FORMULATION INSIGHTS INTO ORAL THIN FILMS FOR ENHANCED DRUG DELIVERY: POLYMERS, PLASTICISERS, AND BEYOND

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ABSTRACT

Among the more practical methods is the oral administration of various pharmaceutical dosage forms, including tablets, capsules, syrup, suspension, and emulsion. Drug delivery techniques that dissolve quickly have created a variety of fast-dissolving preparations, including MDT and mouth-dissolving film. The hydrophilic polymer used to make the novel oral thin film dissolves rapidly in the buccal cavity and mouth. Compared to mouth-dissolving tablets, mouth-dissolving films are better because of their reduced production costs. Due to its self-administration, rapid dissolution, and rapid absorption, oral films offer a flexible dose for juvenile and geriatric patients with difficulty swallowing tablets and capsules. The current study aims to provide information about different polymers and their concentrations. The main topics of this study are the use of plasticisers, polymers, and sweeteners, as well as the many techniques for making oral films and the various standards by which the films are judged.

Keywords: Oral film, mouth, juvenile patients, plasticisers, polymers

INTRODUCTION

The oral thin film is a contemporary technique for oral medication delivery based on transdermal patch technology [1]. The distribution mechanism is a skinny oral strip affixed to the patient's tongue or oral mucosal tissue. The film rapidly hydrates and sticks to the application site since it is moist with saliva. To release the drug for oromucosal absorption, it rapidly breaks down and dissolves [2]. Based on the dry film's total weight, at least 45% w/w of polymer should be present. The kind of polymer and volume employed in the formulation dictate how tough the strip is. The film you get should be strong enough to survive shipment and handling without breaking. Mouth dissolving films are stable, thin-dose formulations that dissolve in the mouth in seconds [3]. Pills, capsules, and syrups are traditional oral solid-dosage forms that are difficult for elderly and pediatric patients to swallow. Due to the high vascularisation of the buccal and oral mucosa, drugs can enter the systemic circulation right away without going via the digestive tract [4].

Drug administration to children, the elderly, and bedridden patients is made simple by these movies. A film should have excellent stability, good taste, and ease of handling [5]. Fast-dissolving oral thin film (FDF) is a solid dose medium; OTFs dissolve or disintegrate in 1 minute when placed in the mouth without chewing or water [6]. As the medication broke down in the mouth, its therapeutic effect was enhanced by pre-gastric absorption from the mouth, throat, and oesophagus as saliva travels into the stomach [7]. Fast-dissolving films may prefer adhesive tablets due to their comfort and flexibility [8]. Several polymers are available for the production of FDF [9]. Although the film is prepared using a variety of materials, including polymers, active pharmacological additives, film stabilising agents, sweeteners, tastes, textures, saliva-inducing agents, preservatives, and surfactants, the first and most crucial component that facilitates film formation is a polymer. Oral thin films, compressed tablet-based applications, and lyophilised devices are the three categories of quick-dissolve technologies [10].

Oral system:

Historically, Oral administration has been the most popular method for traditional and innovative drug delivery systems. This can be attributed to several clear factors, including patient acceptance and the convenience of administration. Almost all currently recognised theoretical mechanisms for oral administration are included in the types of sustained- and controlled-release systems used. As a result of limitations like sterility and possible harm at the administration site being reduced, dose design has more flexibility. As a result, it is easy to start a discussion about the many kinds of dosage forms by utilising those created for oral administration [11].

Oral cavity

The oral tissue epithelium's 40–50 cell layer produces mucus comprising proteins and carbohydrates. The mucosal thickness ranges from 100 to 200 μm at the base of the mouth, tongue, and gums. The submucosal layer secretes a little gel-like fluid called mucus, which is made up of 90%–99% water, 1%–5% water-insoluble glycoprotein, and other substances, such as proteins, enzymes, electrolytes, and nucleic acids [12, 13]. Lobules within the salivary glands, on the other hand, secrete saliva and parotid from the salivary duct near the sublingual canals and submandibular teeth. Usually, the mucosa of the lips and cheeks contains tiny salivary glands. One to two millilitres of saliva are released in a minute [14–15].

