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FAST DISSOLVING SUBLINGUAL FILM OF POORLY SOLUBLE DRUG

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ABSTRACT

Delivery of drugs through oral mucosa is considered to be most promising offering better patient compliance. In some cases of serious illness, treatment is necessary for immediate onset of action. Delivery of drugs in the sublingual mucosa is regarded as a promising route to speed direct absorption of the drug into the systemic circulation. In the buccal cavity, the sublingual area facilitates deep penetration of drug and rapid absorption. Part of the drug absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolism, which leads to greater bioavailability and offer a lot of advantage to geriatric, pediatric, elderly, and psychiatric patients with dysphagia. This review highlights sublingual film, factors that affect sub-lingual absorption, method of preparation, various in vitro and in vivo test parameters and marketed films

KEYWORDS: Sublingual film, permeability, bioavailability, first pass metabolism, dysphagia.

INTRODUCTION

Sublingual delivery refers to the method of drug delivery where the drug is put under the tongue and is absorbed directly by reticulated vein. This delivery of drugs offers various benefits such as avoiding gastro intestinal and hepatic elimination achieving rapid onset of drug action. The sublingual mucosa is thin and more permeable over the buccal mucosa. Moreover, it's harder to keep a buccal tablet on the cheek than to handle the film under the tongue. There has been a growing demand for sublingual film due to more patient patience. The films achieved great importance due to unique advantage such as no need for water dispersion, accurate Dosing, the immediate onset of action, ease of transportation and handling, pleasant taste and improved patient compliance. The sublingual film is a kind of drug delivery system, which when placed in the mouth it disperses quickly and dissolves to release the drug for oromucosal and intragastric absorption, without chewing and intake of water, This technology has emerged in the last few years and had became a novel and widely accepted form by consumers. These films have the power to deliver medicine in an orderly fashion by intragastric, sublingual or buccal route and are also used for local action. Sublingual administration means keeping medicine beneath the tongue and the drug reaches directly into the bloodstream through the ventral of the tongue and down the mouth. The drug solute is rapidly absorbed into the sleeping vein under the oral mucosa, and transported to the facial veins, internal jugular vein, and braciocephalic artery and so on enters the systemic circulation. Basic mechanism for absorption of drug is via passive diffusion into lipoid membrane.[1]

Advantages and Disadvantages of sublingual film

The sublingual drug delivery system offers several benefits such as ease of use for patients who refuse to swallow a pill, such as children, elderly patients and psychiatric patients. Quick onset action can be achieved compared to the oral route. Excessive contact of the oral cavity contributes to the rapid and widespread absorption of the drug. The drug is protected from damage due to pH as well gastrointestinal digestive enzymes tract. The system provides rapid dissolution or dispersion in the oral cavity. This system has various limitations such as medicines cannot be used if the patient is not cooperative or unconscious and this route cannot be used for prolong administration.[2,3]

Sublingual glands

The glands under the tongue are also known for their binding and lubricating activities, making the food smoother and easier to swallow. Saliva plays a major role to establish a system of natural life for oral cavity in terms of pH, fluid volume and composition. Saliva secretion is promoted by 3 major salivary glands namely parotid, sub maxillary, sublingual glands. Saliva regulates oral microbial flora by maintaining oral pH and enzyme activity. About 0.5-2.0L of saliva you have is produced by the salivary gland. Yet the amount of saliva that is regularly available is the same about 1.1ml, thus providing a relatively small amount of fluid available for delivery systems compared to the GI tract. The level of saliva flow also depends on 3 factors such as time of day, type of stimulus and degree of stimulus.[4]

Anatomy and physiology of mucosa

The thickness of the mucosa is 100-200 μm. Mucosa is neutral but also polar lipid e.g. cholesterol sulfate, glucosyl ceramide. Saliva comprises of 99.5% water, protein, glycoprotein, high potassium (7X Plasma), bicarbonate (3X plasma), calcium, phosphorus, chloride, sodium low (1 / 10X Plasma). The gland contains 5% saliva. The saliva has a pH of 5.6-7.0.[5,6]

