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FAST DISSOLVING SUBLINGUAL FILMS AS A PROMISING DRUG DELIVERY ROUTE

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ABSTRACT

As an alternative to traditional dosage forms, fast dissolving drug delivery systems were initially created in the late 1970s. These systems are made up of solid dose forms that dissolve and break down rapidly in the mouth without the need for water. Oral thin films (OTFs) and oral disintegrating tablets (ODTs) are examples of fast-dissolving drug delivery systems. Drugs can enter the body by a variety of ways, including parenteral, buccal, sublingual, oral, transdermal, and rectal. Among these, the sublingual route of administration is a promising strategy for getting medications into the systemic circulation. Sublingual films offer a special chance to act as drug carriers and may release the medication rapidly into the sublingual area for immediate absorption and impact. Because the medicine has a higher bioavailability and passes through the hepatic first-pass metabolic process, the sublingual route of drug administration is particularly useful for providing speedier relief. a number of variables, including the salivary glands' production, other physiological variables, and the drug's physiochemical characteristics, such as its hydrophobicity, ability to attach to the oral mucosa, epithelial thickness, etc. The development of an effective sublingual film medication delivery device requires consideration of these factors. Sublingual films can be evaluated using a variety of criteria, including tensile strength, weight fluctuation, and thickness.

Keywords: Fast dissolving films, Sublingual route, Bypass first pass metabolism, Rapid onset of action, solvent casting and disintegration, oral strips, polymer.

INTRODUCTION

One of the most popular drug delivery methods is oral since it is more practical, economical, and easy to use, all of which increase patient compliance. For elderly and paediatric patients who are frightened of choking, the oral route presents challenges due to swallowing difficulties. Newer and safer drug delivery systems have been introduced as a result of patient convenience and compliance-focused research. Due to its quick disintegration or dissolve and ability to be self-administered without the need for water or chewing, fast dissolving drug delivery methods have recently begun to acquire recognition and appeal as one example with more consumer choice. In order to help children and elderly patients who have trouble swallowing tablets and capsules, fast-dissolving drug delivery devices were initially developed in the late 1970s. This delivery method uses a thin film that dissolves in a matter of seconds when placed on the tongue, avoiding first-pass metabolism and perhaps increasing the drug's bioavailability. Greater surface area accessibility causes fast salivary wetness, which causes disintegration and breakdown in the oral cavity in a matter of seconds. Unlike fast-dissolving tablets, oral dissolving films are flexible, making them less brittle and requiring no additional packaging to keep them safe during storage and transit. Patients with dysphasia have expressed greater satisfaction and acceptance of travelling without water when they are not required to carry it. As opposed to quickly dissolving tablets, there is no risk of choking. Although sublingual absorption is typically rapid, it is generally short. In terms of permeability, the buccal region of the oral cavity is more permeable than the palatal region, and the sublingual region is more permeable than both.

SUBLINGUAL GLAND

Salivary glands are located beneath the tongue on the floor of the mouth. Another name for them is sublingual glands. They generate mucin, which in turn generates saliva. Because saliva is produced by the glands and is essential for chewing and swallowing food, the inside of the mouth stays moisturised. One could say that absorption is directly proportional to layer thickness since it happens when the drug moves from the site of delivery into the systemic circulation. In this manner, the drug is absorbed. Sublingual > Buccal > Gingival > Palatal. The sublingual route can cause a rapid beginning of effect due to its high permeability and robust blood supply, allowing for frequent dosing regimens and the introduction of drugs with short delivery periods. Saliva dilutes the medication, which is then absorbed throughout the mouth cavity. (1,3).

