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A Review on Fast Dissolving Sublingual Films

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ABSTRACT

A new technology that increases patient compliance and acts quickly is called fast-dissolving films. The medicine travels through the hepatic first-pass metabolic pathway and has a higher bioavailability, making the sublingual route of drug delivery particularly helpful for rapid relief. Sublingual medications directly reach the systemic circulation by passing through the floor of the mouth and the tongue's ventral surface. From better lifecycle management to comfortable dosage for dysphagic pediatric, geriatric, and psychiatric patients, new sublingual technologies serve a wide range of pharmaceutical and patient demands. Fast dissolving film of antihypertensive drug used for patient having high blood pressure and heart failure.This article highlights an overview of the formulation aspects, manufacturing methods and evaluation parameters of fast-dissolving sublingual films.Fast-dissolving drug delivery systems are helpful in situations where swallowing tablets or capsules becomes difficult, such as motion sickness, an unexpected allergic reaction, coughing, or a lack of water.

Keywords: Sublingual delivery, Fast dissolving sublingual film, Improved bioavailability ,patient compliance.

INTRODUCTION

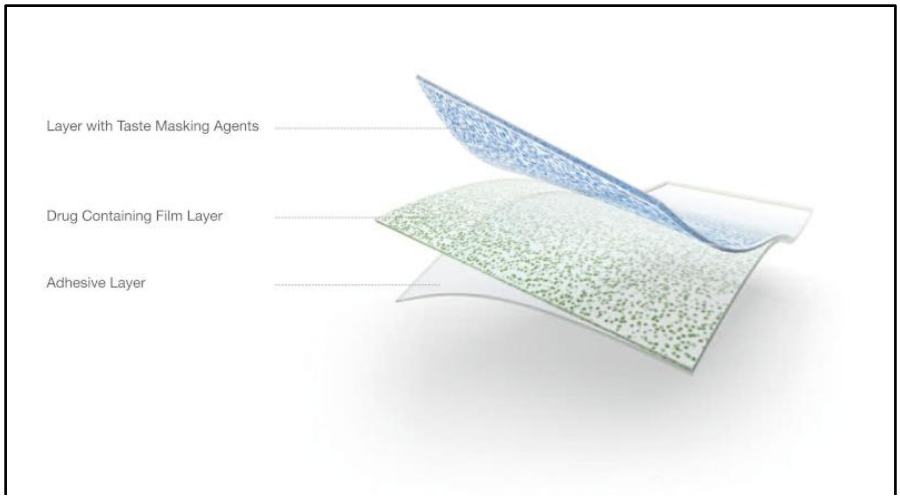
A drug that is administered orally in a fashion that allows for quick absorption through blood vessels beneath the tongue is referred to as sublingual. The medicine is administered sublingually, which means it is placed beneath the tongue and goes straight into the bloodstream through the floor of the mouth and the tongue's ventral surface. Before draining into the systemic circulation, the medication solutes are swiftly absorbed by the reticulated vein under the oral mucosa and subsequently carried through the facial veins, internal jugular vein, and brachiocephalic vein. The highly vascularized buccal mucosa provides a route of absorption that makes it possible for the drug to more directly enter the bloodstream and facilitate systemic medicine.

The term "sublingual" describes a technique for giving a medication orally so that it is quickly absorbed through blood vessels beneath the tongue. When a medication is administered sublingually, it is inserted beneath the tongue and goes straight through the floor of the mouth and the tongue's ventral surface to enter the bloodstream. The medication solutes enter the reticulated vein beneath the oral mucosa and are quickly absorbed. They are subsequently carried through the internal jugular vein, brachiocephalic vein, and facial veins before emptying into the systemic circulation. The highly vascularized buccal mucosa provides a route of absorption that makes it possible for the drug to more directly enter the bloodstream and facilitate systemic administration.[1]

Over the past 20 years, a great deal of work has gone into creating innovative drug delivery systems (NDDS). This technological gain can be attributed to the comparatively lower development costs and time associated with the introduction of NDDSs as opposed to the introduction of new chemical entities. Additionally, there are certain drawbacks to conventional or classical therapy. For example, oral dosage forms can be difficult for elderly and pediatric patients to swallow, and these systems exhibit lower absorption, which causes a delayed onset of action. Additionally, patient compliance can be a challenge for these patients. One of the better medicine delivery strategies is to create a sublingual delivery system.[2]

