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AN OVERVIEW ON RAPID DISSOLVING FILMS

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ABSTRACT

The objective of review article is oral disintegrating films are alternative dosage forms to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. Oral dissolving film technology (ODFT) that can be administered in the buccal cavity for a short period of time in secs and gives better therapeutic action. ODFT offers an alternate platform for molecules undergoes first pass metabolism. ODFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs. So, various pharma companies adopted advance technologies to make ODFT commercialized in large scale despite of several limitations.

Key words: Fast dissolving films, Solvent casting, Semisolid casting, Hot melt extrusion, Solid dispersion extrusion, Rolling Method, Solu Strip.

INTRODUCTION

For the last two decades, there has been an enhanced demand for more patient-compliant dosage forms. As a result, there are now approximately 350 drug delivery corporations and 1000 medical device companies. The demand for their technologies was approximately \$14.20 billion in 1995 and, according to industry reports; this is expected to grow to \$60 billion annually.

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating, and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available.

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing [1] traditional oral

solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar

By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphasia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. Dysphasia is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water [1].

Research and development in the oral drug delivery segment has been led to transition of dosage forms from simple conventional tablets/capsules to oral disintegration tablet (ODT) to wafer to the recent development of oral

films (ODF) can be considered as an ultra thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other pharmaceutical excipients. The advantage of convenience of dosing probability of ODF has led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

The ODT in market was accompanied by educating the mass about the proper way to administer the product like giving instructions “do not swallow” or “do not chew”. The process of manipulating the ODT in oral or buccal cavity was also important. However since the ODT derived products were readily popular in the market in the form of breath-freshening strips, no further effort were needed to re-construct the populace about the technique of administration of this dosage form (ODFT) was already popular amongst the people in the early 2000 year with the introduction and widespread use of Listerine pocket strips, anew launch in the mouthwash range.

Technology catalysts forecasts the market for drug products in oral thin film formulations to be evaluated to be valued at \$500 million in 2007 and could cash reach \$2billion by 2010. However only a few products consisting bitter molecules have been able to be commercialized because of the complexity associated with the ODT.

A number of molecules incorporated into this delivery system. They may include cough/cold remedies (antitussives, expectorants), sore throat, erectile dysfunction drugs, antihistaminic, antiasthmaticis, gastrointestinal drugs, nausea, pain and CNS (e.g. antiparkinsons disease). Other application comprise caffeine strips, snoring aid, multivitamins, sleeping aid etc.

The ODFT technology continues to be viewed as an alternative for ODT products that would afford a superior barrier to generic entry and product differentiation to over the counter brands. From the marketing perspective, a patented ODF technology would be beneficial. The grant of marketing exclusively to the new dosage form would help to gain more revenue. As compared to the other ODTs such as tablets: the product is robust. From the patient point of view of administration and improved compliance. The manufacturing of this dosage form is cost-effective with affordable end-products. From clinical aspect, the improved bio-availability can be advantageous in reducing the dose of the formulation. This would lead to product with minimized side effects. The product can be substituted with more clinical advantage. The disadvantage of ODFT is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50% per dose weight. Novartis consumer Health's Gas-X thin strip has a loading of 62.5mg of simethicone per strip.

Salient features of fast dissolving drug delivery systems

1. Ease of administration for patients who are mentally ill disabled and uncooperative.
2. Require no water.
3. Over comes unacceptable taste of the drugs.
4. Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging
7. Cost effective.

Advantages

These rapid dissolving films offer several advantages like,

- Convenient dosing.
- Fast disintegration or dissolution followed by quick effect which is desirable in some cases such as pain.
- No water needed.
- No risk of choking.
- Enhanced stability.
- Improved patient compliance.
- More patient compliance.
- Life cycle management
- Difficulties caused from swallowing tablets are circumvented, that is especially advantageous for pediatric and geriatric patients are in diseases with nausea or vomiting [2].

Disadvantages

- The disadvantage of OTF is that high dose cannot be incorporated into the strip.
- Expensive packaging of oral film [3].

FAST DISSOLVING FILMS

Oral films are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. Fast disintegrating films (FDFs) have a large specific surface area for disintegration. The films alleviate the danger/ fear of choking, easy to handle and administer, maintain a simple and conventional packaging that is easy to manufacture thus overcoming the short falls of oral fast disintegrating tablets. A major limitation of these dosage forms is low drug loading capacity and limited taste masking options.

- Fast disintegrating film is a thin film of 1-10mm thickness, with an area of 1-20 cm² of any geometry.

Drugs can be incorporated upto a single dose of about 15mg. the immediate dissolution in saliva is due to special matrix made from water soluble polymers it has usually low tack for ease of handling and application. However, on wetting the wet tack and muco-adhessiveness properties of the system are designed to secure the film the site of application. Flexibility and strength of are selected to facilitate manufacturing process and process like rewinding, die cutting and packaging.