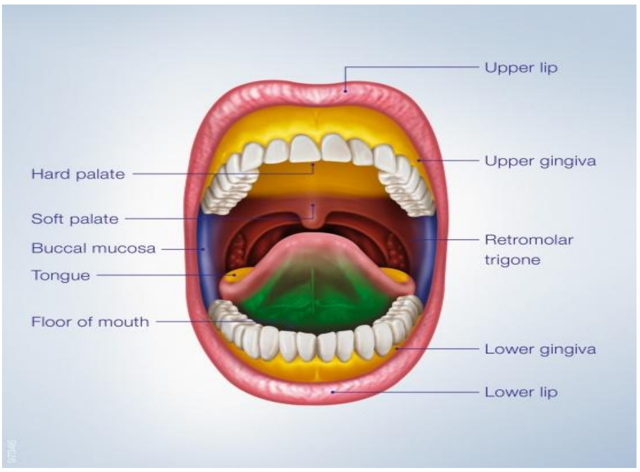

Fig (1): Oral cavity

Saliva comprises mucus, water, the enzymes amylase and lysozyme, mineral salts, immunoglobulins, and blood clotting factors [16]. Additionally, mucus and saliva serve as barriers to the oral mucosa. The lipophilic space between cells, the stratified epithelium's lipophilic membrane, and the more hydrophilic region are two different areas of the mucosal epithelial structure. The oral mucosa is more resilient to substance permeability than the intestinal mucosa and the epidermis [17]. It is estimated that the permeability of the buccal mucosa is 4–4000 times higher than that of the skin. The transcellular (intercellular) and paracellular (intercellular) pathways are the two main drug absorption pathways that the mucosal epithelium provides (fig. Particles with a high partition coefficient can more readily pass through the lipophilic structure that makes up cell membranes. At the same time, hydrophilic molecules can more readily enter the intercellular space because of their polarity. Whether a medication is hydrophilic, hydrophobic, or amphiphilic affects how well it is absorbed [18, 19].

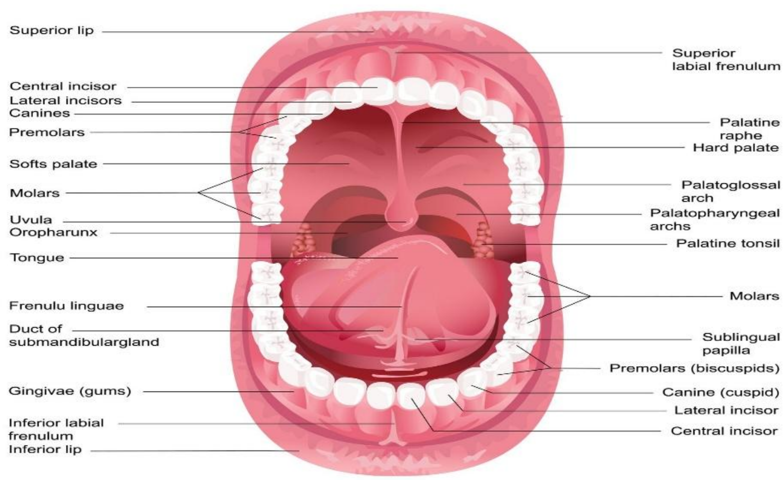

Fig. 2: Structure of the oral cavity

Advantages [20-28] :

1. Superior clarity and thickness homogeneity compared to extrusion.

2] Films have a beautiful sheen and are free of flaws like die lines.

3] Films offer superior physical qualities and are more flexible.

4] The onset of action is faster than using a tablet.

5] Its dosages did not require water during delivery.

6] There is no chance of choking.

7] Travelling is simple.

8] Rapid disintegration & dissolution in the oral cavity is provided due to the large surface area.

9] Ophthalmic thin films can deliver drugs to the eye.

