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Review Article

Mouth dissolving film as a potential dosage form for paediatric usage

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ABSTRACT

Drug delivery systems using thin films are being researched by the pharmaceutical industry. They're a diverse platform that can provide immediate, local, or systemic actions. Furthermore, these systems can be used independently, which is ideal for patients with dysphagia, elderly, pediatric, or bed-ridden patients, as well as those who may have difficulty consuming water. These drug delivery systems can be given by oral, buccal, sublingual, ocular and trans-dermal routes. This study explores mouth thin films in all of their characteristics from the current perspective, providing insight into the world's growing market share as a result of expanding research fields and technological breakthroughs. Simultaneously, It provides a summary of the key factors involved in formulation development that have an impact on thin films, such as thin film design, morphological and physiological limitations, production process selection, characterization techniques, and polymer and drug physicochemical properties. It also gives an overview of the most recent thin-film products made by major pharmaceutical firms.

1. Introduction

1.1. Oral cavity drug delivery

The oral route of administering medications is popular due to convenience, pain avoidance, and high patient adherence.[1] Active pharmaceutical ingredients (APIs) can be Oral mucosa allows for absorption or saliva, making the oral cavity a significant surface area for drug delivery.[2] Traditional medications have low bioavailability, which can be overcome by using orally dissolving tablets (ODTs) or oral thin film (OTF) drug delivery devices.[3,4] Patients who fear asphyxiation may prefer OTFs due to their rapid dissolution and durability,[5] and they have higher patient compliance. However, OTFs have limitations in carrying low-dose APIs.[6]

1.2. Routes of drug transport

The absorption of drugs into cells from saliva can occur through active transport or passive diffusion,[7] with passive diffusion being the most common. The two pathways of passive diffusion are transcellular and para-cellular[8,9] with lipophilic molecules transported via the transcellular pathway and hydrophilic molecules transported through para-cellular pathways. Various physiochemical variables such as drug concentration, molecular weight, delivery method, Salivary acidity,,[10,11] and saliva flow affect drug absorption from membranes. For example, Hydrophilic molecule diffusion is influenced by their molecular size and owing to saliva's pH, low acid dissociation constant (pKa), which can modify the medication ionization and facilitate diffusion.

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1.3. Paediatric dosage forms

1.4. Formulations for children: Issues and Concerns:

To summarize, paediatric formulations face unique challenges due to the differences in physiology and metabolism between children and adults. Children require different dosages and have different taste preferences compared to adults,[12] and thus require different excipients and formulations. However, excipients used in pediatric formulations can be associated with toxicological risks,[13] and the taste and palatability of the medication can be difficult to mask without the use of potentially harmful additives.[14] The creation of pediatric formulations requires careful consideration of all these factors.[15]

1.5. Alternative paediatric dosage forms

Thorough guidelines recommend that pediatric formulations should have fewer doses, smaller sizes, increased convenience, simplicity of use, pleasant flavor, and secure excipients. Disperse systems like granules and pellets can be administered either ingested immediately or combined with food, offering dosage flexibility, but there are concerns about partial ingestion and stability. Chewable tablets and orally disintegrating pills are also potential options, but a careful selection of excipients is necessary for taste-masking. These dosage forms may have limitations in terms of dosage stiffness, integrity, and potential unpleasantness in young children.

1.6. Orally dissolving films: A potentially innovative method

Oral dispersible products have been developed to address the challenges of patients, especially children, who struggle to take traditional oral solid dose formulations. These products come in various forms, including Oral lyophilized products and dissolving tablets. The quick-dissolving medication delivery method was first introduced in the late 1970s and has become a ground-breaking innovation that offers for individuals who are noncompliant, elderly, or pediatric, an alternate oral dose form. Oral disintegrating films (ODFs) have been found to contain a range of water-soluble medications and have shown promise for oral administration since they dissolve quickly and the absence of the need for water for swallowing.

