Review Article

A Review on Fast Dissolving Sublingual Films for Systemic Drug Delivery

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ABSTRACT

Oral fast disintegrating films is an emerging technology with rapid onset of action and improved patient compliance. It improves the efficacy of API's and provides better drug utilisation. These formulations are suitable for cold, allergic rhinitis, asthma attacks, CNS disorders where rapid onset of action is required for faster relief. The sublingual route of drug administration is very effective since the drug absorbed through the sublingual blood vessels by passes hepatic first pass metabolic process and gives a better bioavailability. The present article overviews the formulation aspects, manufacturing methods like solvent casting, evaluation parameters and applications of fast dissolving films by sublingual route.

Keywords: sublingual blood vessels, solvent casting, allergic rhinitis.

INTRODUCTION

The Fast Dissolving Drug Delivery Systems was an advancement that came into existence in the early 1970's and combats over the use of the tablets, syrups, capsules which are the other oral drug delivery systems. Fast Dissolving Drug Delivery Systems serves as a major benefit over the conventional dosage forms since the drug gets rapidly disintegrated & dissolves in the saliva without the use of water[1].

The most popular oral solid dosage forms are tablets and capsules. Many patients find it difficult to swallow tablets and hard gelatin capsules particularly pediatric and geriatric patients and do not take their medicines as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. In some cases such as motion sickness, sudden episode of allergic attack or coughing, fear of choking and an unavailability of water, the swallowing of tablet or capsules may become difficult. To overcome these difficulties, several fast dissolving drug delivery systems have been developed[2].

To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. Fast dissolving films are very similar to ultra-thin strip of postage stamp in their shape, size and thickness. Fast dissolving film is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption. This fast dissolving drug delivery system (FDDS) is suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective[3].

Drug delivery by per-oral administration arise some problems such as hepatic first pass metabolism and enzymatic degradation within the GI tract[4]. For certain class of drugs, these problems can be overcome by their administration through sublingual mucosa.

OVERVIEW OF THE ORAL CAVITY

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. There are considerable differences in permeability between different regions of the oral cavity because of the

diverse structures and functions of the different oral mucosa[5].

SUBLINGUAL GLANDS

Salivary glands are present in the floor of the mouth underneath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional layer thickness. The absorption of the drug follows in this way Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent[6].

PERMEABILITY

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. The permeability's of the oral mucosa decrease in the order of sublingual greater than buccal and and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and on-keratinized, the buccal thicker and nonkeratinized[7].

MECHANISM OF ABSORPTION

Sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, and braciocephalic vein and are then drained into the systemic circulation. Upon sublingual administration drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane .The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection[8].

FACTORS AFFECTING ABSORPTION

- Solubility in salivary secretion
  In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.
- Binding to the oral mucosa
  Systemic availability of drugs that bind to oral mucosa is poor.
- pH and pKa of the saliva
  As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- Lipophilicity of the drug
- For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- Thickness of the oral epithelium
  As the thickness of sublingual epithelium is 100-200 µm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva[9].

ADVANTAGES OF THIN FILMS[10, 11]

1. Thin film is more stable, durable and quick dissolving than other conventional dosage forms.
2. Thin film enables to improve dosage accuracy relative to liquid formulations, since every strip is manufactured in such a way that it contains a precise amount of the drug.
3. Buccal films not only ensure more accurate administration of drug, but also can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration.
4. Buccal films has the ability to dissolve rapidly without the need for water, which provides an alternate way to the patients to swallow and to patients suffering from nausea, such as those patients receiving chemotherapy
5. Permits continuous drug administration and the use of drugs with a short biological half-life.
6. Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds.
7. The large surface area available in the film dosage form allows rapid wetting by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation

without undergoing first-pass hepatic metabolism and on increase the bioavailability.

8. The first pass effect can be avoided, so a reduction in the dose which can lead to reduction in side effects associated with the molecule.
9. It also avoids the risk and inconveniences of intravenous therapy.
10. Sublingual film delivers a convenient, quick-dissolving therapeutic dose contained within an abuse-deterrent film matrix that cannot be crushed or injected by patients, and rapidly absorbs under the tongue to ensure compliance.