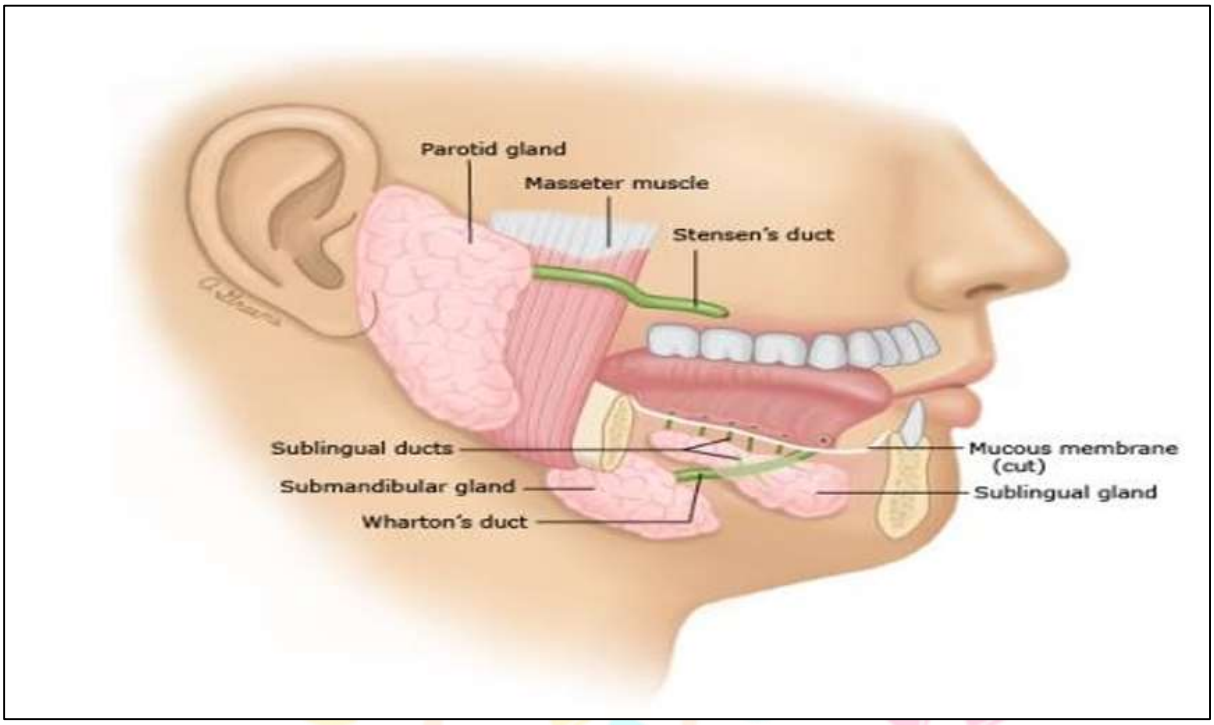

Fig no 1: Sublingual gland

SUBLINGUAL ABSORPTION

Drug solutes administered sublingually are quickly absorbed into the reticulated vein, which is located beneath the oral mucosa. From there, they are carried by the internal jugular vein and facial veins before being emptied into the systemic circulation. The medicine enters the bloodstream straight through the floor of the mouth and the ventral surface of the tongue when administered sublingually. Drug absorption into the oral mucosa primarily occurs by passive diffusion into the pilonidal membrane. Compared to oral absorption, sublingual absorption is three to ten times higher. (3)