Disadvantages :

1. Uniformity of dose is a technological problem.

2. They are hygroscopic.

3. Including high amounts (<40 mg/4 cm2 piece) is impossible.

4. Demand unique packaging to ensure the stability and security of the goods.

5. It is impossible to deliver unstable medications at buccal pH.

6. This method cannot be used to give medications that irritate the mucosa.

7. Only a medication with a low dosage requirement can be given.

8. Taste masking: Most medications require taste masking because of their bitter flavour. [29]

Oral drug delivery system:

The most practical, patient-compliant, economical, and secure method of administering medications for various illnesses is oral drug delivery. Some drawbacks of conventional oral formulations are low bioavailability, short gastrointestinal (GI) tract retention duration, and restricted targeting ability. In recent years, several drug delivery systems (DDSs) have been investigated and used for oral treatments, including the delivery of proteins, peptides, nucleic acids, and small-molecule medicines. Several nanoparticles (NPs), microparticles, hydrogels, or mixtures have improved the gut's bioavailability or target specificity. The primary foundation of the delivery systems comprises natural or synthetic components with characteristics like pH responsiveness, absorption enhancement, stimulation of living cells, and so forth. Additionally, various reactive oxygen species-responsive delivery methods are being employed for administering medications to treat metabolic disorders and inflammatory bowel disease. Because bioinspired and biomimetic systems are nontoxic, selective, specific, biocompatible, and biodegradable, they are regarded as superior oral medication delivery methods. These systems are used for oral medication delivery applications and are adapted or replicated from natural sources. They are highly effective at preventing GI acid and enzymatic breakdown of the medication or treatments and ensuring proper release at the intended location. The biomimetic materials' adaptable surface, motion, and structure significantly impact the oral drug administration system. Furthermore, these materials' loading and releasing profiles are sufficiently high for effective drug delivery. The following sections will discuss the functions of various bioinspired and biomimetic materials in oral drug delivery.

Oral thin films:

Most medications are administered to the local and systemic circulation by various methods, including enteral and parenteral; the most practical and often used route is enteral or oral. For a more extended period, this was the standard and traditional method [30]. The benefits of the oral route include providing a wide variety of medications with high patient compliance [31]. About 80–90% of the active pharmaceutical substances are taken orally; this method was deemed popular for several reasons, including its ease of administration, cost-effectiveness, high patient compliance, and safety. Oral medication delivery encompasses a range of dose forms, including liquids (syrups, suspensions, etc.) and solids (tablets, capsules, etc.) [32]. Oral dispersible tablets, mouth dissolving tablets, and oral dissolving films are recent developments concentrating on oral solid dosage forms' rapid dissolving medication administration. Oral films were a great invention for a quick, portable, and readily ingested medication administration mechanism. Oral films are referred to as "simple soluble film" by the USFDA and "a thin film that readily dissolves in the oral cavity is commonly referred to as orodispersible film by the European Medicines Agency [33].

Methods of preparation

Solvent casting method

Solvent casting is the most popular method for producing OTFs since it is inexpensive to manufacture, simple to use, and requires little preparation. In short, substances that dissolve in water are created by mixing them in a heated magnetic stirrer. The drug and other excipients are added to this mixture to produce a viscous solution. The solvents in this method's solution are allowed to evaporate after being placed on a petri dish. Depending on the solvent system employed, these are kept in the oven for 20–25 or 24-48 hours at room temperature or for a shorter period at 40–50 °C. Films 15-20 mm in diameter and 0.2-0.3 mm thick were carefully removed from the petri plates once the solvents had evaporated. Depending on the proportion of active chemicals they contain, they are chopped into pieces of the correct size. 1, 7 In the solvent casting process, the semisolid gel mass is poured into suitable moulds and dried using gel-forming polymers. They are then trimmed into the proper sizes to prepare them [34, 35]. About 90% of them have used this method to formulate OTF. This approach has the advantage of producing a uniformly thick and flexible film. This approach is also incredibly inexpensive [36, 37].

