system is a new generation delivery system also known as fast dissolving/disintegrating film for the oral delivery of the drugs which came into existence in the late 1970's as an alternative to tablets, capsules, syrups and other

formulations for pediatric and geriatric patients who experience difficulties in swallowing traditional solid dosage forms which combines both the advantages of conventional tablet and of liquid formulation [6]. FDDS is easy to administer and provides better patient compliance in the elderly, pediatric, mentally retarded, nauseated and uncooperative patients [7]. This delivery system consists of the solid dosage forms that dissolve quickly i.e. within a matter of seconds in the oral cavity without the administration of water. The delivery system consists of a very thin oral strip which is simply placed on the patient's tongue or any other oral mucosal tissue and instantly gets wetted by saliva [8]. The film rapidly hydrates onto the site of application.

It then rapidly dissolves and disintegrates to release the medication for oro-mucosal absorption. Fast dissolving oral thin films are widely accepted by patients and also to the caregiver for their ease-of-delivery, portability and accurate dosing [9]. The robustness of the film depends upon the type and amount of polymer used and general dissolution time for orally dissolving film is 5–20 min. as per pharmacopoeia [10,11] They also provide quick onset of action within few seconds as the oro-mucosal absorption of the drug occurs directly from the site of administration to the systemic circulation avoiding the first-pass metabolism to produce the desired effect [12].

Special Features of Mouth Dissolving Films

1. Thin elegant film
2. Unconstructive
3. Available in various size and shapes
4. Fast disintegration
5. Rapid release
6. Give a pleasant mouth feel.
7. Have an acceptable taste.
8. Should not leave residues in mouth. [13]

Advantages [14-22]

1] Great uniformity of thickness and great clarity than extrusion.
2] Films have fine gloss and free from defect such as die lines.
3] Films have more flexibility and better physical properties.
4] As compare to tablet the on set of action is quick.
5] During administration, its doses not required water.
6] No risk of chocking.
7] Transportation is easy.
8] Rapid disintegration & dissolution in the oral cavity is provided due to large surface area.
9] For the drug delivery to the eye, ophthalmic thin films can be used.

Disadvantages

1. Dose uniformity is a technical challenge.
2. Hygroscopic in nature.
3. High doses cannot be incorporated (<40 mg/4cm2 piece).
4. Require special packaging for products stability and safety. [3]
5. Drugs which is unstable at buccal pH cannot be administered.
6. Drugs which irritate the mucosa cannot be administered by this route.
7. A drug with small dose requirement can only be administered.
8. Taste masking- Most drugs have the bitter taste, and need taste masking.[23]

Applications

1. Film forming systems used in field of surgery.
2. It can also be used as substrate for various barrier membranes that are used in Industries.
3. Film forming polymers are used to increase the integrity of soil and elevate the soil temperature which is useful in crop production.
4. Film formers used for non-medical uses such as, the delivery of active ingredients contained in beauty products like silicone film forming technologies used to prepare cosmetic creams and ointments.
5. Film forming systems were used for wound care.

Mechanism Of Film Formation

Film forming system (FFS) is applied directly to the skin and it forms a thin, transparent film *in situ* upon solvent evaporation as shown in fig. 2. After application of the formulation to the skin, the composition of the film forming system changes significantly due to the loss of the volatile components of the vehicle which results in formation of residual film on the skin surface. In this process the concentration of drug increases, reaching saturation level and with the possibility of reaching super saturation level on the skin surface. Supersaturation results in the enhanced drug flux through the skin by increasing the thermodynamic activity of the formulation without affecting the skin's barrier, thereby reducing the side effects or irritation.

The concept of supersaturation can be explained by the modified form of Fick's law of diffusion. Fick's law of diffusion given by Eq.:

$$J = \frac{DKCv}{h}$$

Where

J = rate of drug permeation per unit area of skin per unit time (flux)

D = diffusion coefficient of drug *Cv*= concentration of drug *h* = thickness of barrier to diffusion

From this equation, it is clear that the rate of drug permeation across the skin is proportional to the concentration of the drug. However this is true when the entire drug is dissolved in the vehicle. Equation describes the modified form of Fick's law of diffusion:

$J = \alpha D/\gamma h$

Where a=thermodynamic activity of drug within formulation γ=thermodynamic activity of drug within membrane

According to this equation, the flux of the drug is directly proportional to the thermodynamic activity of the system, which is related to saturation. However increasing the super saturation increases thermodynamic instability.