Fig No 2: Sublingual Film

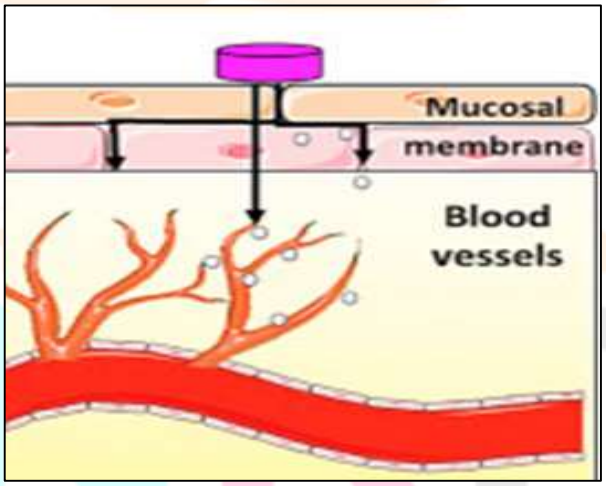

Fig No 3: Mechanism of Sublingual Absorption

MECHANISM OF SUBLINGUAL ABSORPTION

Three separate layers make up the mucosal lining. The epithelial membrane, which is made up of stratified squamous epithelial cells and serves as a protective barrier, is the outermost layer. The basement membrane, which resupplies the epithelium, is the innermost layer of the epithelial membrane. The submucosa and lamina propria are located beneath the epithelium. The lamina propria is a moist and less dense layer of connective tissue containing collagen and elastic fibres. Additionally, the oral submucosa has a substantial blood artery supply. The medication immediately diffuses into venous blood after being absorbed through the mucous membrane in the sublingual area. The venous blood from the oral cavity's sublingual area empties into a common trunk, which subsequently empties into the superior vena cava through the internal jugular vein, subclavian vein, and brachiocephalic vein. As opposed to oral administration, venous return from these areas enters the systemic circulation and avoids the pre-systemic drug clearance. The medicine becomes immediately available throughout the body and acts quickly when it drains directly into the systemic circulation. It should be mentioned that vasoconstriction from smoking may interfere with the absorption of drugs. (3)

FACTORS AFFECTING ON SUBLINGUAL ABSORPTION

1. **Physicochemical Properties of the Drug:** These include the drug's solubility, permeability, degree of ionization, oil/water partition coefficient, pH of the drug solution, and its molecular weight, all of which take part in absorption.

2. **Dosage Form Design:** The design of the dosage form, such as thickness, surface area, and the presence of permeation enhancers, can affect absorption.
3. **Permeability of the Sublingual Membrane:** The permeability of the sublingual mucosa can be affected by hydration, disease states, and the presence of food or other substances in the mouth.
4. **Blood Flow:** The rich blood supply in the sublingual area will promote rapid absorption but is subject to the limitations of blood flow, such as vasoconstriction or systemic disease.
5. **Patient Factors:** Individual patient factors like age, saliva production, oral health, and the presence of mucosal lesions can also have an effect on sublingual absorption. (4,7).

CRITERIA FOR SUBLINGUAL FAST DISSOLVING DRUG DELIVERY SYSTEM

1. **Molecular Weight:** Smaller molecules (typically less than 500 Da) preferred as they can easily penetrate the sublingual mucosa.
2. **Lipophilicity:** Drugs with moderate lipophilicity (log P between 1 to 3) are ideal as they can dissolve in the lipid rich environment of the oral mucosa.
3. **pH Stability:** The drug should be stable at the pH of the oral cavity (around 6.8). It should be partially unionized at this pH to facilitate absorption.
4. **Dose:** Drugs with low dose (up to 40 mg) are suitable for sublingual films.
5. **Taste:** The drug should have pleasant or neutral taste to ensure patient acceptability.
6. **Solubility:** The drug should be sufficiently soluble in saliva to ensure rapid dissolution and absorption.
7. **Stability:** The drug should be stable in water and saliva.
8. **Bioavailability:** The drug should have good bioavailability when administered sublingually, bypassing the first-pass metabolism. (9).

ADVANTAGES OF SUBLINGUAL FAST DISSOLVING FILMS

1. This delivery method is significantly easier to use than tablets or capsules, which patients with mental, paediatric, and elderly conditions may find difficult to swallow.
2. Compared to liquid dose forms, this method of administration allows for more accurate dosing and more comfortable medication delivery.
3. It facilitates rapid or direct absorption of the medication through the mucosal lining of the mouth beneath the tongue, resulting in an instant systemic action.
4. The drug's bioavailability is increased by avoiding the GI tract, the hepatic portal system, and the hepatic first pass metabolism.
5. Quick absorption because of the tongue's high vascularization.
6. The medicine will be more stable because the pH in the mouth is comparatively neutral.
7. Better adherence from patients.(10,11).