1.7. Various types of oral films

Various oral film kinds are employed based on formulation style, application places, and disintegration speed. In contrast to the quickly disappearing film, which is applied to the tongue, As techniques for buccal continuous medication administration, Oral patches and mucoadhesive films were made available for purchase. Types of ODFs contain Fast release films, mucoadhesive films, and Muco-adhesive enduring wafers. They are differentiated in the form of area, thickness, structure, components, delivery area, and dissolution time.

1.8. Particulars of oral dissolving films

ODFs are becoming more significant in the pharmaceutical sector as a result of their distinctive qualities and advantages. They quickly dissolve without water, resulting in improved patient compliance, quick action, no choking risk, higher bioavailability, simplicity of administration, and portability. For pediatric formulations, ODFs can be advantageous due to their small size and precise dosing. Additionally, ODFs are more stable and persistent than ODTs, a greater surface area for accelerated degradation, and eliminate the anxiety of ingesting tablets. Although liquid dosage forms are adaptable and convenient, precise measurement can be challenging, and poor stability is a significant limiting factor.

1.9. Marketed oral dissolving films

Many companies like *Pfizer, Paladin Labs, Strativa, Novartis, etc.* already marketing their products with ingredients like cool mint, B6, B12, vitamin C, Ondansetron 4mg & 8mg, Diphenhydramine (12.5mg), Dextromethorphan HBr (15 mg).

1.10. Patented technologies

1.11. Summarizes some of the orally dissolving film's patent technology platforms[16,17]

2. Limitations for ODFs

In addition to the challenges mentioned above, the cost of producing ODFs may also be a limiting factor, as the manufacturing process can be complex and require specialized equipment. Additionally, regulatory issues must be considered, as the approval process for ODFs may differ from that of traditional dosage forms, requiring additional studies to assess safety, efficacy, and stability. However, despite these challenges, ODFs have demonstrated significant potential in improving patient compliance and convenience, particularly in pediatric and geriatric populations, and continued research and development in this area may lead to further innovations in drug delivery.[18]

2.1. Techniques to increase ODFs' loading capacity

2.1.1. Solubilization of medicines with limited water solubility

Enhancing the solubility of substances by solid dispersion medications that aren't very soluble by combining them with a neutral polymeric carrier, which increases the effective surface for wettability and inhibits aggregation.

Table 1: proprietary technology platform ODF.

Proprietary technology	Technological platform
Soluleaves™	Edible thin films with a variety of flavors, vitamins, and APIs are added for gradual release after adhering to the oral mucosa.
WaterTab™	In order to limit heat and moisture exposure and to increase product stability, a technique was developed to load a precise dosage of API into the pre-assembled body of digestive strips. Orally or topically using it is an option.
Foam burst™	A unique patent for a foam film capsule with a honeycombed structure that delivers flavors for speedy dissolving and a satisfying mouthfeel was generated using Soluleaves technology.
Rapid Film®	According to a patent from Labtec GmBH, medications (up to 30 mg) can be included in water-soluble polymers rather than adhesives for rapid oral release.
Bio-erodible mucoadhesive (BEMA®)	The technique is designed for multiple, adherent bioerodible coatings on the oral mucosa and disperse APIs from the backing layer in a single direction for an instant impact.

Micronization and the use of nanoparticles are also effective methods for increasing drug solubility and dissolution rates. Edible strips made with hydroxypropyl methylcellulose been utilized to enhance the dissolving performance and inadequately soluble medication bioavailability like naproxen, fenofibrate, and griseofulvin.

2.2. Methods for masking flavor

Using an appropriate agent, there is an obvious decrease in the bad taste.

Taste masking technology includes two aspects- (1) suitable taste-masking substances, such as polymers, sweeteners, flavors, and amino acids, etc. (2) Using procedures that effectively disguise flavor.

Both the procedure's efficiency and the taste masking's quality may be significantly influenced by an appropriate taste masking approach. They are as follows- Adding flavorings and sweeteners, and adding complexing agents, Solid dispersion, and Complexation with ion exchange.