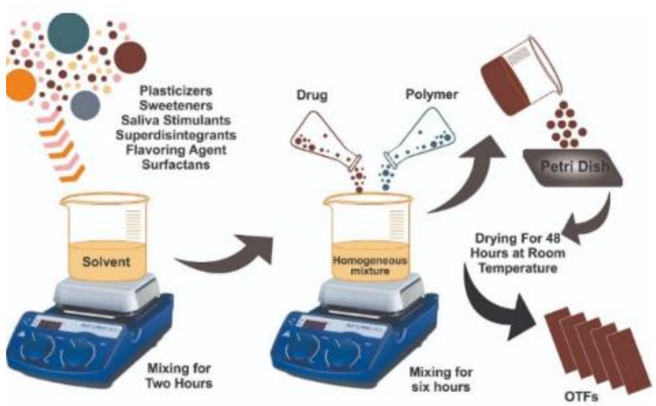

Fig. 3: Solvent casting method

Hot-melt extrusion method

Hot Melt Extrusion has created granules, sustained-release tablets, and transdermal administration systems. It draws inspiration from the industry that produces plastics. Oral film production components, such as combinations of medicines, polymers, and plasticisers, are extruded into different end forms to create specified drug-release profiles [42].

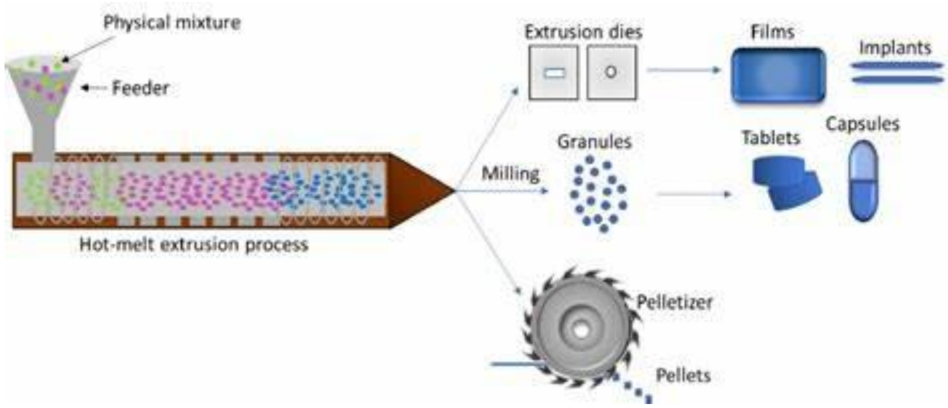

Fig (4): Hot melt extrusion

The heat treatment and absence of solvent make it unique. Heat is applied through the extruder's heaters to produce a molten mass driven out of the orifice once the API and other excipients have been mixed in a dry state. The films are allowed to cool before being cut to the appropriate size. Despite persistent problems with the films' thickness and breakdown, Hoffmann had talked about applying this technique to continuous-release oral films [43, 44]. The HME process has the following limitations: it may be challenging to locate heat-resistant film-forming polymers, and it is most effective with thermostable medications.

Solid dispersion method

Solid dispersion is the process of dispersing one or more solids (such as medications or therapeutic actives) into an inert carrier (like an amorphous hydrophilic polymer) using methods like HME. The drug is first dissolved in a suitable liquid solvent to form a solution. Then, without removing the liquid solvent, the solution is combined with the polyol melt, like polyethene glycol [45–48]. The medication or preferred solvent could not mix properly with the melted polyethene glycol. The drug's immiscible ingredients are pushed through dies to create the film's structure when it cools and solidifies into a dispersion. The type of liquid solvent used can affect the polymorphic form of the medication that precipitates in the solid dispersion [49].