Mechanism of sublingual absorption

The absorption capacity of the oral mucosa is influenced by lipid dissolution and therefore solution permeability (osmosis); ionization (pH); and the molecular weight of objects. For example, the absorption of other drugs through the oral mucosa is shown to increase when the carrier pH is lower (more acidic) and decreases with a decrease in pH (more alkaline). Cells of the oral epithelium and epidermis are also competent to absorb by endocytosis (particles are uptaken by cells as if by hollowly itself wrapping around it, these engulfed particles are usually larger in size to diffuse through its wall). It is not possible for this process to be applied to all stratified epithelium. It is also not possible that effective transport processes work within the oral mucosa. However, it is believed that the acidic stimulation of the salivary glands, as well as the associated vasodilation, facilitates absorption and entry into the circulatory system. The mouth is lined with a mucous membrane covered with squamous epithelium and contains mucous glands. The mucosal tissues beneath the tongue are similar to the buccal mucosa. The salivary glands contain lobules that secrete saliva through the salivary glands to the mouth. The three pairs of salivary glands are parotid, submandibular and sublingual lying down in the mouth. As the taste of the acid increases, so does the excretion of saliva; serve to avoid possible damage to the acid-resistant tooth enamel by washing the mouth with copious neutralizing fluid. The sublingual artery extends to sublingual gland and supplies to gland and neighboring muscles and to the mucous membrane of mouth. Two symmetrical branches go behind the jaw under the tongue to meet and meet at tip. The other branch also joins the anastomoses and the branches below the facial vein. The sublingual artery originates in the lingual artery - the main body in the tongue and lower lip - that flows out of the outer carotid artery. The proximity of the internal carotid artery allows rapid access to its root those supplies to greater part of the cerebral hemisphere.

Osmosis

In order for the drug to be absorbed sublingually, it needs to be capable to travel across buccal mucous membrane; by a process known as osmosis that works in all types of absorption; governing both intestinal absorption and sublingual absorption. The distribution of water throughout the cell walls depends on the osmotic differences in the blood between the intracellular and the fluid that comes out of the cell. Small particles that easily dissolve in water rarely cause problems in penetration and diffusion, so they can move freely between body tissues. Active movement in cells leads to rapid metabolism of substance. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have been developed to facilitate their rapid diffusion and penetration over cell membrane.[4,7]

Drugs for sublingual administration

Medically, low-dose sublingual drug administration is used in the field of cardiac drugs, steroids, other barbiturates and enzymes. It has been a progressive platform for the management of many vitamins and minerals that are found to be easily and completely absorbed by this method. A nutritious diet absorbed under the tongue, which avoids exposure to the digestive system and liver, means the direct benefits of a nutritious diet, especially for those with gastro-intestinal disorders such as ulcers, hyperactive gut, and celiac disease, those with digestive problems, the elderly and the disabled - nutritious foods. The benefit is independent of gastro-intestinal influences. Examples of drugs administered by this route include antianginal such as nitrites and nitrate, antihypertensive such as nifedipine, analgesics Such as morphine and bronchodilators such as fenosterol. Certain steroids such as estradiol and peptides such as oxytocin can also be administered e.g. fentanyl citrate, apomorphine, prochlorperazine dimaleate, and hydrazine HCl},

No bitter taste.
The dose is lower than 20mg, e.g. nifedipine.
Moderate to less molecular weight.
Good stability in water and saliva.
It is partially ionized in oral cavity pH.
Undergoing first pass metabolism e.g. ketotifen fumarate

Factors affecting the sublingual absorption

Lipophilicity of drug

For the medicine to absorb completely by using a sublingual route, the drug should have a slightly higher lipid Solubility than what is required for GI absorption for passive permeation.

Solubility in salivary secretion

Addition to lipid solubility, drug should posses solubility in aqueous buccal fluid i.e. drug with biphasic solubility.

PH and pKa of the saliva

Since the average pH of saliva is 6.0, this pH favors the absorption of drugs that are unionized. In oral mucosa drug absorption occurs when pKa is greater than 2 for acid and less than 10 for base.

Thickness of oral epithelium

The sublingual epithelium thickness is 100-200 μm that is thinner compared to the buccal thickness. So the absorption of drugs is faster due to being thinner epithelium and immersion of the drug in a small volume of saliva.