Fast dissolving sublingual films

The concept of sublingual films has been introduced to overcome the problems associated with conventional oral dosage forms and improve bioavailability there by optimization of therapy. Fast dissolving films are most advance form of solid dosage form due to flexibility. It improve efficacy of active pharmaceutical ingredient [API] dissolving in short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet.[3]



Ideal characteristics for a drug to formulate it into sublingual film [**4]**:

- The drug should have pleasant taste.
- The drug that is incorporated should have low dose up to 40mg.
- The drug with smaller and moderate molecular weight is preferable.
- The medication must to be well-stabilized and soluble in both water and saliva.
- It should be have partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissues.

OVERVIEW OF THE ORAL CAVITY [5]

The target sites for local drug delivery in the oral cavity include the following: Buccal, Sublingual, Periodontal region, Tongue, Gum. The tonsils, pharynx, larynx, and adenoids are additional desirable targeted locations that are close to the mouth cavity.Three types of medication administration through the oral cavity's membranes are distinguished within it:

i) Sublingual delivery.
ii) Buccal delivery.
iii) Local delivery.

When a medication is administered sublingually, it is inserted beneath the tongue and enters the bloodstream through the floor of the mouth and the tongue's ventral surface. The reticulated vein, which is located beneath the oral mucosa, quickly absorbs the medication solutes and transports them through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation**.**

SUBLINGUAL GLANDS[6]

Salivary glands are located on the floor of the mouth, beneath the tongue. Another name for them is sublingual glands. They create mucin, which then creates saliva. The food is mixed with the gland-produced fluid, which facilitates easy chewing. One could say that absorption is directly proportional to layer thickness since absorption is the movement of the medication from the site of administration into the systemic circulation. This is how the medication is absorbed. Sublingual > Gingival > Palatal > Buccal. The sublingual route can produce a rapid onset of action due to its high permeability and rich blood supply, allowing for frequent dosing of drugs with short delivery periods.

SUBLINGUAL ABSORPTION

The absorption capability of the buccal mucosa is impacted by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the molecular weight of the substances. For example, absorption of few drugs via the buccal mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline) 7.9. [7,8]

The oral epithelium and epidermis cells are also capable of retaining particles through a process known as endocytosis, which is the uptake of particles by a cell that appears to wrap itself around a particle hollowly. These flooded particles are usually too big to permeate through its partition).This mechanism cannot possibly be applied to the entire stratified epithelium. Furthermore, the possibility of active transport mechanisms functioning within the oral mucosa is low. Nonetheless, it is acknowledged that the circulatory system is stimulated and absorbed acidically. [9]

Special Features [10]

- Thin elegant film
- Various sizes and shapes
- Unobstructive
- Mucoadhesion
- Fast disintegration
- Quick dissolving
  Rapid release

FACTORS AFFECTING THE SUBLINGUAL ABSORPTION [11]

1) Solubility in Salivary Secretion
2) Binding to Oral Mucosa
3) pH and pKa of The Saliva
4) Lipophilicity of Drug
5) Thickness of Oral Epithelium

ADVANTAGES OF FILM [12]

- Convenience in drug administration and accurate dosing compared to liquid formulations.
- Administration ease for patients (pediatric, geriatric, and psychiatric) who refuse to take a tablet.
- One useful feature for patients who are traveling and do not always have access to water is that water is not necessary for swallowing the dosage form. The basic perception of medication as a "bitter pill" is changed by the good mouth feel property, especially for younger patients.
- Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach; in such cases, the bioavailability of drugs is increased.
- Fast dissolution and absorption of medication will result in a rapid, onset of action.
- It offers solid dosage form with the benefits of liquid formulations.
- Because pregastric absorption occurs at a lower dosage and with fewer side effects, it can lead to increased bioavailability and improved clinical performance.