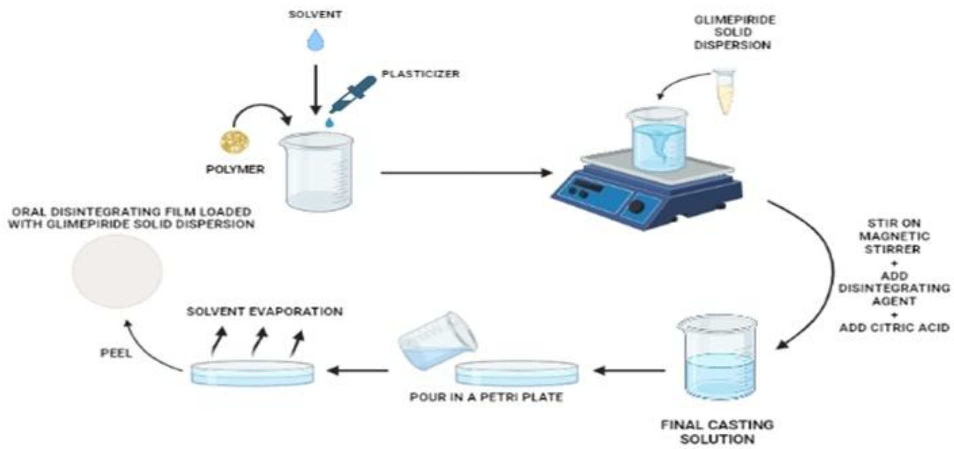

Fig. 5): Solid dispersion method

Rolling method

In the rolling process, the active component is added after the pre-mix has been prepared, and the film is formed. Along with other ingredients such as polar solvents, film-forming polymers, and API, the pre-mix batch is added to the main batch feed tank. A predetermined amount of the masterbatch is then fed by the first metering pump and control valve [50]. The right amount of medication is added to the mixer, then mixed for a sufficient amount of time to produce a homogenized matrix. A specific quantity of matrix is fed into the pan by the second metering pump. The metering roller measured the thickness of the film.Finally, the support roller removes the film that has been created on the substrate. The wet material is dried by controlled bottom drying [51–53].

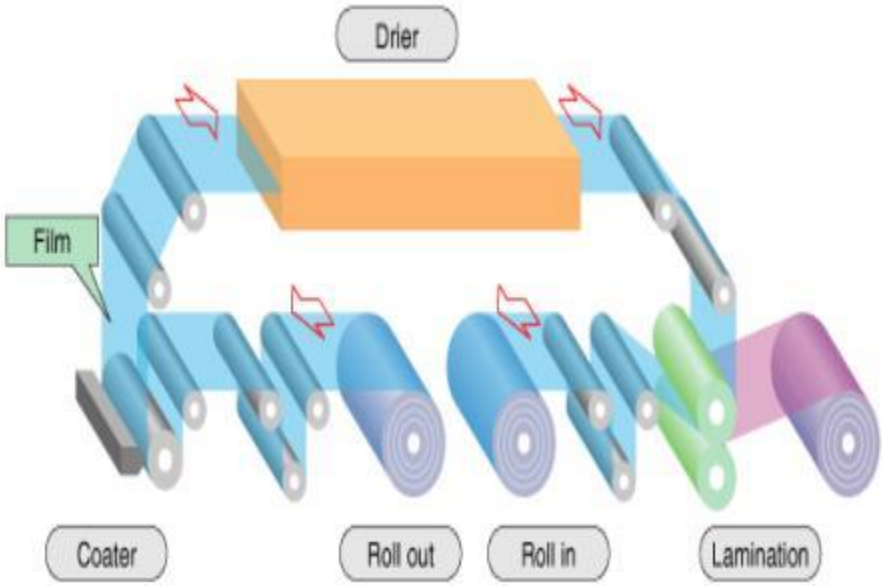

Fig (6): Rolling method

Evaluation of Oral Thin Films:

1. Thickness [54]: The Thickness of the films was measured at five points using a micrometre to ensure the uniformity of film thickness. After calculating the mean thickness, the analysis did not include patches with a more than 5% thickness variation.

2. Folding endurance: To determine the film's folding endurance, films with a constant cross-sectional area (4*4 cm2) were folded repeatedly until they broke.

3. Swelling index: The Swelling Index analyses the film's swelling caused by the polymers HPMC E-15 and gelatin.

4. Drug content: Dissolve a 4 cm2 film in 100 millilitres of 6.8 pH phosphate buffer to find the drug content. After appropriately diluting the solution, measure the absorbance at 259 nm.

5. Surface pH: A pH meter was used to measure the film's surface pH. With the aid of water, OTF was somewhat moistened. The pH was determined by touching the electrode to the film's surface.

Maintaining the film's pH is essential since an acidic or alkaline pH might irritate the oral mucosa; the goal was to keep the surface pH as close to neutral as feasible.

6. In vitro Disintegration time [55,56]: The first method involves a single drop of dissolving medium onto the firmly clamped film from a 10-millilitre pipette. Disintegration time (DT) is the time it takes for water to pierce the film. The second approach involved placing 2 millilitres of water in a petri plate with a film on the water's surface, then measuring how long it took for the film to dissolve. The disintegration time was calculated as the average of the three test results.