Oil to water partition coefficient

Favorable oil to water coefficient is necessary for the drug to be absorbed through sublingual mucosa. The oil-water partition-coefficient range of 40-2000 is considered the most suitable for the absorption of drugs in sublingual mucosa.[1,8]

Formulation of Sublingual Films

Sublingual film is a thin film with a surface area of 5-20 cm2 that contains an active ingredient. The rapid dissolution in water or saliva is achieved by a special matrix from water-soluble polymers. The typical composition consists of the following.

Table 1: Composition of sublingual film.

Sr. no	composition	Quantity (%)
1	Active pharmaceutical agent	1-25%
2	Film forming polymer	40-50%
3	Saliva stimulating agent	2-6%
4	plasticizer	0-30%
5	Sweetening agent	3-6%
6	Colouring agent	1%
7	Flavoring agent	10%

1. Active pharmaceutical agent

Drugs selected for sublingual films should be stable in saliva and water with low dose. The film should contain 1- 25% w / w of API. Small dose drug are the best candidates for inclusion in sublingual film. Multivitamins up to 10% w / w of dry film weight are included in films with a dissolution time of less than 60 seconds. It is always useful to have a micronized API that will improve the texture of the film as well as better scattering and uniformity of the sublingual film.

2. Film forming polymer

A variety of polymers are available for the preparation of sublingual films. Polymers can be used alone or in combination with other polymer to possess the desired film properties. The films formed should be strong enough to withstand damage during handling or during transport. Film strength depends on type of polymer and concentration of Polymers. Polymer can be used alone or in composite to find the features of the strip you want. Water-soluble polymers are used as films. Use of filmmaking polymers into soluble films has attracted a great deal of medical and nutritional attention application. Water-soluble polymers achieve rapid dispersion, good mouth taste and mechanical properties in films. The disintegration rate of polymers decreases with increase in polymer concentration. Both natural and synthetic polymers can be used in the preparation of sublingual film. To formulate water soluble film, excipients or polymer must be Soluble in water and has a low molecular weight and an excellent film-forming capacity. At least 45% w / w of polymer should be present normally based on the total weight of the dry film but usually 60-65% w / w of polymer prefers to find desirable properties. The polymer in film should be non-toxic, non-irritating and free of impurities. Polymer should possess good wetting and spreadibility. Polymer should have good peel, shear and tensile strength. Various natural and synthetic polymers used in formulation of sublingual film include extracts from cellulose or cellulose, pullulan, gelatin, hypromellose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, xanthan gum, tragacanth gum and guar gum. Pullulan is a natural polymer derived and does not require chemical modification.

3. Saliva stimulating agent

The purpose of using stimulating agents is to increase the rate of saliva production which can assist in the rapid dissolution and disintegration of soluble ingredients. These agents are used alone or combined 2-6% w / w of the total weight of dry film. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are just some examples of salivary stimulating agent.

4. plasticizer

It helps to improve strip flexibility and reduce the brittleness of film. Plasticizer significantly improves strip properties by reducing the glass transition temperature of film. Glycerol, propylene glycol, low weight molecular propylene glycols, extracts from phthalate such as dimethyl, diethyl and Dibutyl phthalate, citrate extracts such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the most widely used plasticizer for film formulation. Usually plasticizers are used in a proportion of 0-20% w / w of dry polymer weight.

5. Sweetening agent

Sweeteners have become an important part of pharmaceutical products for the purpose of disintegration and dissolution in oral cavity. The source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. Polyhydric alcohols such as sorbitol, mannitol and isomalt can be used in combination as they additionally give a good mouth feeling and a cool feeling. Synthetic sweeteners such as Saccharin, cyclamate and aspartame are the first generation of synthetic sweeteners followed by acesulfame-k, sucralose, talame and neotame that fall under the second generation of synthetic sweets. Usually sweeteners are used in a combination of 3 to 6% w / w of dry film alone or in combination.

6. Coloring agent

A full range of colors is available including FD & C colors, EU colors, natural color agents and natural juice concentrates, compounds such as titanium dioxide, silicon dioxide and zinc oxide and colors that match the custom Panton.