DISADVANTAGES OF SUBLINGUAL FAST DISSOLVING FILMS

1. Not appropriate for patients who are unconscious or unwilling.
2. Not appropriate for bitter medications.
3. Smoking, eating, and drinking are prohibited.
4. It is prohibited to provide highly ionic drugs.
5. It is inconvenient to hold the dose in the mouth; if any is swallowed, the part needs to be handled as an oral dose and go through first pass metabolism.
6. It is not feasible to administer large dosages of medication.
7. The films are sensitive to moisture, and their packaging is not cost-effective. (10,11).

METHOD OF PREPARATION

1. Solvent Casting Method

It is a very old technique for making films. This process involves first dissolving the water-soluble polymers in water at 1,000 rpm and then heating the mixture to 60°C. Every other excipient colors, flavourings, sweeteners, etc. is dissolved independently. After that, both of the solutions are fully combined while being stirred at 1,000 rpm. The API is dissolved in an appropriate solvent and added to the resultant solution. Vacuum is used to remove the trapped air. The final solution is formed into a film, left to dry, and then cut into the desired size pieces. (5).

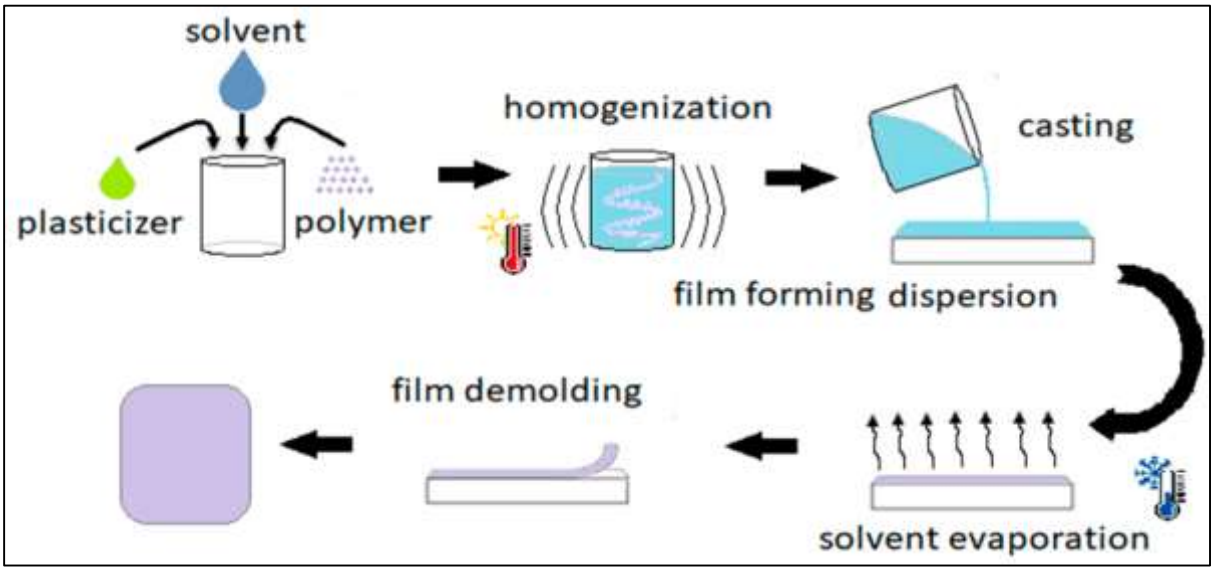

Fig No 4: Solvent Casting Method

2. **Semisolid Casting Method**

When working with acid-insoluble polymers, the semisolid casting process is typically employed. This process creates a water-soluble film-forming polymer solution, which is subsequently added to an acid-insoluble polymer solution created with sodium or ammonium hydroxide. To create the gel mass, plasticiser is then added. The gel mass's properties are influenced by the amount of plasticiser supplied. A heat-controlled roller/drum is then used to cast the gel mass into a ribbon film. the proportion of film-forming and acid-insoluble polymers. This process creates a film that is between 0.015 and 0.05 inches thick.