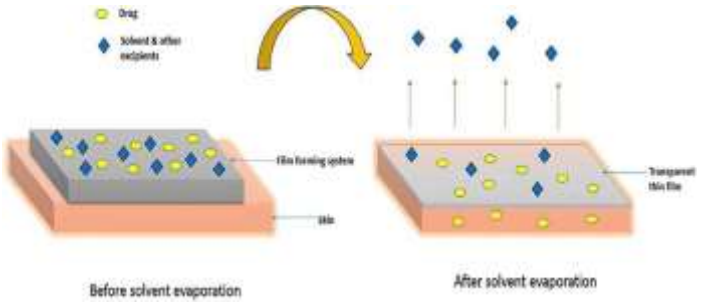

Fig:2 Mechanism of film formation

FFS creates supersaturated systems immediately after application to patch (EVRA®) through human epidermis *in vitro*. The film forming the skin, overcoming the problem of instability. Thus, it improves the formulations showed a higher permeation than the commercial patch. Drug permeation through skin compared to other transdermal dosage without enhancer the formulation transported more than double the forms. The delivery efficiency of the film forming solutions for ethinyl estradiol than the marketed patch. With enhancer, the estradiol was investigated. The permeation of ethinyl estradiol from formulation delivered about seven times as much ethinyl estradiol as the film forming solution prepared with enhancer or without enhancer that of the marketed patch. Thus, these systems prove to be useful in was compared to the permeation from the commercially available enhancing the drug permeation.[24]

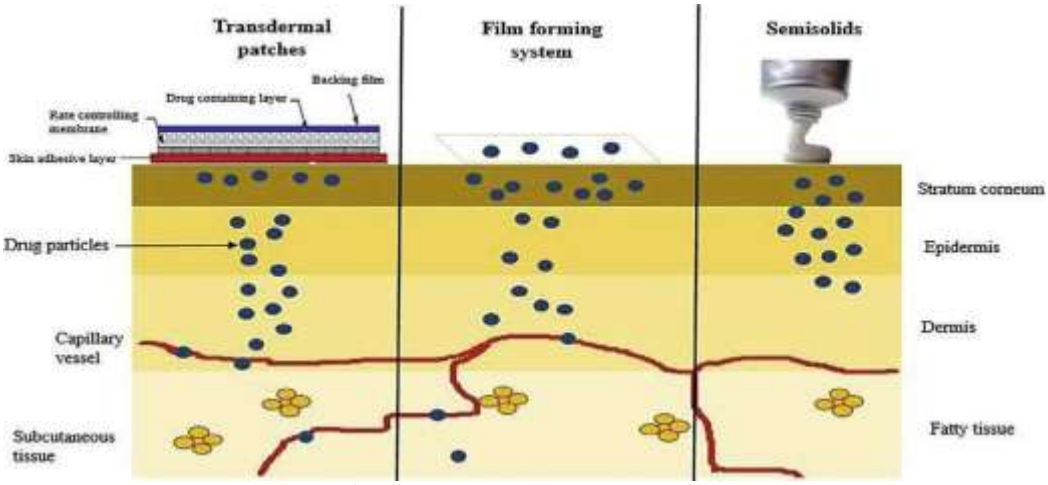

Fig:3 Release Profile of the topical and transdermal drug delivery systems

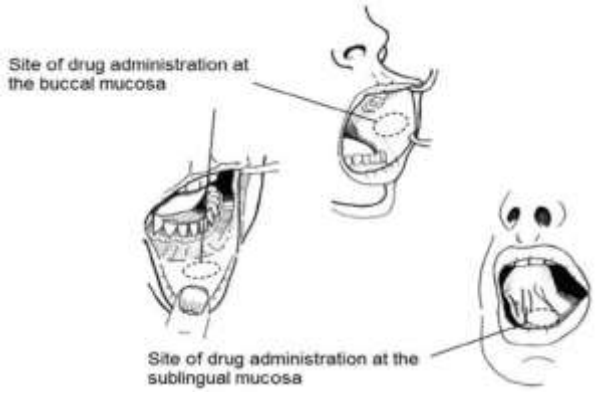

FIG: 4 Demonstration of common site for application of film in buccal and sublingual mucosa

FORMULATION ASPECTS FOR MOUTH DISSOLVING FILMS:

Active Pharmaceutical Ingredient:

Various classes of drugs can be incorporated into ODFs e.g., anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc. Dimenhydrinate can also be incorporated into ODFs for taste masking. Common examples of drugs incorporated into ODFs are salbutamol sulfate, rizatriptan benzoate, verapamil ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine**,** tianeptine sodium, indomethacin, etc.