7. Flavoring agent

Ideally up to 10% w / w flavor is added in the formulation of sublingual film. Acceptance of film flavor by individual largely depends on first taste quality observed in the first few seconds after the product is ingested and the taste which persist at least 10 minutes. Geriatric patient like mint or oranges while the younger generation likes fruit-like flavors, raspberries etc. Flavor agents can be selected from artificial flavor oils, oleo resins, extracted from various parts of plants such as leaves, fruits and flowers. Any flavor can be added such as essential oils or extracts of methanol, strong mint such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, and sweet flavors like lemon, orange or sweet confectionary. Fruits flavor like vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple.[9]

MANUFACTURING METHODS

The following methods can be used in manufacture of sublingual film.[10,11]

1. Solvent casting
2. semi solid casting
3. rolling method
4. Solid dispersion extrusion
5. Hot melt extrusion

1. Solvent casting method

In this method the water soluble polymers are dissolved in water and the drug and excipients are dissolved in a suitable solvent and both solutions are mixed and stirred and finally poured into a dry Petri plate and cut in appropriate dimension**.**

2. Semi solid casting method

In the semisolid casting method first water-soluble film polymer solution is prepared. The resulting solution is added to acid insoluble polymer solution (eg cellulose acetate phthalate, cellulose acetate butyrate), prepared by ammonium or sodium hydroxide. Then the right amount of plasticizer is added to get the appropriate mass of the gel. Finally the gel mass is casted in films using controlled temperature drums. The thickness of the film is 0.015-0.05 inches. The ratio of the insoluble acid polymer to the film-forming polymer should be 1: 4.

3. Rolling method

In rolling method, drug in solution or suspension is rolled on a carrier. The solvent is usually water and a mixture of water and alcohol. The film is dry on the rollers and cut into desirable shapes and size.

4. Solid dispersion extrusion

In solid dispersion method, immiscible components of film are extruding with drug and solid dispersion is prepared. Solid dispersion is further casted in to dies for film formulation.

5. Hot melt extrusion

In hot melt extrusion method initially the drug is mixed with the carriers in a solid form. Then the extruder consist of heaters melts the mixture. Eventually the melted mixture is converted into films with the help of dies. Benefits of hot melt extrusion.[10]

· Few operating units
· Content uniformity
· No need of water

Packaging

In the pharmaceutical industry, it is important that a selected package should sufficiently maintain the integrity of the product. Expensive packaging, special processing and special care are required during production and storage to protect the sublingual film. Various packaging options are available for quickly finished films. Single package is compulsory for films. An aluminum bag is the most widely used packaging format.

1. Foil, paper or plastic pouches

A flexible pouch is a packaging concept that can provide not only a heat-resistant package, but also with the right material selection, a package with a high level of environmental protection. A flexible pouch is usually construct during filling the product by either horizontal or vertical forming, filling or sealing equipment's. Pouches can be single or aluminum pouch.

2. Single pouch and aluminum pouch

Soluble film drug delivery pouch is a pouch for "rapid dissolve" films with high barrier properties. The pouch is transparent for clear view of film inside. Using a 2-layer combination allows one side to be clear and the other to use inexpensive foil lamination. Foil lamination has zero transmission of both gas and moisture. The package offers an alternative to a flexible film for nutraceuticals and pharmaceutical application. The single dose pouch gives protection to product as well as dosage form. Aluminum pouch is most widely used.

3. Blister card with multiple unit

The blister container consists of two parts: a blister, which is a built-in cavity containing the product, and the lid stock which is the material that seals the blister. The blister pack is made by heat softening a thermoplastic resin sheet followed by vacuum-drawing soft plastic sheet into a mold. After cooling the sheet is removed from the mold and preceded to the filling station of the packing machine. The previously formed semi rigid blister is filled with the product and sealed with a sealing material. Film selection should be based on the level of protection required. The lid stock is usually made of aluminum foil. The materials used to make the cavity are usually plastic, which is designed to protect the film from moisture.[10,12]

Evaluation parameters

1. Thickness

The thickness of the film is measured using digital Vernier Caliper with a value of at least 0.01 mm in different parts of the film. .thickness is measured at three

different spot of film and average is taken to calculate SD.[13]

2. Weight variation

Four centimeter square of the film is cut at three different places from the casted film. The weight of each film is noted and weight variation is calculated.[14]

3. Folding endurance

Folding endurance is determined by folding of the film repeatedly at the same place till the film break. The film is folded no of times and the point at which it breaks is noted as the folding endurance value.[15,16]

4. Tensile strength

Tensile strength is the maximum amount of stress applied to a point at which the film breaks. It is calculated by the applied load of failure divided by the cross-sectional area of the film as given below.