7. In-vitro dissolving Studies [57]: Using 900 millilitres of phosphate buffer as the dissolving medium, an in-vitro dissolution test was conducted in a USP II paddle dissolution equipment. The temperature was set to 100 rpm and kept at 37±0.5oC °C. A 4 cm2 piece of film was cut and adhered to the side wall of the basket. Every 30 seconds, 5 ml aliquots of the samples were obtained, and 5 ml of fresh phosphate buffer was added. Spectrophotometric analysis was performed on the extracted materials at a wavelength of 259 nm.

8. Dissolution rate using Conductometry [58]: Conductivity measurements can also be used to calculate the dissolution rate. The conductivity of 300 millilitres of water in a beaker was measured to get the background value. Set up the impeller and conductivity probe, and keep the temperature at 37±0.5oC °C. Set the stirrer to 100 rpm after the film has adhered to the beaker. Until the conductivity remained consistent, measurements were made every 15 seconds.

MECHANISM OF FILM FORMATION:

When the solvent evaporates, the film-forming system, which is applied straight to the skin, creates a thin, transparent layer. Because the volatile components of the carrier were lost after the formulation was applied to the skin, the composition of the film-forming system changed significantly, producing a pleasant residual film on the skin. The drug concentration rises during this process, attaining saturation and possibly oversaturating the skin. By preventing the skin barrier from being impacted by the formulation's thermodynamic effect, supersaturation enhances the drug's passage through the skin and lessens irritation and adverse effects.

Fick's diffusion equation can be modified to explain the idea of supersaturation. The formula for Fick's law of diffusion is

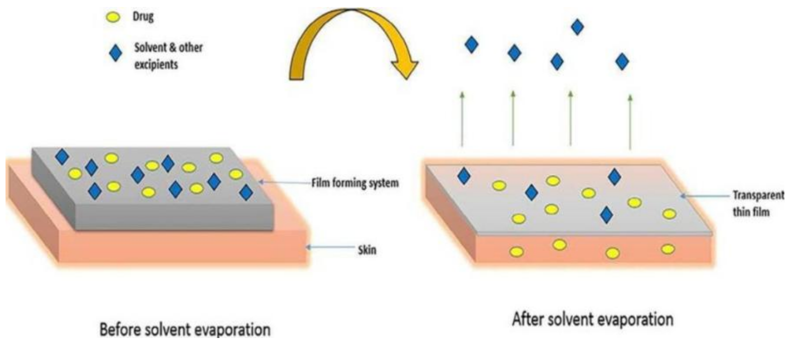

Fig. 8: Mechanism of film formation

The following equation describes the modified version of Fick's law of diffusion:

$$\mathbf{J = \alpha\ D/\gamma h}$$

Where a = Thermodynamic activity of drug within formulation

Γ= Thermodynamic activity of drug within the membrane

This equation states that the drug's flux is directly proportional to the system's thermodynamic activity, which is correlated with saturation. On the other hand, thermodynamic instability grows when supersaturation rises.

Active ingredients used in oral thin films

For absorption to take place, the API needs to dissolve. Absorption may not be appropriate if the active ingredient is very lipophilic, meaning it is insoluble in aqueous media. As a result, the drug's lipophilicity and solubility are delicately balanced. Passive diffusion is the primary method of medication absorption. Therefore, drug transport across oral mucosal membranes is significantly influenced by the partition coefficient, degree of ionisation, and molecular weight. When evaluating bioavailability, the pKa of the API and the level of ionisation at room pH must be considered. The lipophilicity or partition coefficient of the API is typically correlated with the degree of absorption. However, the drug's solubility is also significant. The drug's nonionized form diffuses through cellular membranes because it exhibits more lipid-soluble qualities.

Active Pharmaceutical Ingredients

1-25% w/w of the medication is typically present in the film. Fast-dissolving films can have various APIs added to them. With a dissolving time of less than 60 seconds, multivitamins up to 10% w/w of dry film weight were incorporated into the film. Numerous APIs that would be suitable options for producing fast-dissolving films have the potential to leave an unpleasant aftertaste. This makes the recipe unpleasant, particularly for pediatric settings. Therefore, the flavour must be concealed before adding the API to the fast-dissolving films.