3. **Hot Melt Extrusion**

First, the medication and carriers are combined in a solid state using the hot melt extrusion process. The mixture is then melted by the extruder's heaters. Lastly, the dies form the melt into films. Hot melt extrusion has some advantages. Better content uniformity and anhydrous process with fewer operating units. Improved bioavailability and dissolution rate are the results of the API and other components. heated to a point where the mixture melts and is subsequently extruded to create thin films. Using the right method, the solvent is totally eliminated.

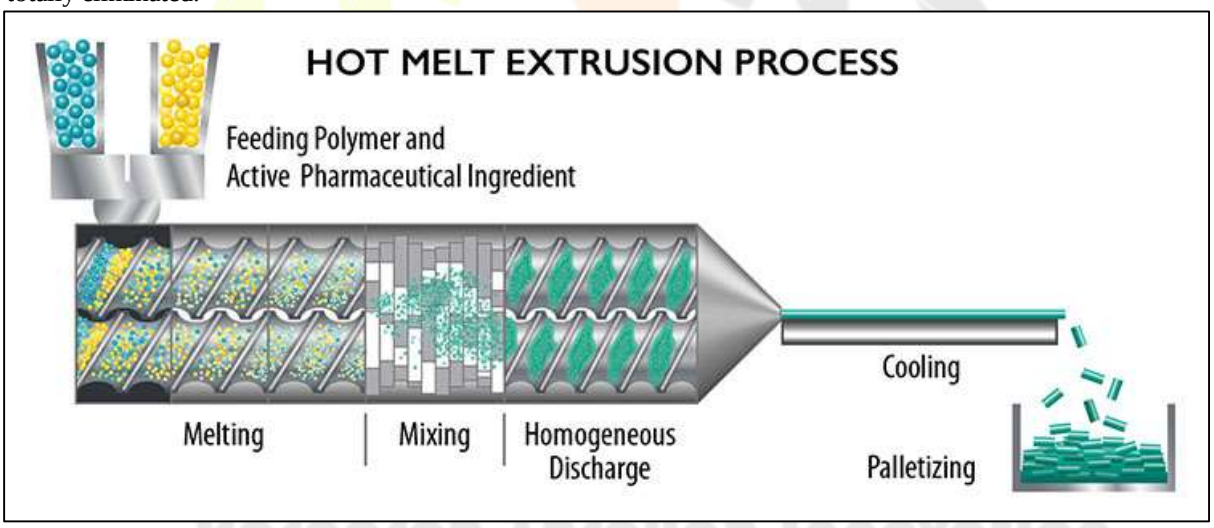

Fig No 5: Hot Melt Extrusion

4. **Rolling method**

The rolling method involves rolling a drug-containing solution or suspension on a carrier. Alcohol and water make up the majority of the solvent. Using a high shear processor, the film is dried on rollers and a cutter to the appropriate shapes and sizes. Additional ingredients, such as active agents, are dissolved in a tiny amount of aqueous solvent. A homogeneous, viscous solution is created when water-soluble hydrochloride is dissolved in water.