2.3. Advantages of taste masking

The capacity to disguise the bitter taste of medications increases patient compliance, certain medications' stability, therapeutic effectiveness, some medications' bioavailability, and some medications' organoleptic properties.[19]

2.4. Taste masking methods

2.4.1. Inclusion complexation with β-cyclodextrins

To disguise the taste of bitter medications, cyclodextrin complexation is a helpful approach. The drug molecule is incorporated into the cyclodextrin molecule's cavity during this procedure, which increases the solubility, stability, and bioavailability of the drug. Beta-cyclodextrins are commonly used in this technique owing to their capacity to encapsulate a broad variety of pharmaceuticals. However, the size of the cavity and the medication molecule determine how well the flavor is covered up.[20] Alpha-cyclodextrins are smaller and may not be suitable for some drugs, while gamma-cyclodextrins are larger but may have lower complexation ability.[21] It has been suggested that cyclodextrin complexation works better in covering up the taste of low-dose medications.[22] It is important to consider appropriate taste masking techniques for pediatric drug formulations. Incorporating cyclodextrin complexes into films can achieve good uniform distribution of the drug.[23]

2.4.2. API preparation example using cyclodextrins complexation

Alpha, beta, gamma, and HPCD CDs, as well as API, were precisely weighed in a 1:1 ratio (drug: carrier). The kneading technique.[24] where F1 is the CD/API complex, F2 is the CD/API complex, F3 is the CD/API complex, and F4 is the HPCD/API complex, was utilized to produce API-CD complexes. In order to make a paste, the API was first dissolved in 2 mL of ethanol and then added to the CD slurry in ethanol. The paste was then homogenized by being mixed with a mortar and pestle for an hour, and all solvents were then removed by drying the mixture at 80°C for 24 hours.[25]

2.5. Solid agglomeration

A solid agglomeration is a collection of solid products that generally consists of a hydrophilic matrix and a hydrophobic medicine, each containing at least two distinct components. The matrix can either be crystalline or amorphous. Crystalline or amorphous particles (clusters) can be used to disseminate the medication molecules. The carrier dissolves when watery liquids are used to mix the solid dispersion, releasing the medication as minute colloidal particles. Poorly water-soluble medications dissolve more quickly and have a better bioavailability thanks to the larger surface area.

2.6. Type of carriers

1. Crystalline carriers from the first generation include urea, carbohydrates, and organic acids.
2. Synthetic polymers including povidone (PVP), polyethylene glycols (PEG), and polymethacrylates are second-generation carriers. HPMC, HPC, or starch derivatives such cyclodextrins are examples of natural

polymers.

3. Surface-active self-emulsifying carriers of the third generation include poloxamer 408, Tween 80, and Gelucire.

2.7. Techniques of solid dispersion

1. Melting (Fusion) Method
2. Solvent Evaporation Method
3. Kneading method

2.7.1. Melting (Fusion) Method

A physical combination of a medication and a water-soluble carrier is created using a mortar and pestle to get a homogeneous dispersion, and then the mixture is heated until it melts. This is the melting or fusing method that was initially suggested by.[26] The melting solution is then instantly solidified in an ice bath while being aggressively mixed. Crushed, pulverized, and sieved are applied to the final solid bulk.

2.7.2. Technique for solvent evaporation

The physical mixture of the drug and carrier (vitamin-E, PVP K-30, PEG 6000, PEG-8000) ratio 1:1, 1:2, 1:4 by weight, using the solvent evaporation method. The medication was dissolved in ethanol, followed by the dissolution of additional carriers. The solvent was then removed by evaporation while the mixture was kept at 40°C for 24 hours with careful stirring, as seen inFigure 1. Following collection, the solid dispersions were dried for 48 hours at room temperature. Utilizing a porcelain mortar and pestle, the solid mass was then ground up before being sieved with no. 80 mesh. and kept at room temperature and desiccated for future use.