DISADVANTAGES OF FILM:[13]

- Sublingual medication cannot be used on an unconscious or uncooperative patient.
- Despite its unsuitability for sustained delivery systems, sublingual medication is generally considered unsuitable for prolonged administration because it interferes with eating, drinking, and talking.

It is recommended that the patient abstain from smoking while taking sublingual medication as smoking narrows blood vessels. The medication will be reduced as a result**.**

FORMULATION OF FAST DISSOLVING FILMS[14-15]

A mouth dissolving film is a thin film with a surface area of 5–20 cm^2 and an active component. This rapid dissolution in water or saliva is accomplished by means of a special matrix composed of polymers that dissolve in water. Typically, a composition has the following elements:

Table 1: Composition of fast dissolving films

Sr. No	Composition of film	Quantity
1.	Active pharmaceutical agent	1-25%
2.	Film forming polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva stimulating agent	2-6%

5.	Sweetening agent	3-6%
6.	Flavoring agent	10%
7.	Coloring agent	1%

1. Active pharmaceutical agent

The medications selected for oral films ought to be soluble in water and saliva at low concentrations. The drug should have a 1 to 25% w/w concentration in the film. The most likely dosage molecules to be included in an oral fast-dissolving film are small ones. For better dissolution and uniformity in the oral fast-dissolving film, as well as for improving the texture of the film, micronized API is always advantageous. It should have the ability to permeate the oral mucosal tissue Examples of some drugs that can be incorporated in Oral Fast dissolving films are listed below :

- Antimigrane
- Antihypertensive
- NSAIDs
- Cough Suppresents
- Antiemetics
- Anti Alzheimer`s

Table 2: List of medications that can be added to films that dissolve quickly

API Category	Therapeutic Category	Dose
Nicotine	Smoking cessation	1-15mg
Nitroglycerin derivatives	Vasodilator	0.3-0.6mg
Omeprazole	Proton pump inhibitor	10-20mg
Loratidine	Anti histaminic	5-10 mg
Zolmitriptan	Anti migraine	2.5mg
Loperamide	Antidiarroheal	2mg
Famotidine	Antacid	10mg
Oxycodone	Opoid Anagesic	2.5-10mg
Chlorpheniramine maleate	Anti allergic	4mg
Cetrizine	Antihistaminic	5-10mg
Sumatriptan succinate	Antimigraine	35mg

2. Film forming polymer

A wide variety of polymers are available for use in the production of quickly dissolving films. The films acquired ought to be robust enough to endure handling and transportation without suffering damage. The kind and quantity of polymer utilized in the formulation affect the toughness of the strip. The polymers can be used singly or in combination to achieve the required strip qualities. Film formers are made of water-soluble polymers. The films' mechanical properties, pleasant mouthfeel, and rapid disintegration are all due to the water-soluble polymers. The rate at which the polymers disintegrate is slowed by raising the molecular weight of the polymer film basis. Sublingual films can be formulated using either natural or synthetic polymers. Polymers or excipients must have low molecular weight and be soluble in water and excellent film forming capacity in order to make a water-soluble film formulation.Generally, based on the total weight of the dry film, at least 45% w/w polymer should be present. Naturally occurring and artificially produced polymers, including cellulose or its derivatives, pullulan, gelatin, hypromellose, hydroxyethyl, hydroxypropyl, polyvinyl pyrrolidone, carboxymethyl, polyvinyl alcohol, sodium alginate, xanthan gum, tragacanth gum, and guar gum, are used to create fast dissolving films. Natural polymer derived from non-animal sources, pullulan doesn't need to be treated chemically.

3. Plasticizers

It lessens the brittleness of the strip and aids in improving its elasticity. Plasticizer lowers the glass transition temperature of the polymer, which significantly improves 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, and triacetin, and castor oil are a few frequently used plasticizer excipients. Usually, plasticizers are used at weight percentages of the dry polymer ranging from 0% to 20%.

4. Saliva stimulating agent

Saliva-stimulating agents are used with the goal of accelerating salivation, which will help the rapid dissolving strip formulations dissolve more quickly. The amounts of these agents range from 2 to 6% weight percent of the strip when used

singly or in combination. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are examples of salivary stimulants.