DISADVANTAGES OF THIN FILMS[12]

1. High doses cannot be incorporated.
2. Dose uniformity is a technical challenge.

IDEAL CHARACTERISTICS OF A DRUG TO BE SELECTED[13]

- The drug should have pleasant taste.
- The drug to be incorporated should have a low dose upto 40mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionised at the pH of oral cavity.
- It should have the ability to permeate the oral mucosal tissue.

FORMULATION OF FAST DISSOLVING FILMS[14, 15, 16, 17]

Mouth dissolving film is a thin film with an area of 5-20 cm^2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers. A typical composition contains the following:

Table 1: Composition of fast dissolving oral film

S. No.	Composition of strip	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.	Colouring agent	1%

1. **Active pharmaceutical agent**
The drugs selected for oral films should possess good stability in saliva and water with low dose. The film should consist of 1-25% w/w of the drug. Small dose molecules are the best candidates to be incorporated in Oral fast dissolving film. Multivitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the Oral fast dissolving film.

Table 2: Drugs that can be incorporated in fast dissolving films

Active pharmaceutical category	Therapeutic category	Dose
Nicotine	Smoking cessation	1-15mg
Nitroglycerin derivatives	Vasodilator	0.3-0.6mg
Zolmitryptan	Anti migraine	2.5mg
Loratidine	Anti histaminic	5-10mg
Omeprazole	Proton pump inhibitor	10-20mg
Ketoprofen	Anti inflammatory	12.5-25mg
Chlorhexidine gluconate	Anti microbial	0.12%
Oxycodone	Opoid analgesic	2.5-10mg
Dicyclomine	Muscle relaxant	25mg

2. **Film forming polymer**
The polymers can be used alone or in combination to obtain the desired strip properties. Both natural as well as synthetic polymers can be used in the formulation of oral films. In order to prepare a film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. At least 45% w/w of polymer should generally

be present based on the total weight of dry film. The various natural as well as synthetic polymers to make fast dissolving films include cellulose or cellulose derivatives, 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 obtained from nonanimal origin and does not require chemical modification.

3. **Plasticizers**
It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. Glycerol, propylene glycol, low molecular weight propylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0-20% w/w of the dry polymer weight.

4. **Saliva stimulating agent**
The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. These agents are used alone or in combination between 2-6% w/w of the strip. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants.

5. **Sweetening agents**
Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical 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 provide good mouth feel and cooling sensation. The artificial sweeteners like Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-k, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

6. **Flavouring agents**
Preferably up to 10%w/w flavors are added in the Fast dissolving film formulations The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from the synthetic flavor oils, oleo resins, extracts derived from various parts of plants like leaves, fruits and flowers. Any flavour can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweetmint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary. Flavors such as vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple.

7. **Colouring agents**
A full range of colors is available including FD&C colors, EU colors, natural coloring agents and natural juice concentrates, pigments such as titanium dioxide, silicon dioxide and zinc oxide and custom pantone-matched colors.

MANUFACTURING METHODS[18, 19]

Following processes can be used to manufacture fast dissolving films:

1. Solvent casting
2. Semi solid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

1. Solvent casting method
In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable

solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate dried and cut in to uniform dimensions.

2. **Semi solid casting method**
In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

3. **Hot melt extrusion method**
In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion.
· Fewer operation units
· Better content uniformity
· An anhydrous process.

4. **Solid dispersion extrusion**
In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5. **Rolling method**
In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and sizes.

PACKAGING[20]

In the pharmaceutical industry, it is vital that the package selected adequately should preserve the integrity of the product. Expensive packaging, specific processing and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films. An aluminum pouch is the most commonly used packaging format.

1. **Foil, paper or plastic pouches**
The flexible pouch is a packaging concept capable of providing not only a package that is temper- resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling or sealing equipment. The pouches can be single pouches or aluminum pouches.