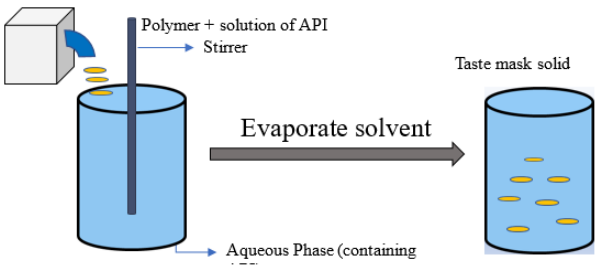

Figure 1: Technique for solvent evaporation

Advantage: The solvent technique is that because organic solvents must evaporate at low temperatures and Drug or carrier breakdown due to heat can be prevented.

2.7.3. Kneading technique

This process involves soaking the carrier in water to make it into a paste, adding the medicine, and kneading for a predetermined period of time. The dough is then passed after being dried. As necessary, filter through a sieve.

3. Complexation With ion-exchange

As demonstrated in Figure 2 Polymers with acidic or basic functional groups make up ion exchange resins (IERs), which are insoluble that can exchange counter-ions with the surrounding fluids. Low-molecular-weight minerals like calcium and magnesium are used in this ion exchange process in industrial and home water treatment. This exchange occurs in vitro and in vivo in the pharmaceutical sector for bigger organic ions with molecular weights up to several hundred Daltons.

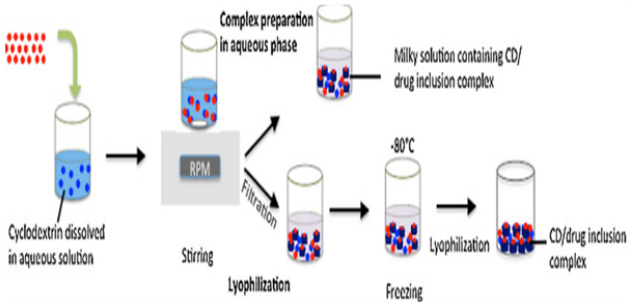

Figure 2: Preparation of API - cyclodextrins complexation

IERs are safe and harmless because All solvents cannot dissolve them. and at all PH values, and their high molecular weight prevents absorption by the body. They have been used by pharmaceutical companies as both excipients and active compounds in various solid and liquid formulations, including ODTs, chewable tablets, fast-melt formulations, thin film strips, gums, candies, and stick packs, to change API release, taste masking, and improve API stability. IERs are beneficial for taste masking because they form a complex with APIs that inhibits direct contact with taste buds. Additionally, IER polymers have a small particle size, resulting in a less gritty mouthfeel, which enhances palatability. IERs can achieve superior taste masking effectiveness and longevity compared to conventional methods, as seen in a study where a IERs (AMBERLITE) were combined with BCS Class I API at a 1:1 API-to-resin (w/w) ratio. When the Cmax of the API-resin complex was divided by the Cmax of the API%, the resultant resinate had a taste-masking duration of 20 minutes and a taste-masking effectiveness of 94%.

Since the mid-1950s, IERs have been used in pharmaceutical formulations to improve the stability of vitamin B formulations (Edward F). One of the most effective antitussives and cough suppressants.

Advantage: long-lasting high taste-masking effectiveness simple transition from laboratory to industrial scale, application to fluids and suspensions, superior palatability, a smoother mouthfeel elimination of innovative flavor.

4. Formulation of Oral Thin Films That Dissolve Quickly

Mechanical characteristics, flavor muffling, quick-dissolving, physical attributes, and mouth sensation are all factors to consider while formulating. Oral thin films that dissolve quickly have a surface area of 5-20 cm^2. APIs can be used in amounts of up to 30 mg. All excipients utilized should be labeled as generally recognized as safe (GRAS) from a regulatory standpoint. and used in accordance with the Inactive Ingredients Limit (IIG limit). Table 2 Describes the many parts of oral thin films that dissolve quickly.