5. Sweetening agents

Sweeteners are becoming a necessary part of pharmaceutical products that dissolve or dissolve in the mouth. The most popular sweeteners are sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose. Combining polyhydric alcohols that offer a pleasant mouth feel and a cooling effect, like sorbitol, mannitol, and isomalt, is possible. First-generation artificial sweeteners include saccharin, cyclamate, and aspartame. Second-generation artificial sweeteners include acesulfame-K, sucralose, alitame, and neotame. Typically, sweeteners are used alone or in combination in concentrations between 3 and 6%w/w.

6. Flavouring agents

Flavors should be included in fast-dissolving film formulations up to 10%w/w. When it comes to oral disintegrating or dissolving formulations, an individual's acceptance is mostly based on the flavor that they taste in the first few seconds after ingesting the product and the flavor that lingers for at least ten minutes afterward. The younger generation likes flavors like fruit punch, raspberry, and so forth, while the elderly prefer flavors like orange or mint. A range of artificial flavor oils, oleo resins, and extracts made from different plant parts, like leaves, fruits, and flowers, are available for use as flavoring agents. Lemon, orange, or other sour fruit flavors; strong mints like peppermint, sweetmint, spearmint, wintergreen, cinnamon, and clove; essential oils or water-soluble extracts of menthol; or sweet confectionary can all be added.Chocolate, vanillin, or fruit essences like pineapple, raspberry, apple, or cherry.

7. Colouring agents

Available colors include FD&C, EU, natural coloring agents, natural juice concentrates, pigments like silicon dioxide, zinc oxide, and titanium dioxide, as well as custom Pantone-matched colors.

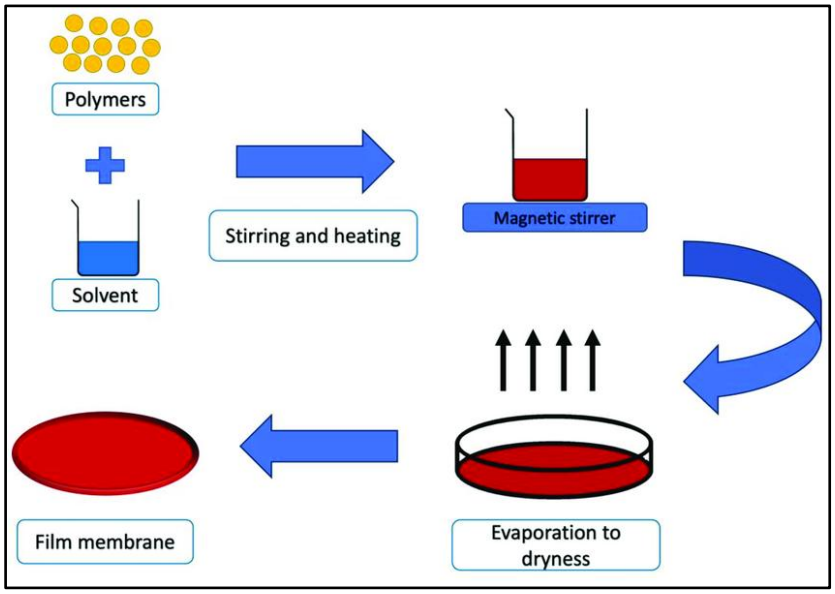
Manufacturing Methods

Fast-dissolving films can be manufactured by one of the following processes

a) Solvent casting.
b) Semisolid casting.
c) Solid dispersion extrusion.
d) Rolling Technique.
e) Hot melt extrusion.

1. Solvent casting method [16]

The drug is dissolved in an appropriate solvent along with other excipients in the solvent casting method, which involves dissolving water-soluble polymers in water. Following a mixing and stirring process, the two solutions are cast in a Petri plate, dried, and sliced to uniform size.



2. Semi solid casting [17]
First, a water-soluble film-forming polymer solution is made using the semisolid casting method. The resulting solution is combined with a sodium hydroxide or ammonium hydroxide solution of an acid insoluble polymer (such as cellulose acetate butyrate or phthalate). After that, enough plasticizer is added to create a gel mass. Using heat-controlled drums, the gel mass is finally molded into the films or ribbons. The thickness of the film is between 0.015 and 0.05 inches. The ratio of film-forming polymer to acid-insoluble polymer ought to be 1:4.