Film Forming Polymer:

Water-soluble polymers are used as film formers as they provide quick disintegration, good mouth feel, and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations. A variety of polymers are available for preparation of films of which pullulan, gelatin and hypromellose are most commonly used. Examples of water-soluble polymers include: Pullulan, Gelatin, guar gum, xanthan gum, Hydroxyl propyl methyl cellulose (HPMC), Modified starches, PVPK30, PVA etc. HPMC E3/E5/E6/E15.

Ideal properties of the polymers used in the oral film:

1. Polymers should be nontoxic, non- irritant and non-bitter.
2. Polymers should be tasteless3. It should be devoid of leachable impurities
3. It should be devoid of leachable impurities
4. It should be inexpensive and readily available
5. It should not be an obstacle in the disintegration time
6. It should have good wetting and spreadibility property
7. It should exhibit sufficient peel, shear and tensile strength

8. It should not cause secondary infection in the oral cavity and should have sufficient shelf life. [25, 26]

Hydrophillic polymers:

The successful development of an ODF is a function of justified selection and concentration of polymers as the mechanical strength of films is strongly associated with these factors. They can be used either alone or in combination with other polymers to modify film properties. The concentration of used polymers is also important factor while developing an ODF. The integrity of fast dissolving oral films is dependent upon careful selection of polymer nature and concentration. Generally, polymer concentration used in preparing ODFs is aroun4d 5% w/w of total weight of dry thin strip, however, it can be increased up to 60–65% w/w in order to attain the film of desired attributes and characteristics. Polymer used as a film forming agent in formulation of thin strips should possess certain properties. In recent era, both natural and artificial polymers are used for developing ODF formulation[27]. Different polymers are employed to modulate diverse properties of films. Pullulan has increased solubility next to the property of enhancing flexibility and films incorporating pullulan have high tensile strength and stability over a wide range of temperature. Molecular weights of gelatins affect the properties of prepared films and a significantly appealing film can be attained by using polymers with higher average molecular weight. The combination of chitosan and high methoxy pectin (HMP) or low methoxy pectin (LMP) provides excellent quality of strip. Cellulose derived film forming polymers viz hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC) and carboxymethyl cellulose (CMC) give films with less water vapor barrier due to their hydrophilic nature. Polyethylene glycol (PEG) also has a good film forming properties either alone or in combination with other polymers [28].

HPMC is a very good film former and different grades viz Methocel E3, Methocel E5, Methocel E15 Premium LV, etc. are available. The development of fast dissolving film of triclosan prepared by using different grades of HPMC indicated that Methocel E15 Premium LV resulted into the films with appropriate properties[29]. Fast dissolving film of famotidine fabricated using HPMC and polyethylene glycol (PEG) depicted desired physico-chemical properties[30]. A water insoluble drug (piroxicam) was incorporated into fast dissolving films prepared using maltodextrins (MDX) and equivalent low dose dextrose [31]. ODFs of nebivolol HCl prepared from HPMC, pullulan, polyvinyl pyrrolidone (PVP) illustrated that changing polymer concentration profoundly affects mechanical properties and percentage drug release[32]. As polymers govern the release profile, mono- and double-layered buccoadhesive films of chlorhexidine were prepared to portray this fact. Films prepared with alginate and/or HPMC and/or chitosan-controlled drug release in a better way [33]. ODFs of granisetron hydrochloride manufactured using pullulan and HPMC illustrated the effect of polymer concentration on mechanical properties and strength of film. Pullulan with 40–45% concentration did not yield films with good properties whereas HPMC up to 40% amount resulted into films which were difficult to peel. Furthermore, the stickiness of film increased when the concentration of HPMC was above 50% [34]. A study of preparing fast dissolving films of losartan potassium applying different concentrations of maltodextrin (MD) and polyvinyl alcohol (PVA) demonstrated that in vitro disintegration time varied directly as a function of increased polymer concentration [35]. Another study revealed that pullulan serves as a best film forming agent among all investigated polymers [36]. Fast dissolving films of cetirizine using 2% w/v pullulan were thin and brittle, thus, slightly higher concentration was used[37]. Affectivity of ODFs might be judged by comparing the

pharmacokinetic properties (bloodprofile) of the reference (oral solution of pure drug) and the sample film of levocetirizine containing pullulan
by testing on Sprague–Dawley rats[38].