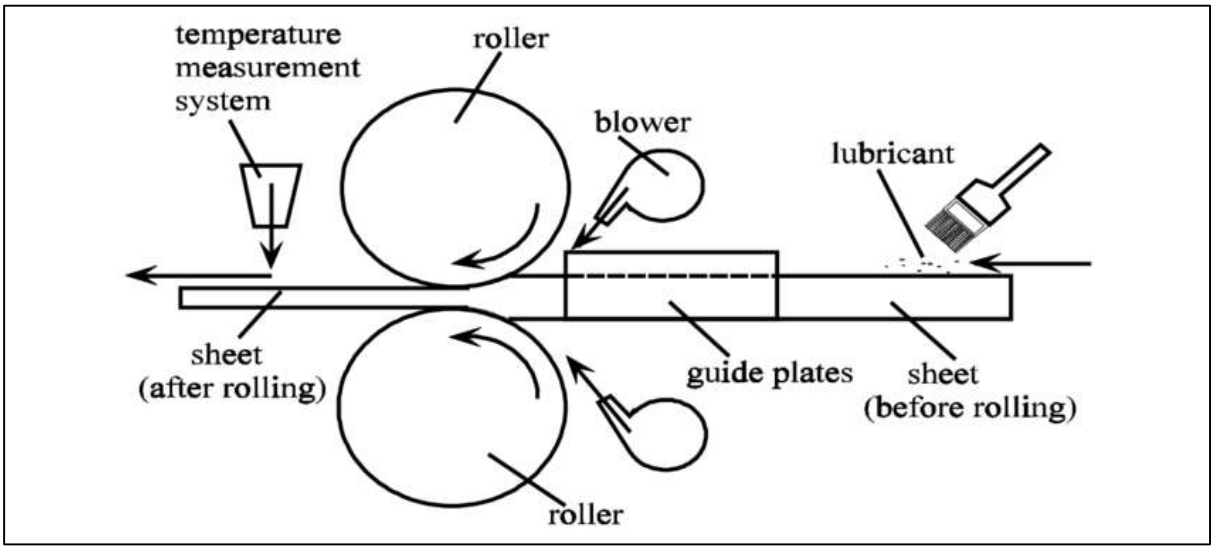

Fig No 6: Rolling Method

5. **Solid Dispersion Extrusion**
When amorphous hydrophilic polymers are present, the term "solid dispersion" describes the dispersion of active substances in an inert carrier in a solid form. The medication is first dissolved in an appropriate liquid solvent, and then this solution is added to a polyethylene glycol melt at a temperature lower than 70 °C without the liquid solvent being removed. Finally, the solid dispersions are run through dies to form them into strips.

FORMULATION OF SUBLINGUAL FAST DISSOLVING FILMS

Table No 1: Composition of Sublingual Film

Sr.no.	Composition of film	Quantity
1.	API	1-2 %
2.	Film forming agent	45-50 %
3.	Plasticizer	0-20 %
4.	Saliva stimulating agent	2-6 %
5.	Sweeting agent	3-6 %
6.	Flavouring agent	10 %
7.	Colouring agent	1%

1. **Active pharmaceutical agent:** At low dosages, the medications selected for oral films should remain stable in water and saliva. The medicine should have a 1-25% w/w concentration in the movie. The most promising options for inclusion in an oral fast-dissolving film are tiny dosage compounds. Multivitamins up to 10% w/w of dry film weight were added to the films, and they dissolved in less than 60 seconds. For better dissolution and uniformity in the oral fast-dissolving film, as well as for enhancing the texture of the film, micronized API is usually advantageous.
2. **Film-forming polymer:** The polymers can be used singly or in combination to produce the required strip characteristics. Oral films can be formulated using both natural and synthetic polymers. To create a water-soluble film formulation, excipients or polymers need to have a low molecular weight, be water soluble, and have a good ability to form films. The polymer that is utilised needs to be devoid of leachable contaminants, non-toxic, and non-irritating. It needs to be able to distribute and wet well. The polymer's tensile, peel, and shear strengths should all be sufficient. Cellulose or cellulose derivatives, pullulan, gelatine, Hypromellose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, xanthan gum, tragacanth gum, and guar gum are among the natural and synthetic polymers used in genera to create fast-dissolving films. Pullulan, a naturally occurring polymer that comes from non-animal sources and doesn't need to be chemically processed, should make up at least 45% of the dry film's weight.
3. **Plasticisers:** They reduce the brittleness of the strip and help to increase its flexibility. By reducing the glass transition temperature of the polymer, plasticiser greatly enhances strip characteristics. Glycerol, propylene glycol, low molecular weight propylene glycols, phthalate derivatives like dimethyl, diethyl, and dibutyl phthalate, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin, and castor oil are examples of plasticiser excipients. The usual range of concentrations for plasticisers is 0–20% w/w of the dry polymer weight.
4. **Saliva stimulating agent:** The purpose of using saliva-stimulating agents is to speed up the production of saliva, which will help the formulations of rapid-dissolving strips dissolve more quickly. These compounds are applied in amounts between 2 and 6% w/w of

the strip, either alone or in combination. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are examples of salivary stimulants.