3. Hot melt extrusion method
The current method first creates the mass and controls the steering speed and temperature. The film is finally coated and evaporates in a drying tunnel, where the temperature, airflow, and accelerate lines are once again controlled. The last step involves punching and sealing the films, which is followed by slitting. The hot melt extrusion process is first combined in solid form for the drugs and carriers. The mixture is then melted by an extruder fitted with a heater. The dies to form the melt into films, at the very least [18,19]

The use of hot melt extrusion has certain advantages.

- Less operational units.
- Improved consistency of content
- A procedure without water.

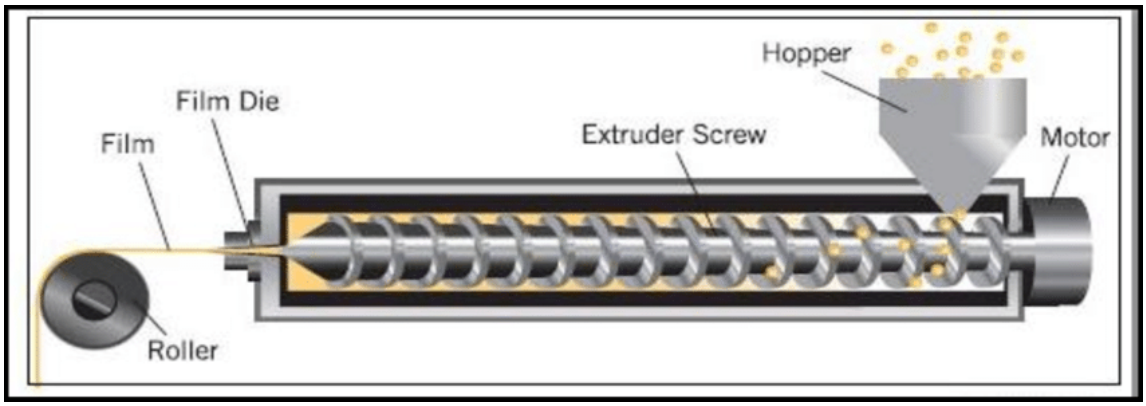


Fig. Hot melt extrusion technique

4. Solid dispersion extrusion method
The dispersion of one or more active ingredients in an inert carrier in a solid state while amorphous hydrophilic polymers are present is referred to as a solid dispersion.
A suitable liquid solvent is used to dissolve the drug.

After that, the solution is mixed with the polyethylene glycol melt, which can be reached below 70^0C.

Ultimately, dies are used to form the solid dispersions into the films.

Precautions when making solid dispersions: The liquid solvent used may affect the polymeric form of drug that precipitates in the solid dispersions, and the chosen solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. [20]

5)Rolling method
This method prepares the film by first making a pre-mix, adding an active, and then forming the film.Make a pre-mix using polar solvent, film-forming polymer, and additional additives—a drug is not included. Fill the master batch feed tank with pre-mix. It was fed to the first or both of the first and second mixers using a first metering pump and control valve. Add the necessary quantity of medication to the preferred mixer. To create a uniform matrix, blend the medication with the master batch pre mix. The pan is then supplied with a predetermined volume of homogeneous matrix via the second metering

pumps. Finally, the film forms on the substrate and is removed by the support roller. After that, the wet film is dried using controlled bottom drying [21]

PACKAGING[22]

In the pharmaceutical sector, it is crucial that the product's integrity be preserved by the package that is chosen. Safeguarding the dosage of other rapidly dissolving dosage forms during manufacturing and storage necessitates costly packaging, particular processing, and extra caution. For fast-dissolving films, there are numerous packaging choices. For films, single packaging is required. The most popular type of packaging is an aluminum pouch.

1. Foil, paper or plastic pouches
2. Single pouch and Aluminum pouch
3. Blister card with multiple units

FAST-DISSOLVING FILM EVALUATION

The physical characteristics, surface quality, and other following parameters of all the produced films were assessed.