Plastisizers:
In general, mechanical properties such as tensile strength and percent elongation are improved by adding plasticizer to the formulations. The concentration of plasticizer usually ranges from 0% to 20% w/w. Common examples of plasticizers are PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, etc.

Sweetening Agent:
Sweeteners have become an important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. Some suitable sweeteners include:
(1) Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc.
(2) Water soluble artificial sweetener: sodium or calcium saccharin salts, acesulfame-K etc.
(3) Dipeptide based sweetener: aspartame

Saliva Stimulating Agent:
Salivary stimulants are generally acidic in nature stimulating the production of saliva in buccal cavity, consequently, promoting the disintegrating of ODFs. Some commonly used saliva stimulating agents are citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid.

Surfactant:
Surfactants are used as solubilizing or wetting or dispersing agents as a result that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal films. E.g.: Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and spans etc.

Flavour:
Flavours are needed to mask the bitter or nauseating taste of incorporated drug. Amount of flavor depends upon its nature and strength. Any US-FDA approved flavor can be used such as sweet, sour or mint flavor one of the research work verified that mint, licorice and sucralose mixture flavors appropriately mask the bitter taste of diclofenac sodium. Electronic tongues are used to discriminate the effect of various taste masking agents (TMAs)

Colouring Agent:
Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in oral strips when some of the formulation ingredients or drugs are present in insoluble or suspension form**.**

METHOD OF PREPARATION OF FAST DISSOLVING FILM:

One or a combination of the following processes can be used to manufacture the Mouth dissolving film:
1. Solvent casting
2. Hot-melt extrusion
3. Semisolid casting
4. Solid dispersion extrusion
5. Rolling

1. Solvent Casting Method:
Solvent casting is the most commonly used method for the preparation of ODFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor. Then, the prepared solution is poured onto petri plate and the solvent is allowed to dry by exposing it to high temperature in order to attain good quality films. An orodispersible film of tianeptine sodium was successfully prepared through solvent casting technique using different grades of Lycoat and HPMC. In

solvent casting technique, film forming polymer is usually soaked in an appropriate solvent for overnight. The type of API, which has to be incorporated in ODF, governs the selection of a suitable solvent depending on critical physico- chemical properties of API such as melting point, shear sensitivity and polymorphic form. Compatibility of drug with solvent and other excipients is also brought under consideration before finalizing a formulation. During formulation, entrapment of air bubbles can hinder the uniformity of prepared films. Thus, deaeration of the mixture is carried out with the help of a vacuum pump. Orodispersible film formulation of mosapride was also successfully prepared by using solvent casting method. Viscosity of the solution to be poured is an imperative aspect in casting method. The concentration of pullulan varying from 2% to 8% results into low viscosity solution, as a result, enabling easy casting of films. Fast disintegrating films of anastrozole were also effectively prepared with the help of solvent casting method employing HPMC (E5) and polyvinyl alcohol (PVA**)** [39,40].

Advantages:

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

Disadvantages:

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

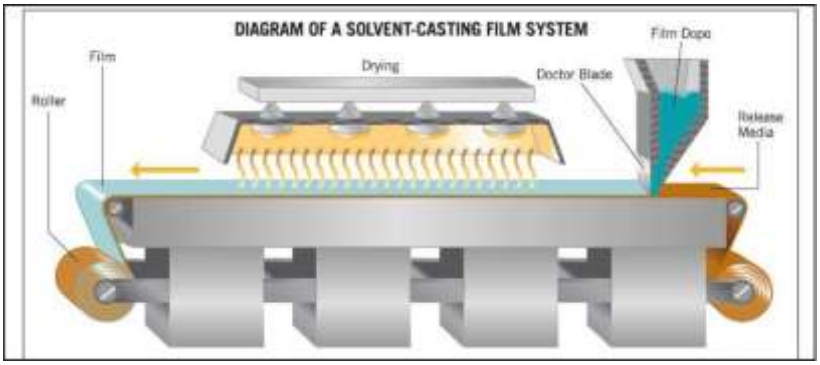

FIG: 5 Discription of Solvent Casting Method

2. Hot Melt Extrusion:

It is a process in which polymer undergoes melting due to applied heat and pressure. It is mostly used in the preparation of SR-tablets, granules.