Table 2: omponents ofrapid- oral thin film dissolver

Components	% w/w
Active component of a medication	6-30
polymers that create films	Upto40
Plasticizers	0-21
Surfactants	q. s.
Agents for sweetness	2-4
substances that stimulate saliva	2-4
Extreme disintegrates	Upto 6
colored substances	Upto 1
Agents for flavor	Upto10

4.1. *Examples of natural and synthetic polymers*

1. *Natural polymer:* Pullulan, Starch, Pectin, Sodium alginate, Maltodextrin, Lycoat NG 73.
2. *Synthetic polymer:* Hydroxy propyl methyl cellulose (HPMC), Polyvinyl pyrrolidone (PVP), Kollicoat, Hydroxypropyl cellulose, Carboxy methyl cellulose (CMC), Poly ethylene oxide

4.2. *Examples of natural and artificial sweeteners*

1. *Natural:* xylose, ribose, glucose, sucrose, maltose, steviosides, dextrose, fructose, liq. Glucose, sorbitol and mannitol.
2. *Artificial:* sodium or calcium saccharin salts, Neotame & Altitame.

4.3. *Examples of flavoring agents*

1. *Flavor oils:* Peppermint oil, cinnamon oil, spearmint oil, nutmeg oil
2. *Fruity flavors:* Vanilla, cocoa, coffee, chocolate, and citrus
3. *Fruit essence type:* Apple, raspberry, cherry, pineapple

5. Manufacturing Methods

Solvent casting is a common method used to produce thin films for drug delivery. This method involves dissolving the medication and polymer in separate solutions and then mixed to create a uniform mixture. This mixture is then cast onto a petri dish and let to dry. After that, the film may be reduced to the appropriate size for administration. In this particular case, the films were produced using varying concentrations of polymer and loaded with a specific amount of API. Careful attention was paid to ensuring a uniform distribution of the medication and polymer in the solution and eliminating any air bubbles before casting. Films with any imperfections were excluded from the study.

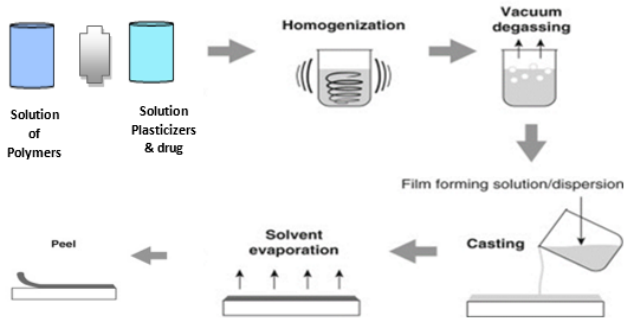

Figure 3: Petri dish film manufacturing method

The method used most frequently for producing oral thin films that dissolve fast.

5.1. *Steps*

(i) Water dissolves polymers that are water-soluble. (ii) Under high shear, more excipients and An aqueous solution is used to dissolve APIs. (iii) The two liquids are mixed to create a homogeneous, viscous solution. (iv) Before being transported to the casting station, The remedy is aerated. It is cast into the film at the casting station using a 30-120 cm thick release liner.

Process parameters: (I) (20–90 °C) mixing temperature. (ii) 40–120 minutes for agitation. (III) Rotating speeds range from 1000 to 2000 RPM. (iv) 80 liters per hour flow rate when defoaming. (v) Casting process time is 40 to 45 minutes**.** (vi) The drying range is 50–130 °C.

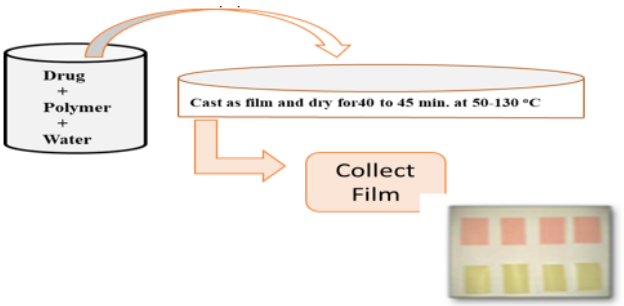

Figure 4: Solvent casting method

The method has the following benefits: (1) It is less expensive; (2) It is preferred to hot melt extrusion because it does not expose API to high temperatures, which could lead to heat-sensitive APIs deteriorating; (3) The consistency of thickness and clarity of films is improved; (4) They shine beautifully; (5) They don't have flaws like die lines; and (6) They are more flexible and have better physical properties.