Film Forming Polymers

The final film must be water-soluble since the main application of all thin film oral dosage forms is based on its dissolution in the oral cavity's saliva. Excipients or polymers must be water-soluble, have a low molecular weight, and have a higher film-forming potential to be used to create water-soluble thin film components. The polymer needs to have sufficient tensile, peel, and shear strengths. Both effectiveness and affordability are requirements for the polymer. The polymers can be employed alone or in combination to enhance the mouthfeel, flexibility, hydrophilicity, and solubility of films that dissolve quickly. The amount of polymer in the system and its form determine the strip's stiffness [59].

Plasticizer

One essential component of the fast-dissolving films is a plasticiser. Plasticiser lessens the films' brittleness and increases the strip's flexibility. Lowering the polymer's glass transition temperature significantly enhances the film-forming properties. The choice of plasticiser will be based on how well it works with the polymer and what kind of solvent is used for film casting. An unnecessary plasticiser can also cause the film to break, peel, and crack. It is also proposed that the use of specific plasticisers may impact the drug's absorption rate. Glycerol, propylene glycol, polyethene glycol, dimethyl, diethyl phthalate, tributyl, triethyl, acetyl citrate, triacetin, and castor oil are among the several plasticisers utilised in the production of the oral films.

Sweetening Agent

Sweeteners are now a necessary component of pharmaceutical medicines intended to dissolve or disintegrate in the mouth. Sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose are the traditional sources of sweeteners. Sorbitol, mannitol, and isomalt are examples of polyhydric alcohols that can be combined since they also have a pleasant mouthfeel and cooling effect. However, it should be mentioned that people on diets or those with diabetes should limit their use of natural sugars in these arrangements. Artificial sweeteners have become increasingly popular in food and medicinal preparations.

Saliva Stimulating Agent

The goal of utilising saliva-stimulating dealers is to raise the cost of producing saliva, which could be a helpful resource in accelerating the dissolution of formulations for rapid dissolving strips. Acids typically used in food preparation can also be utilised as salivary stimulants. Ascorbic acid, tartaric acid, lactic acid, malic acid, and citric acid are a few examples. Between 2 and 6% of the film's weight comprises these agents, alone or in combination.

Flavoring Agents

In the OFDF Formulations, flavours are added, preferably up to 10% w/w. The initial flavour standard is detected in the first few seconds after the product has been consumed, and the aftertaste of the components, which lasts for at least ten minutes, determines if an oral disintegrating or dissolving formulation is accepted with a person's assistance. The type of medicine in the system determines the flavour selection. Age has a significant role in taste susceptibility.

Coloring Agents

Various colours are available, including bespoke Pantone-matched hues, EU colours, FD&C colours, and herbal hues. When the medicine is present in the film as an insoluble particle or suspension, colouring agents must be incorporated into the oral film.

The ideal properties of a drug for the development of an oral film formulation[60]:

• The medication should be able to pass metabolism first.

• The taste should not be harsh.

• It should start working right away.

• The medication should be BCS class I, meaning it should be soluble and permeable.

•low dose frequency.

• The drug should have extensive high

Conclusion

OTFs' enhanced therapeutic impact, responsiveness, and patient compliance make them a more promising and beneficial delivery technique. They might be able to revive breath. Many companies are now producing oral films instead of tablet formulations due to the higher response of oral films. This kind of technology is quite promising and has been studied. OTF dosage forms have shown great promise as a cutting-edge alternative to traditional dosage forms.This is due to their cost-effective manufacturing, easy handling, storage, and transportation, as well as the possibility of incorporating various medication ingredients, including chemical medications, vaccinations, probiotics, and herbal extracts. They are also easy to administer for pediatric, geriatric, and uncooperative patients. Furthermore, ODF is gaining popularity as a delivery technique for a variety of ailments, such as lung diseases, mental or emotional disorders, pain management, nausea and vomiting, cardiovascular disease, oral inflammation, and erectile dysfunction.It is one of the most important oral dose forms that can be employed in an emergency and when a rapid onset effect is required. Therefore, it can be claimed that OTFs with high patient compliance and a host of advantages offer innovative, progressive potential.

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