This method breaks the ancestral way used for preparation of ODF. In this film is prepared through heating process. Ingredients are mixed in a dry state after the process of heating it's taken out in a molten state. Molten mass obtained is used to cast film. Then films are cooled and cut. Major drawback of this technique is the Active Ingredients is deactivated due to the high temperature. Vital step in this technique is casting and drying (Figure 2).

Correlated to HME technique solvent casting occurred to be more up righted process for production of ODF [41- 43].

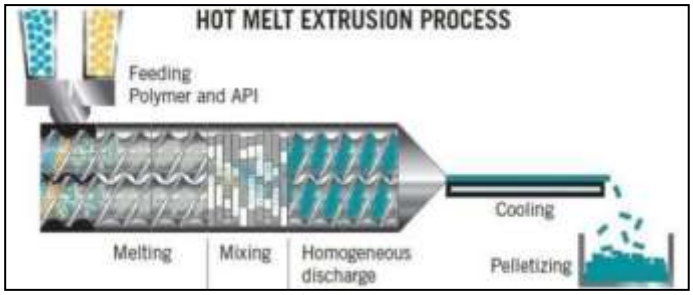

FIG: 6 Diagram of Hot Melt Extrusion Process

Advantages:

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

Disadvantages:

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

3.Semi Solid Casting Method:

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. Acid insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4

Solution of water-soluble film forming polymer is prepared

⇩

Resulting solution is added to a solution of acid insoluble polymer

⇩

Appropriate amount of plasticizer is added so that gels mass is obtained

⇩

Finally, the gel mass is casted in to the film or ribbons using heat-controlled drums

4. Solid Dispersion Extrusion Method:

Solid dispersion of domperidone using beta-cyclodextrin, PEG400 and HPMC E15 was successfully prepared and films were casted using solid dispersion extrusion method. [44,45]

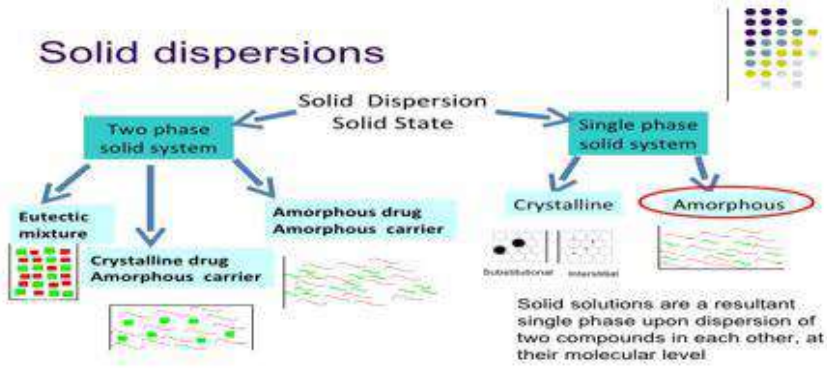

FIG: 7 Solid Dispersion Extrusion Process

5. Rolling Method:

Plot of rolling method is prepared solution should possess specific rheological properties for rolling onto the drum. Preparation of suspension of drug and polymer in water or alcohol Suspension is subjected to rollers Suspension is subjected to rollers Evaporation of solvent Evaporation of solvent. [46,47]

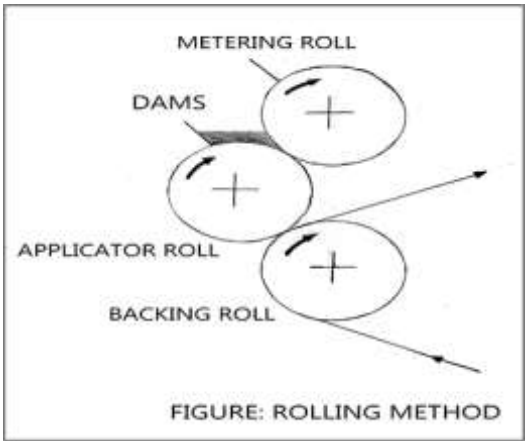

FIG: 8 Description of Rolling Method

6. Spray technique:

Drug substance, polymers and all other excipients are dissolved in a suitable 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., 2012). [48]

Classification of Fast Dissolve Technology:

Fast-dissolve technologies may be divided in to 3 broad groups:

- Lyophilized systems.
- Compressed tablet-based systems.
- Thin film strips.