6. Formulation of Sustained-Release Oral Thin Films

6.1.

6.1.1. Polymers use in sustained release oral thin films layer:

Eudrasget RS 100, Ethylcellulose, PVP k30, Cellulose propionate, Glycerine, poly (lactide) (PLA), poly (lactide-co-glycolide) (PLGA) copolymers, poly (ε-caprolactone) (PCL), and poly (amino acids), Natural polymers like alginate, chitosan, gelatin, and albumin.

7. Methodology

7.1. Polymeric nano- and mocroparticles

A method for making nanoparticles called solvent evaporation uses ethyl acetate to make emulsions out of polymer solutions made in organic solvents. Evaporating the solvent turns the emulsion into a suspension of nanoparticles, which is then allowed to permeate into the continuous phase of the emulsion. High-speed homogenization or ultrasonication are utilized with single and double emulsions. By magnetic stirring or at low pressure, the solvent evaporates and solidifies. Ultracentrifugation is used to collect nanoparticles, which are then rinsed to get rid of the surfactants before being lyophilized.

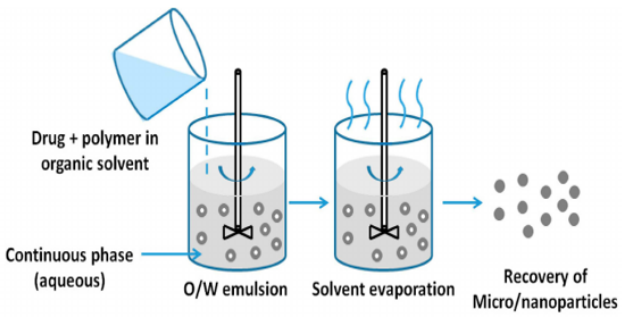

Figure 5: Solvent evaporation technique

Advantages: Improve the water-soluble medication solubility, Targeted delivery system of drugs**,** Controlled and sustained release of drugs.

8. Matrix polymer/co precipitation method:

The co-precipitation (CP) process uses the anti-solvency principle to produce particles. Initially, the carrier molecule is dissolved in an organic solvent, and the drug is added to the solution under stirring conditions. Water, acting as an anti-solvent, is then added dropwise to create particles and induce precipitate formation. To get rid of any leftover solvent, the resulting suspension is filtered, washed and dried.

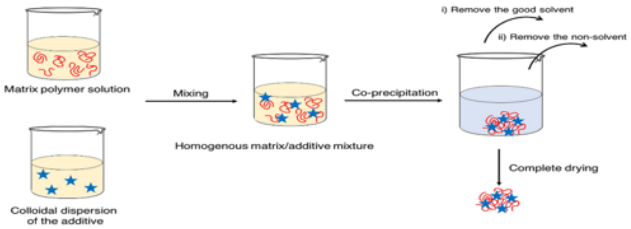

Figure 6: Co-precipitation method

The co-precipitation (CP) process uses various polymer ingredients, including HPMC, HPMCAS, Polymethacrylates, cellulose acetate phthalate, polyvinyl phthalate, polymethyl methacrylate, and sodium alginate. Solvent systems such as dimethylacetamide, N-methyl-pyrrolidone, and dimethylformamide are popular for drugs that melt quickly, those with low solubility, and long-chained polymer matrix. The ionic characteristics of the polymer matrix facilitate precipitation of drug and polymer components into SD solid mass under appropriate pH circumstances. CP process benefits include easy production, versatility, efficiency, affordability, and modification for release of high molecular weight molecules. Sustained release formulations can sustain therapeutic concentrations for a long time, avoid high blood concentrations, increase patient compliance, decrease toxicity, increase drug stability, reduce adverse effects, increase therapeutic effectiveness, and enable chronic dosing to reduce drug accumulation and increase bioavailability.