Tensile strength = Load at failure × 100Film thickness × film width.[17]

5. Percent elongation

The film expands when the stress is applied to film it is called as strain. Strain is basically a film deformation divided by the original size of film. As the content increase elongation of film takes place.

Percent elongation = [(L-Lo) / Lo] × 100

Where, L = Increase the length of the film. Lo = initial length of film.[18]

6. Young's modulus

Young's modulus is the measure of strength of a film. It is represented as a measure of stress applied over stress in the area of elastic deformation as follows.

Young's Modulus = Slope × 10Thickness of the film

7. **Surface pH**

The formulated film is placed in a Petri dish and moistened with 0.5ml of distilled water and stored for 30sec. The pH is observed after bringing the electrode connected to pH meter in contact with surface of moisten film and allow to stand for 1min. Average of three readings for each film is done.[19]

8. Disintegration test

Disintegration test is done to check the time required for film to start breaking or disintegrates. It gives indication about dissolution characteristic of film. Two methods of disintegration include drop method, petridish method.

Drop method: In this method one drop of distilled water is dropped by a pipette onto the oral films. The films are placed on a glass slide and then the glass slide is placed on a petridish. The time until the film dissolved and caused a hole within the film is measured. The estimations are carried out in triplicate.

Petridish Method.

In this method 25ml of distilled water is taken in a petridish and one film is added on the surface of the water and the time required until the oral film dissolved completely is measured. Drug-loaded films are investigated under both methods. The estimations are carried out in triplicate.[12]

Uniformity of drug content

Drug content is 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 or sonicating. From this, 10 ml was diluted to 100 ml with simulated salivary fluid. The absorbance is measured using an UV spectrophotometer. The experiments are carried out in triplicate for the films of all formulations and average values are recorded.[20]

9. In vitro dissolution studies

Dissolution profile of fast dissolving film is carried out using USP type II (paddle apparatus) with 500/900 mL of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37 ± 0.50C. Medium is stirred at 50 rpm. Samples of about 5 ml is withdrawn at every 5 min interval and replacing the same amount with the fresh medium. The Samples are suitably diluted and estimated spectro photometrically at λmax by using UV-Visible Spectrophotometer and release pattern of drug and amount of drug released is determined.[20-22]

In vivo evaluation

Pharmacokinetic data analysis and bioavailability evaluation

A rabbit is one of the few laboratory animals that do not have keratinized mucosa, thus closely resembling human sublingual mucosal tissue. The maximum plasma concentration (Cmax) and the time to reach maximum plasma concentration (Tmax) can be obtained from the plasma data. The area under the plasma concentration curve (AUC) can also be calculated using the trapezoidal rule and then the bioavailability of the film containing drug can be determine.[23]

Ex vivo permeation studies through porcine oral mucosa

Ex vivo permeation research on porcine oral mucosa is performed using a modified Franz cell distribution of 2.5 cm in diameter. The buccal mucosa is cut evenly from the sides and cleaned in isotonic phosphate buffer pH 6.6 and immediately used. The mucosa is stabilized before installation to remove the soluble components. The mucosa is suspended between donor and receptor compartments. The receptor site is filled with 200 ml of isotonic phosphate buffer of pH 7.4 which is kept at 37 ± 0.2 ° C and hydrodynamics was maintained by stirring at 50rpm by magnetic bead. One film of dimension 2 × 2 cm and previously moistened with a few drops of stimulated saliva. The donor chamber is filled with 1ml of saliva pH 6.8. Samples are withdrawn at required interval and replaced by same amount of fresh medium. The percentage of drug permeation is determined by measuring absorption using a UV-Visible spectrophotometer.[24,25]

CONCLUSION

The sublingual films are designed for oral use and are a relatively new dose especially for pediatric patients and older patients. These types of doses are especially

important in emergency situations such as allergies and asthma attacks when prompt action is required. Sublingual films are effective as the percentages of drug absorbed by sublingual route are usually higher. Sublingual films are therefore an acceptable technology for system delivery of poorly soluble APIs.