5. **Sweetening agents:** In pharmaceutical medicines that dissolve or disintegrate in the mouth, sweeteners are now a necessary ingredient. The most widely used sweeteners include sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose. Sorbitol, mannitol, and isomalt are examples of polyhydric alcohols that can be mixed because they provide a pleasant mouthfeel and a cooling effect. First-generation artificial sweeteners include cyclamate, aspartame, and saccharin; second-generation artificial sweeteners include acesulfame-K, sucralose, alitame, and neotame. Usually used alone or in combination, sweeteners have concentrations between 3 to 6%w/w.
6. **Flavouring agents:** Up to 10%w/w of flavours should be present in formulations for fast-dissolving films. Both the aftertaste of the formulation, which lingers for at least 10 minutes, and the initial flavour quality noticed in the first few seconds after the product has been consumed play a significant role in determining an individual's acceptability of an oral disintegrating or dissolving formulation. While the younger generation prefers flavours like fruit punch, raspberry, and so forth, the elderly prefer flavours like mint or orange. A range of synthetic taste oils, oleo resins, and extracts made from different plant components such leaves, fruits, and flowers are available for use as flavouring agents. You can add menthol-containing essential oils or water-soluble extracts, strong mints like peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavours like lemon or orange, or sweet candies. Chocolate, vanillin, or fruit essences like pineapple, apple, raspberry, or cherry.
7. **Colouring agents:** pigments including titanium dioxide, silicon dioxide, and zinc oxide, natural colouring agents and concentrates, FD&C colours, EU colours, and custom Pantone-matched colours are also available.

EVALUATION PARAMETERS FOR SUBLINGUAL FILM

1. **Thickness:** The thickness of patch was measured by the using of digital vernier calliper whose least count was taken 0.01 mm from different points of film. The thickness was measure from 3 different locations from the patch and average of it was taken thereafter calculating the SD. (9)
2. **Weight variation:** Weight variation is calculated by weighing any five films from the formulation individually on a digital balance and then computing the average weight.
3. **Folding Endurance:** This was determined by folding the film at the same place repeatedly until the film broke apart. The maximum turns by which the film folded without breaking was taken as the folding endurance.
4. **Tensile strength:** Tensile strength is the maximum pressure that is applied at a point after which the film breaks up. It is found by the pressure applied at that break point divided by the cross-sectional area of the film as given in the following formula: same formula: Tensile strength = Load at failure × 100/ Film thickness × film width. (21).
5. **Uniformity of drug content:** This parameter is determined by dissolving a single film with the following dimensions of 2 x2 cm2 by placing it in a homogenized for some time of 30 mins immersed in a 100ml beaker containing stimulated saliva of pH 6.8 which is agitated continuously. From the obtained solution take out 1ml sample and mix proportionally in simulated saliva solution dilute the solution; make the observation of absorption measurement under UV spectrometer. Carried out the experiments for three times and noted for mean value. (17)
6. **Surface pH:** The film to be tested was taken in a petri dish was moistened with 0.5 ml of DW and left for 30 seconds. The pH was measured by allowing the electrode of the pH meter to come in contact with the formulation and allowing it to equilibrate for 1 minute. It was performed in triplicates and the mean was found.
7. **Percent elongation:** A film under pressure expands and such phenomenon is known as strain. It is usually deviation from the normal shape which elevates as the force applied elevates. In vitro dissolution studies: In vitro dissolution studies were done by using USP type II (Paddle Apparatus) which comprise 300 ml of pH 6.8 simulated salivary fluid as the dissolution medium which was maintained at 37 ± 0.5°C and RPM at 50. Samples at an interval of 30 seconds were pipette out with the amount removed replaced immediately with a fresh one to avoid sink condition which after subsequent removal of samples measured the per cent release determined and the plot against time.
8. **Ex vivo studies:** The permeating study was conducted in Franz diffusion cell with an internal diameter of 2.5cm. The buccal pouch of the slaughtered pig was purchased from a local slaughterhouse. The buccal mucosa was cut and trimmed to the same dimensions on all sides and then moistened with isotonic phosphate buffer 6.6 and used immediately. The mucosa was slapped between the receptor and donor compartments. The receptor compartment was loaded with 200 ml of the buffer of 7.4 pH and which was held at 37±0.2°C and RPM was kept at 30. A film of a specific dimension was weighed and kept with intimate contact with the excised mucosa which was wetted with a simulated salivary fluid of pH 6.8 after which at precise time intervals samples were taken out and analysed using a UV spectrophotometer. (17).
9. **Stability:** Stability studies were carried out under different experimental conditions. The film was covered with butter paper and then packed in aluminium foil and kept at room temperature in a stability chamber at 45-50°C RH for about 3 months. After this time period was passed films were again evaluated for their evaluation parameters. (15).