The lyophilized systems:

This system is that the most undefeated among them in terms of sales worth, sales volume and range of worldwide product approvals. Through the utilization of a mound or packing, suspension or resolution of drug with alternative structural excipients can convert into tablet-shaped units. The units or tablets square measure then frozen and lyophilized within the pack or mould. The ensuing units having high consistence square measure to blame for speedy water or spittle penetration and really speedy disintegration. Dose-handling capability for these systems differs reckoning on whether or not the active ingredients square measure soluble or insoluble medicine, with the dose capability being slightly lower for the previous than for a few pills based mostly systems. The unit's square measure capable of incorporating a spread of taste-masked materials and have a lot of speedy disintegration than tablet based systems.

Compressed tablet-based systems

This system is created exploitation customary pill technology by direct compression of excipients. The pill technologies have totally different levels of hardness and break ableness reckoning on the strategy of manufacture. The speed of disintegration for fast-dissolve pills compared with a customary tablet is achieved by formulating exploitation water soluble excipients, or superdisintegrant or effervescent parts, to permit speedy penetration of water into the core of the pill. The one exception to the present approach for tablets is Biovail.s Fuisz technology. It uses the proprietary Shear kind system to supply drug-loaded candy floss, that is then used for tableting with alternative excipients. These systems will in theory accommodate comparatively high doses of drug material, together with style disguised coated

particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dose forms. The loose compression pill approach has progressively been employed by some technology homes, branded firms and generic pharmaceutical firms, for in-house development of line extension and generic fast dissolve dose forms.

Oral thin film strips

Oral films, conjointly known as oral, the third category, are living for variety of years, they have recently become the new space of interest in fast dissolve pharmaceutical drug delivery. Dissoluble Oral thin films or oral strip evolved over the past few years from the confection and oral care markets within the sort of breath strips and have become a unique and wide accepted kind by customers for delivering vitamins and private care product. This film will reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is factory-made as an oversized sheet then take away individual dose units for packaging in an exceedingly vary of pharmaceutically acceptable formats.

RECENT MANUFACTURING TECHNOLOGIES

XGel:

This type of film is mostly preferred by vegetarians as the film is not made from sources of animals. It is used to mask the taste, the colour, the layer and they have enteric properties .it also include API. As they are water soluble, it can be used for developing any kind of oral dosage form [49]. It can be prepared in various shapes and sizes. It is an excellent method for delivering the medicines.

Soluleaves:

The soluleaves are added for those agents that release flavours such as confectionaries, fresheners and vitamin. It is used to deliver the pharmaceutical active ingredient to the oral cavity in efficient and pleasant way; this technology is used for wide range of products for ODFs. The soluleaves are made to dissolve quickly when the film comes in contact with the saliva, which release the API quickly. Due to this reason soluleaves are excellent for wide range release by oral administration. This technology is often suited for paediatric, geriatric patients who have difficulty in swallowing tablet and capsules [49].

Wafertab:

Wafer tab is one of the different processes to load a drug in then films for topical or oral administration. After casting into the films API ingredients are added to it. In this system in which drug is in the form of ingestible filmstrip, this technology gives quick dissolution and release of the drug when it comes in contact with saliva. Wafertab is also used for making and improving the taste. The drug is accruable weighed included in the pre manufactured film to prevent moisture and heat and helps in increasing the stability of the product. Wafertab helps to achieve more possibilities in innovation of drug. Wafertab are formulated in various shapes and sizes and it helps in quick release of drugs and also the patients who can't swallow easily [49].

Foamburst:

Their new potent was accepted in 2004 on the month of September. In which using foamed film capsules are prepared. Foamburst is an alternative of Soluleaves. Honeycombed structure is formed due to the gas blown into the film during the manufacturing process gases filled in the free space of the film. It causes melt in mouth sensation due to the honeycombed structure which is formed lightly as a result capsule dissolves quickly [49].

Micap:

In the year 2004 Micap signed a bond which was a choice to merge its facility in micro encapsulation process with Bio progress water soluble film. They are Bioscience Company using a single cell organism they develop patented micro-encapsulation processing single cell organism they produce

a natural micro capsule for Agro chemical, food and pharmaceutical industries [49].

Packaging of orally disintegrating films

Packing considerations are critical for storage, protection and stability of dosage form. Packaging for oral thin films 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 extremely moisture sensitive [50]. Rapid film technology developed by Labtec 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 [51]. Table 1 summarizes the list of commercially available thin film oral dosage form products.