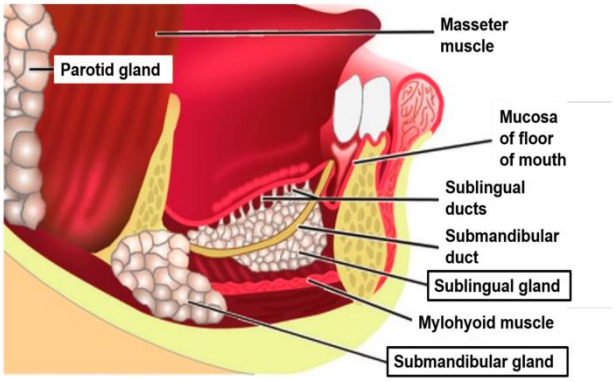

Fig. 1: Oral mucosa.

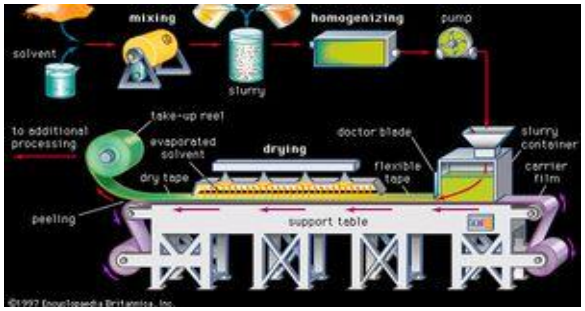

Fig. 2 Solvent casting method.

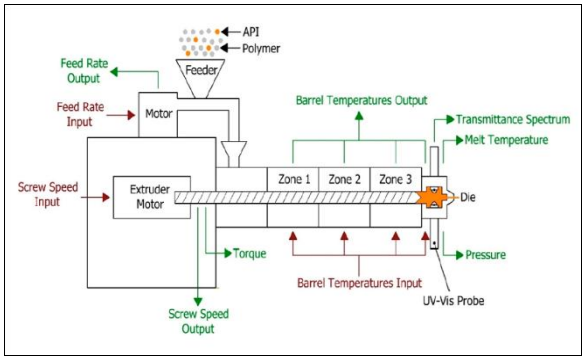

Fig. 3 Hot melt extrusion process.

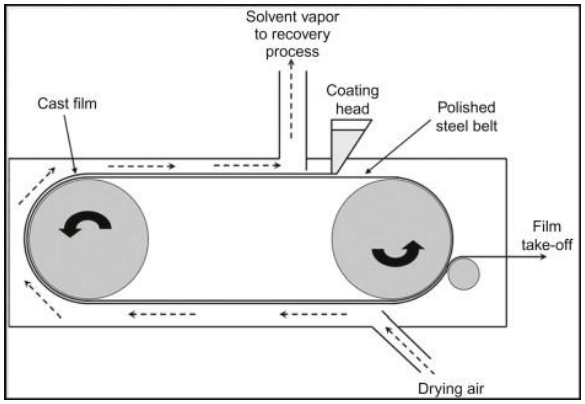

Fig. 4 Rolling method.

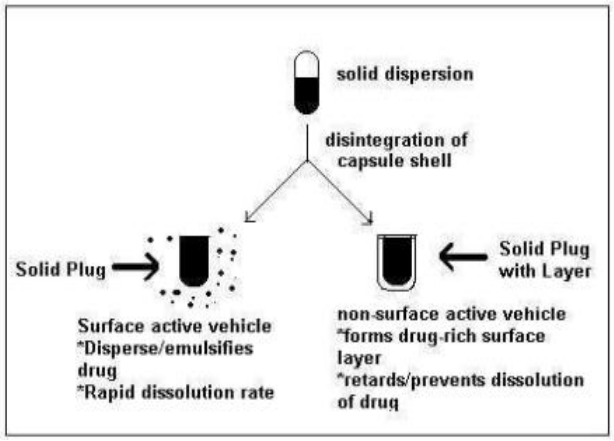

Fig. 5 Solid dispersion extrusion method.

Marketed sublingual film

Example: suboxone.

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