2. **Single pouch and Aluminium pouch**
Soluble film drug delivery pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

3. **Blister card with multiple units**
The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mold. After cooling the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

EVALUATION PARAMETERS[21,22,23,24]

1. **Thickness**
   The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

2. **Weight variation**
   Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

3. **Folding endurance**
   Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

4. **Tensile strength**
   Tensile strength is the maximum stress applied to a point at which the film specimen breaks31. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

   Tensile strength = Load at failure × 100/ Film thickness × film width

5. **Percent elongation**
   A film sample stretches when stress is applied and it is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Elongation of film increases as the plasticizer content increases.
   Percent Elongation= L * 100/ Lo
   where, L = Increase in length of film, Lo = Initial length of film.

6. **Surface pH**
   The film to be tested was placed in a petri dish and was moistened with 0.5ml of distilled water and kept for 30sec.The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equlibriation for 1min. The average of three determinations for each formulation was done[23].

7. **Uniformity of drug content**
   This parameter was determined by dissolving one film of dimension 2 x 2 cm by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking. . From this, 10 ml was diluted to 50 ml with simulated salivary fluid. The absorbance was measured using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations and average values were recorded.

8. ***In vitro* dissolution studies**
   Dissolution profile of fast dissolving films was carried out using USP type II (paddle apparatus) with 300 mL of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37 ± 0.5^0C. Medium was stirred at 100 rpm. Samples were withdrawn at every 30 sec interval, replacing the same amount with the fresh medium. Amount of drug in the withdrawn samples was determined by UV spectrophotometer. The percent drug released was plotted against time.

9. **Ex vivo permeation studies through porcine oral mucosa**
   Permeation studies were carried using the modified Franz diffusion cell of internal diameter of 2.5 cm. The buccal pouch of the freshly sacrificed pig was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.6 and used immediately. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 200 mL of isotonic phosphate buffer of pH 7.4 which was maintained at 37 ± 0.2ºC and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One film of dimensions 2 x 2 cm, previously weighed, was placed in intimate contact with the mucosal surface of the membrane that was previously moistened with a few drops of simulated saliva. The donor compartment was filled with 1 mL of simulated saliva of pH 6.8. Samples

were withdrawn at suitable interval, replacing the same amount with the fresh medium. The percentage of drug permeated was determined by measuring the absorbance in UV Visible Spectrophotometer.

MARKETED PRODUCTS[25]

List of various floating sublingual marketed formulations is given in table no 2 below.

Table 3: List of various sublingual marketed formulations

DRUG	CATEGORY	BRAND NAME	DOSAGE FORM	MANUFACTURERS
Fentanyl citrate	Opioid analgesic	Subsys®	Spray	Nsys therapeutics
Zolpidem tartarate	Sedative	Intermezzo®	Tablets	Prostrakan Inc
Lorazepam	Antianxiety	Avitan®	Tablets	Wyeth- Ayerst
Buprenorphine-hydrochloride + Naloxone	Narcotic Opioid Antagonist	Subozone®	Films	Reckitt- Benckiser Pharmaceutical
Buprenorphine	Opioid analgesic	Subutex®	Tablets	Reckitt- Benckiser Pharmaceutical
Nitroglycerine	Anti anginal	Nitrostat®	Tablets	Parke-Davis
Isosorbide dinitrate	Vasodilators	Isordil®	Tablets	Wyeth- Ayerst

APPLICATIONS[26]

- Oral mucosal drug delivery via sublingual, buccal and mucosal route by oral thin films could become a preferential delivery methods for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties and central nervous system disorders.
- Topical applications: The use of dissolvable films may be feasible in the delivery of active agents such as analgesics and antimicrobial ingredients for wound care and other applications.
- Gastroretentive dosage systems: Dissolvable films are being considered in dosage forms for which water soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution could be triggered by the pH or enzyme secretions of the gastrointestinal tract and could potentially be used to treat gastrointestinal disorders.
- Diagnostic devices: Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device.

CONCLUSION

Fast dissolving films are intended to be applied in the mouth and it is a very innovative dosage especially to paediatric and geriatric patients. These dosage forms are of great importance in case of emergency conditions such as allergic reactions and asthmatic attacks where immediate onset of action of action is desired. Sublingual absorption is efficient since the percent of drug absorbed by this route is generally higher than that achieved by oral route. Therefore oral thin flims are an accepted technology for systemic delivery of API's.