PACKAGING

The final packing material used in the pharmaceutical industry must preserve and protect the product's quality. Regarding fast-dissolving dosage forms, special and expensive materials are required for processing, and storage must be carefully considered to maintain the fast-dissolving dosage form. For sublingual films that are further packaged in one of the materials listed below, a single package is required. (10,12).

1. Paper, plastic, or foil pouches: These elastic pouches are a packing technique that can provide more resistance to environmental harm and are also resistant to damage. These pouches are created using either vertical or horizontal forming, sealing, or filling machinery during the product manufacturing process.

2. Single and aluminium pouch: These unique pouches are utilised for soluble films that dissolve quickly and have excellent barrier qualities. In addition to offering cost-effective foil lamination, this transparent pouch enables visual inspection of the product from

one side. Because foil lamination doesn't allow gas or moisture to pass through, it shows promise for use in nutraceutical applications. The most widely used pouches are made of aluminium.

3. Multiple-unit blister card: The blister, which has a depression in it and thus stores the formulation, and the lid, which closes the blister, are the two parts of a blister container. A heat-softening sheet of thermoplastic resin is used to create this blister packaging, and the softened sheet is vacuum-pressed into a mould of a specific size. When the cooling process is finished, the sheet is released from the mould and moves on to the filling line, where the formulation is placed inside the sheet and sealed with heat-sealable material. The material is selected based on the formulation's level of protection. Aluminium is utilised to create the foil, while plastic is employed to create the blister's depression, which serves as a moisture barrier.

MARKETED PRODUCTS

Table No 2: List of Marketed Sublingual Films

Sr.no.	Brand Name	API	Manufacturer
1.	Ondansetron	Ondansetron	Labtech
2.	Maxalt MLT	Rizatriptan	Merck
3.	Febrectol	Paracetamol	Pyrographer
4.	Nimulid	Nimesulide	Panacea Biotech
5.	FazaClo	Clozapine	Azur Pharma
6.	Triaminic	Phenylephrine HCl	Novartis
7.	Donepezil	Donepezil HCl	Labtech
8.	Romilast	Montelukast	Ranbaxy
9.	Sudafed	Phenylephrine HCl	Pfizer
10.	Chloraseptic	Benzocaine	Prestige

CONCLUSION

As previously said, sublingual films are becoming increasingly popular because of their special qualities, which include quicker medication administration into the bloodstream, convenience of use, quick commencement of effect, etc. The oral cavity's anatomy and the roles of its numerous components were next covered, and finally, the different aspects that must be considered while creating a high-quality product. Evaluation parameters were considered because it is a necessary criterion for assessing the final product's value. Last but not least, the many types of packaging requirements that are selected based on demands were examined because they play a crucial part in shielding the product from environmental hazards.

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