9. Manufacturing of Bilayer Films

The following is a summary of the manufacturing processes described in Figures 8, 9, 10 and 11.

9.1. Five approaches

1. Method I (double-casting)
2. Method II (compressing)
3. Method III (pasting)
4. Method IV (dropping)
5. Method V (spraying)

9.2. Method I (double-casting)

After the first film was cast at a height of 300 meters on the coating apparatus and dried, the second film was cast on top of it (overnight, room temperature).[27]

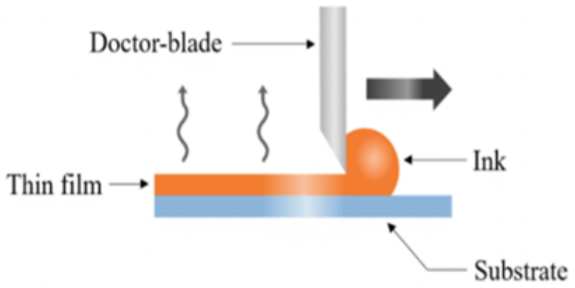

Figure 7: Double-casting method

9.3. Method II (compressing)

There were two films piled on top of one another. Due to incomplete solvent evaporation and incomplete drying, one film still had a sticky surface. The layers were rolled up and squeezed. A metal plate was then used to weight the resulting double-layer down overnight in order to strengthen the bond between the two layers.[27]

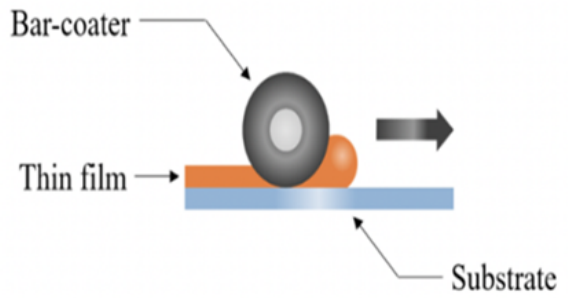

Figure 8: Compressing method

9.4. Method III (dropping)

Using the syringe from the Drop-Shape-Analyzer, precise volumes of liquid (10-30 μl) of various aqueous and The previously created first layer film was covered with drops of ethanolic polymer solutions, which was a film with a surface area of 2 to 3 cm^2, and the behavior of the films was examined.[27]

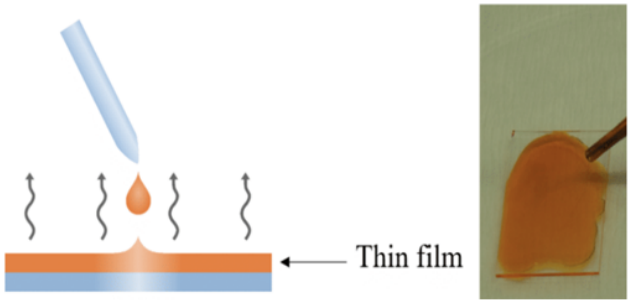

Figure 9: Dropping method

9.5. Method IV (pasting)

Previously prepared first layer film. Each fragment of a film measured 1 cm by 2 cm. These pieces were adhered to a 2 cm-3 cm base film. Giving stickiness to encourage adhering at the base film surface, The solvents utilized in the suitability studies were used as binders to begin progressively dissolving the smaller film. Using a Drop-Shape-Analyzer, the solvents' contact angle was determined.[27]

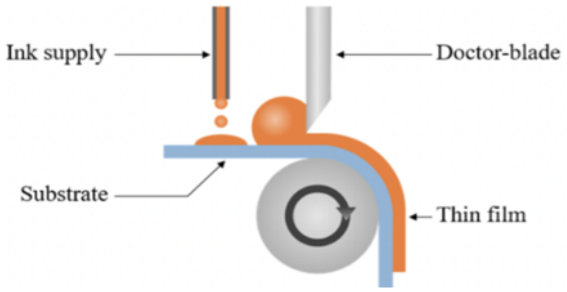

Figure 10: Pasting method

9.6. Method V (spraying)

The remedy was prepared by dissolving it, together with polymers and other excipients, in 5ml of 95% ethanol or another appropriate organic solvent. Then, using a spraying gun and nozzle, this solution was administered to the backside (also known as the opposing side) of the pre-dried selected formulation for the primary dissolving layer in a petri dish. To achieve a uniform distribution and quick drying without compromising the integrity of the fast-dissolving layer, the spraying procedure was carried out step-by-step.[27]