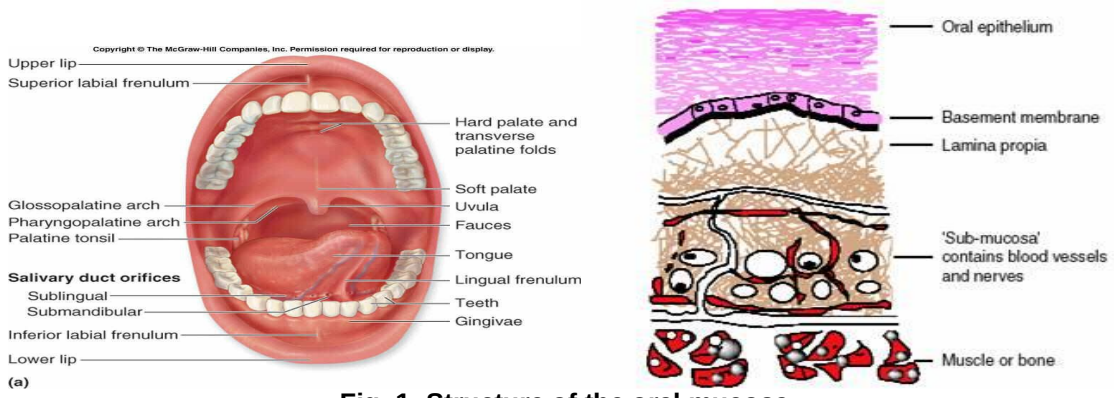

Fig. 1: Structure of the oral mucosa

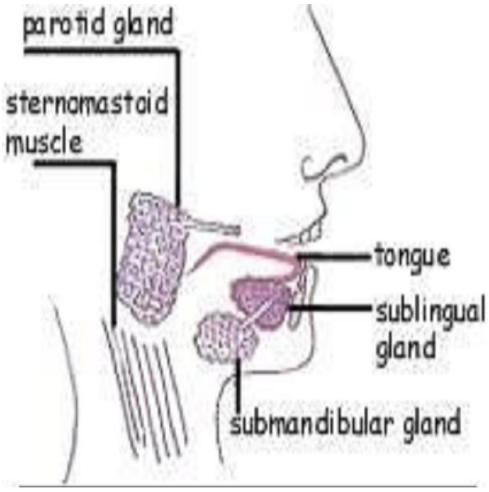

Fig. 2: Diagram of the sublingual gland

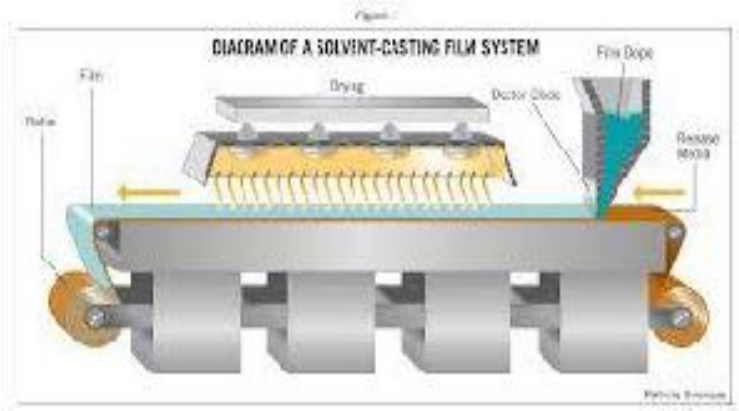

Fig. 3: Solvent casting method

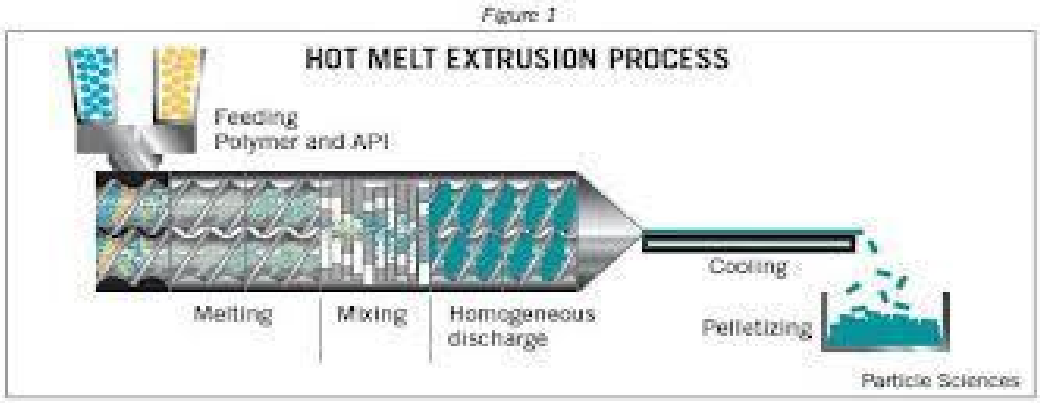