1) Weight variation: To account for weight, three films of each formulation were taken and weighed independently on a digital balance variance; the average weight was then determined[23]

2)Film thickness: Each film's thickness was measured using a micrometre screw gauge a various points on the film, and the average thickness was calculated .[24]

3)Surface pH: With the assistance of water, the film is slightly moist. By applying the electrode against the oral film's surface, the pH is determined. Three films of each formulation were used in this study, and the ±S.D. was determion. [25]

4)Folding endurance : The folding endurance is expressed as the number of folds (number of times the film is folded at the same place, either to break the specimen or to develop visible cracks). This test is crucial for determining how well the sample can resist folding. This also gives an indication of brittleness. The folding endurance of the strips can be determined by repeatedly folding one film at the same place till it broke ribbons using heat. The average weight shouldn't be much different from the average weight of controlled drums.

5)Uniformity of drug content: This parameter was determined by dissolving one film of dimension 2 x 2cm by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking. 10 ml of this was then diluted with 50 ml of artificial saliva. An UV spectrophotometer was used to quantify the absorbance. The experiments were carried out in triplicate for the films of all formulations and average values were recorded. [26]

6)Tensile strength : Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is computed using the following equation: applied load at rupture divided by strip cross-sectional area.

$$\textbf{Tensile strength} = \frac{\textbf{Load at Failure} \times 100}{\textbf{Strip thickness} \times \textbf{Strip Width}}$$ [27]

7) Percent elongation: When stress is applied, a strip sample stretches and this is referred to as strain. In essence, strain is the strip's deformation divided by the sample's initial dimension.In general, strip elongation rises with increasing plasticizer concentration.

$$\textbf{\% Elongation} = \frac{\textbf{length increses} \times 100}{\textbf{Original length}}$$ [27]

8)Swelling index: The studies for swelling index of the film are conducted in stimulated salivary fluid. The film sample is weighed and placed in a preweighed stainless steel wire sieve. The mesh containing the film is submerged into 50 ml of stimulated salivary medium contained in a mortar. Increase in weight of the film is determined at each interval until a constant weight is observed. The following formula is used to determine the degree of swelling:

$$\textbf{SI} = \textbf{wt} - \textbf{wo} / \textbf{wo}$$

Where SI is the swelling index,
wt is the weight of the film at time "t", and wo is the weight of film at t = 0 [27]

9)Disintegration time: The USP disintegration time test instrument was used for the disintegration test. The disintegration apparatus IP tubes each received one film from the formulation. The tube received a disc. The apparatus was operated while suspended in 0.1 N HCl until the film disintegrated

10)In-vitro dissolution studies: The fast-dissolving film's in-vitro dissolution was investigated using 0.1N HCl as the dissolution a medium in a USP paddle dissolution test apparatus. The experiment was achieved at a constant temperature of 37± 0.5°C. At every two minutes, a 5 ml sample was taken out and replaced with 0.1 N HCl in the same quantity. A UV-visible spectrophotometer was used to determine the total percentage of drugs released at 205 [28]

11)Morphology Study : Morphology of the prepared film can be observed under a motic electron photomicrograph. motic electron photomicrographs can be recorded at 100 X magnification.

12)Stability Studies: Stability studies on the optimized formulation of fast dissolving film is carried out to determine the effect of temperature and humidity on the stability of the drug. The film can be stored in an aluminum foil and subjected to stability at room temperature. The sample can withdraw at 90 days and 180 days and subjected for disintegration test and in vitro dissolution studies to determine disintegration time and cumulative % drug release. [29]

DRUG-EXCIPIENTS INTERACTION STUDIES:

Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (X-RD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalipies of the reaction [30]

CONCLUSION

Since the percentage of drug absorbed by this route is typically higher than that achieved by the oral route, sublingual absorption is considered efficient. Due to its quick onset of action, improved patient compliance, and direct absorption of the medication into the systemic movement. Films are superior to traditional dosage forms in a number of ways. And so, they crucial in an emergency situation such as an allergy, hypertension.Temporary spasm and asthma whenever it's preferred to take action right away.Thin films are therefore an recognized technology for API system delivery.

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