The evaluation of mouth-dissolving films often involves a variety of tests meant to confirm the product's dependability, efficacy, and quality. The tests include thickness measurements, folding endurance, moisture

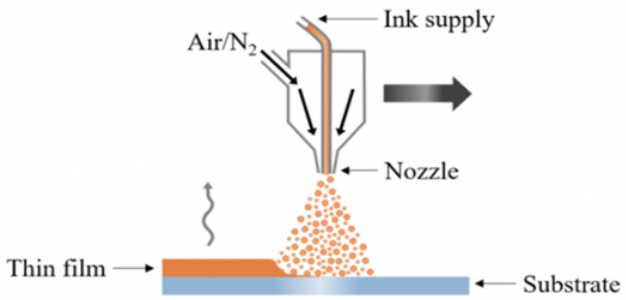

Figure 11: Spraying method

uptake, surface pH, weight variation, content uniformity, in vitro disintegration time, in vitro dissolution study, morphology studies (appearance) using SEM, FT-IR, DSC, surface and structural morphology using SEM, and palatability study.

Thickness measurements are performed using micrometre screw gauges to ensure that the film's thickness is consistent throughout. The film's flexibility is measured by folding it 300 times without breaking or 180 degrees in the same plane till it fails to assess folding resilience. Moisture uptake is determined to ensure that the amount of moisture in the film is controlled and does not impact the product's characteristics.

The film is placed on a 1.5% w/v agar gel surface, and Then, pH paper is used to test the film's surface pH. To make sure the medication content is consistent, weight fluctuation is assessed, and By calculating the API content in each strip, one may gauge the consistency of the material. Determining the film's ability to dissolve and disintegrate, Studies on in vitro dissolving and in vitro disintegration time are performed. Morphology studies using SEM are used to investigate surface and structural morphology.

FT-IR and DSC are used to investigate any undesirable interactions between formulation elements and pure API and to show that the medicine is compatible with other auxiliary chemicals. Finally, a palatability study is performed to evaluate the taste of the product.

Overall, these tests help ensure that the mouth dissolving film is of high quality, has consistent drug content, and is safe and effective for use.

9.7. Nanoparticle recovery

9.7.1. Drug incorporation efficiency

$$\text{D} \quad \% \text{ Yield} = \frac{\text{Actual weight of product}}{} \times 100$$

$$\text{Drug Entrapment \%} = \frac{\text{Mass of drug in Nanoparticles}}{\text{Mass of drug used in formulation}} \times 100$$

9.7.2. OTF stability

OTF stability is preserved throughout a 12-month period in controlled environments (25 °C and 40 °C with 60 % and 75 % relative humidity, respectively), on the basis of International Council on Harmonisation recommendations. Weight homogeneity, morphological qualities, film density, tensile characteristics, the presence of water, and dissolution evaluations must all be checked on OTFs during storage.[28–30]

10. Conclusion

Pharmaceutical businesses across a range of industries have expanded their research and development efforts to incorporate this technology into a variety of product categories as a result of the pioneering trend known as oral thin films (OTFs). This development offers a cutting-edge medication delivery technique, which is especially advantageous for people who have trouble swallowing, such young children and aged people. OTFs also provide a number of benefits over increased bioavailability, alternative dose formulations, etc. and an instant onset of action. One of the most important oral dose forms, it is especially helpful in emergency situations or when quick therapeutic effects are required. It follows that OTFs, which are distinguished by good patient compliance and a variety of advantages, contain promising creative potential for the future.

11. Source of Funding

None.

12. Conflict of Interest

None

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