Fig. 4: Hot melt extrusion process

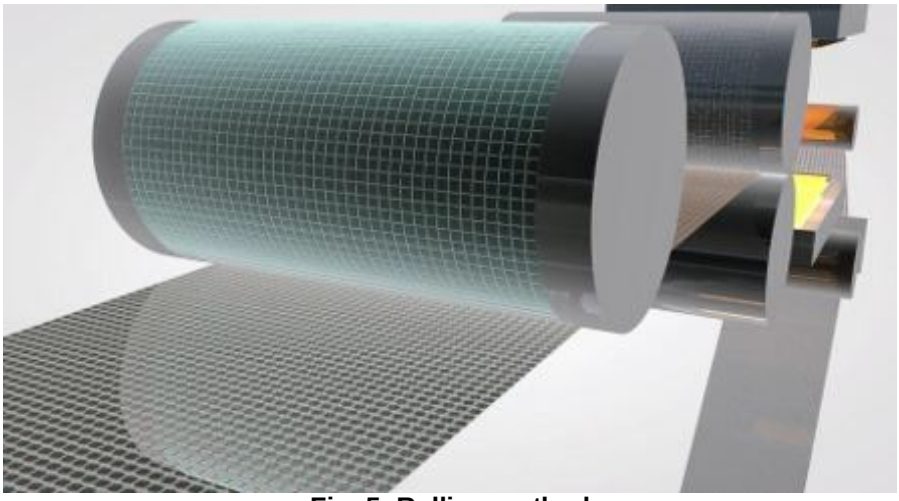

Fig. 5: Rolling method

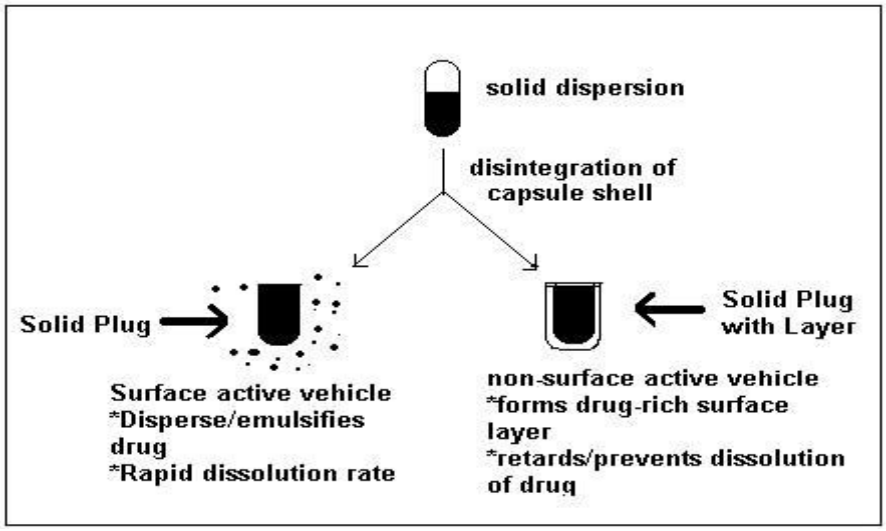

Fig. 6: Solid dispersion extrusion method

Fig. 7: Blister card

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