Table 1: Commercially available Thin Film oral Dosage Form Products

Product	Manufacturer	Active Pharmaceutical Agent	Strength(mg)
Triaminic	Novartis	Dextromethorphan HBr	7.5
Triaminic	Novartis	Diphenhydramine HCl	12.5
Therafly	Novartis	Dextromethorphan HBr	15
Gas-X	Novartis	Simethicone	62.5
Sudafed	Pfizer	Phenylephrine HCl	10
Benadryl	Pfizer	Diphenhydramine HCl	12.5
Chloroseptic	Prestige	Benzocaine Menthol	3/3
Suppress	InnoZen	Menthol	2.5
Orajel	Del	Menthol/Pectin	2/3
Listerine	Pfizer	Cool mint	-

EVALUATION PARAMETERS:

1. **Thickness test:**
   Thickness of a film is determined by using calibrated digital micrometer and then subsequently mean average is calculated. Generally, three readings from all the batches are determined and average is calculated. Weight variation of a film is calculated in triplicate by cutting the film and determining weight of each film. Uniformity in thickness is important to ascertain as it is directly proportional to dose accuracy of the film [52].

2. **Tack test:**
   Tack is the tenacity with which the film adheres to the accessory that has been pressed into contact with strip. This test also determines the dryness [53].

3. **Tensile strength:**
   Tensile strength is defined as maximum stress applied at which the film breaks. Basically, this test is performed to measure the mechanical strength of films. It can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below [53,54]

$$\text{Tensile strength} = \frac{\text{Load at breakage}}{\text{Strip thickness}} \times \text{strip width}$$

4. **Percentage elongation:**
   When the sample films are subjected to tensile stress, deformation of the films occurs resulting in stretching or elongation of sample. It is performed to predict the ductility of polymers using a texture analyzer. It is calculated by formula:

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

5. **Folding endurance:**
   To determine folding endurance, a portion of film is cut and repeatedly folded at the same point till it breaks. The number of times the film could be folded at the same point without breaking indicates the folding endurance value. Typical folding endurance for a film range between 100- 150[55].

6. **Swelling property:**
   Simulated saliva solution is used to check 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:

$$\text{Degree of swelling} = \frac{\text{Final weight(Wt)} - \text{Initial weight(W0)}}{\text{initial weight(W0)}}$$

Wt = weight of film at time interval t, w0 =weight of film at time 0.

7. Tear resistance:

Tear resistance of film is the intricate function of its ultimate resistance to rupture. Maximum force required to tear the film is measured as tear resistance value. This test is typically attributed to plastic industry. The rate of loading employed is 2 in/min which is planned to determine the magnitude of force required to initiate tearing in the film specimen. The maximum amount of force necessary for tearing is generally found near the tearing onset which is ranked as tear resistance value [56].

8. Transparency:

Transparency of a strip is determined by using a UV-spectrophotometer. This test is performed for visual appearance of the formulation. Film specimen are cut into rectangular shapes and placed on the internal side of the photometer cell. Transmittance of the film is worked out at 600 nm wavelength.

9. Contact angle:

Contact angle of a film is usually measured at room temperature with the help of a device known as goniometer. On the dry film surface, a drop of double distilled water is placed. Water droplet images are recorded within 10 s after the placement of drop with the help of a digital camera. These digital pictures are analyzed by using image 1.28 V software for determining contact angle. Contact angle is measured on both sides of droplets and mean is calculated. Contact angle is determined at least five times at different positions to have a clear idea about the nature of films.

10. Visual inspection and surface morphology:

Visual inspection of a prepared orodispersible film gives information about color, homogeneity and transparency [57]. For surface morphology, scanning electron microscopy is performed. Absence of pores and surface uniformity depicts good quality of films.

11. Surface pH:

The pH value of a film is usually determined by putting the prepared film in Petri dish and subsequently film is made wet by using distilled water and noting pH by touching the film surface with a pH meter electrode. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation.[58]

12. Content uniformity:

Contents of a film are determined by standard assay method specified for individual drug in different pharmacopoeia. This test is performed on 20 samples using analytical techniques. The acceptance value of the test is less than 15% in accordance with Japanese pharmacopoeia. According to USP27, the contents should range from 85% to 115% with the standard deviation of less than or equal to 6% Content uniformity is worked out for estimating drug contents in individual film [59,60].

13. Disintegration time:

Disintegration apparatus mentioned in official pharmacopoeias is used for determining the disintegration time of a film. Normally, the disintegration time is the function of composition of film as it

varies with the formulation and generally ranges from 5 to 30 s. Mostly, the USP disintegration apparatus is used for this test. There are no official guidelines available for determining disintegration time of orally fast disintegrating films. There are two methods for determining disintegration time of film [61].

13.1 Slide frame method: A drop of distilled water is poured onto the film
clamped into slide frames placed on petri dish. Time taken by the film to dissolves noted [62].

13.2 Petri dish method: A film is placed into 2 ml distilled water taken in Petri
dish. Time taken by the film to dissolve completely is considered as the disintegrating [63].

14. Youngs modulus:

It is use to estimate stiffness. It is found as balance applied stress to the strain in the region. It is determined by,[64]

$$\text{Youngs modulus} = \frac{\text{force of corresponding strain}}{\text{cross sectional area}}$$

15. Thermodynamic stability test:

Optimize formulations then subjected to different thermodynamic stability study test namely centrifugation and freeze thaw cycles by thermodynamic stability test.

16. Viscosity:

Evaluate the viscosity of the optimized formulation by Brookfield viscometer.[65]

17. Weight of films:

Oral fast dissolving films can be weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper number of excipients and APIs. [66]

18. Stability Studies:

Stability studies on the optimized oral fast dissolving film is carried out for determination of effect of temperatures and humidity on the stability of the drug. The film are stored in an aluminum foil and subjected to stability at room temperature. The sample can withdraw at 3 months and 6 months and subjected for cumulative % drug release and in vitro dissolution studies to determine disintegration time and disintegration test. [67]

19. In-vitro dissolution test:

Standard official basket or paddle apparatus is used for conducting dissolution studies on films. Sink conditions should be maintained during dissolution. Sometimes while performing this process, film floats over the medium making it difficult to perform the test properly. This problem is more likely to occur in case of paddle method thus the basket apparatus is mostly preferred. Media used are 6.8 pH phosphate buffer (300 ml) and 0.1 N HCl (900 ml). Temperature is maintained at 37 ± 0.5 C and rotation speed of 50 rpm is usually adjusted. Samples of drug dissolved are collected at pre-determined intervals and are analyzed by using UV-spectrophotometer. Despite its extensive use, dissolution test is still prone to noteworthy inaccuracy and tests let down [68,69].

One chamber method: In this method set up is based on USP Ⅱ in this method different sample application used. in the first way the film is put to dissolution medium and in secondary the film is to be kept in a cylindrical shaped sinker containing a mean size of 0.36to 0.44m. This is done to avoid the floating of the films. In the third way the film is attached to glass, because of the improper film adhesiveness, No bilayer adherence tape is required [68].

Punch and Filter method: This method is based on the setup of paddle apparatus this device contains filter paper and it is to be cut into a required dimension to create flat interface between the stainless frame and the filter. ODF's are held at a top of filler after adjusting the ODF and the punch. The ODF" s were kept in the dissolution media from bottom to top side to identify the status of dissolution, in this process active pharmaceutical ingredient diffuses inside the filter located in the second chamber, this method is used to calculate the stimulated saliva flow and it helps in masking the taste of new ODF" s or to improve the absorption of the films

20. Moisture uptake and moisture loss:

Percent moisture loss is a parameter that determines the hygroscopicity of a film. Usually, this parameter is determined by first finding the initial weight of the film, afterward, putting this film in a desiccator for three days. Desiccator contains calcium carbonate. After three days, strips are taken out and weighed again. Moisture loss is determined by applying the following formula [70].

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Moisture uptake of a film is determined by first cutting the film with the dimension of 2 · 2 cm2. Afterward these strips are exposed to environment with a relative humidity of 75% at room temperature for 7 days. Moisture uptake is determined as percent weight gain of the strips (Gorle and Gattani, 2009).

$$\text{Percentage moisture gain} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

FUTURE PROSPECTS

In the pharmaceutical industry, great advancements have been made in oral drug delivery technologies. The market has come a long way from the conventional tablets/ capsules to modern-day fast disintegrating and rapidly acting tablets/films. Various limitations such as lower bioavailability of oral solid drugs, the inconvenience of administering injections, inaccurate dosing by liquid formulations is keystone which has turned the focus of pharmaceutical companies to develop novel oral dosage forms that eliminate these limitations. Fast dissolving oral thin films are designed 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. This emerging area is gaining 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 lifecycle 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. According to the 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 are no clinical studies associated with 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 processes 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. The future looks very promising for the film technology in the time to come as new technologies are rapidly introduced to prepare thin films.

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