- Fast disintegrating film is placed on the patient tongue or any mucosal tissue, which gets instantly wetted by saliva. The film hydrates rapidly and adheres on to the site of application. It then rapidly disintegrates and dissolves to release drug for oral mucosal absorption, or for gastric absorption on swallowing.

Differences between ODT and OFT

FORMULATION CONSIDERATIONS

Formulation of a oral strip (OS) involves the intricate application of aesthetic and performance characteristics such as the taste masking, fast dissolving, physical appearance, moth-feel etc. The excipients used in formulation of OS are given below as per their categories. From the regulatory perspectives, all excipients used in the formulation of OS should be generally regarded as safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

Active pharmaceutical ingredient

A typical composition of the film contains 1-25% of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to incorporate in ODFs. 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 ODFs. Many APIs, which are potential candidates for ODF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the api into the OFDF, the taste need to be masked. Various methods can be used to improve palatability of the formulation. Among the techniques employed, the simplest method involves mixing and co-processing of bitter tasting API with excipients with palatable Taste. This is often termed as obscuration technique [4]. Some examples for the drugs incorporated into films are

Strip forming polymers

A variety of polymers are available for preparation of OS. The polymers can be used be alone or in combination to obtain the desired strip properties. The film obtained should be tough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of the polymer

and the amount in the formulation. The various polymers available, pullulans, gelatin and hyperomellose are most commonly used for the preparation of OS. Pullulan is a naturally occurring polymer obtained from non-animal region and does not require chemical modification. Modified starches are also used for preparation of OS. Due to the low cost of these excipients it is used in the combination of pullulans to decrease the overall cost of the product. Combination of microcrystalline cellulose and maltodextrin has been used to formulate OS [5].

Plasticizers

Plasticizer is a vital ingredient of OS formulation. 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 [6,7]. The selection of plasticizer will depend upon its compatibility with the polymer and also type of the solvent employed in the casting of the strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer, glycerol. Phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0-20% w/w of dry polymer weight. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizer may also affect the absorption rate of the drug.

Surfactants

Surfactants act as solubilizing or wetting or dispersing agent in formulation so that the film is getting dissolved within seconds and release active agent quickly. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is poloxamer 407 that is used as solubilizing, wetting and dispersing agent [8].

Sweetening agents

Sweeteners have become the more important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener sucrose, dextrose, fructose, liquid glucose, glucose and isomaltose. The sweetener of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The artificial sweeteners have gained more popularity in food and pharmaceutical predations. Saccharin, cyclamate and

aspartame are the first generation of the artificial sweeteners followed by Acesulfame-k, sucralose, alitamate and Neotame which all under the second generation artificial sweeteners. Acesulfame-k and sucralose have more than 200 and 600 time sweeteners. Neotame and alitamate have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebaiana which is a herbal sweetener, derived from plant known as Stevia rebaudiana has more than 200-300 time sweeteners [9,10].

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. Generally acids which are used in the preparation of food can be utilized as salivary stimulants, Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are few examples of salivary stimulants, citric acid being the most preferred amongst them [11].

Flavoring agents

It was observed that age plays a significant role in the taste fondness. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plant like leaves, fruits and flowers.. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, oil of nutmeg are examples of flavors like while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple, are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength [12].

Coloring agents

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated Not exceeding concentration levels of 1%W/W) in OS when some of the formulation ingredients or drugs are present in insoluble or suspension form [13].

METHODS OF PREPARATION OF FAST DISSOLVING FILMS

One or combination of the following process can be used to manufacture the mouth dissolving films.

- i) Solvent casting
- ii) Semisolid casting
- iii) Hot melt extrusion
- iv) Solid dispersion extrusion
- v) Rolling Method

1) Solvent casting method:

In solvent casting method water soluble polymer are dissolved in water to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The

entrapped air is removed by vacuum. The resulting solution is cast as a film and followed to dry, which is then cut into pieces of the desired size.

Advantages

- 1) Better uniformity of thickness and bitter clarity than extrusion.
- 2) Film has fine gloss and freedom from defects such as die lines.
- 3) Film has more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 μ m, although various thicknesses are possibly to meet API loading and dissolution needs.

Disadvantages

- 1) The polymer must be soluble in a volatile solvent or water
- 2) A stable solution with a reasonable minimum solid content and viscosity should be formed.
- 3) Formation of a homogeneous film and release from the casting support must be possible [14,15].

2) Semisolid casting

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. Both mixtures are mixed to form homogenous viscous solution degassed under vacuum. Bubble free solution is coated on non-treated casting film coated film is sent to aeration drying oven. Film is cutted in to desired shape and size.

3) Hot melt extrusion

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

Advantages:

- Without use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance
- Better alternative for poorly soluble drugs.

- More uniform dispersion because of intense mixing and agitation
- Less energy compared with high shear methods.

4) Solid dispersion extrusion

In this method immiscible components are extruded with drug and then solid dispersions were prepared. Finally the solid dispersions are shaped into 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 into desired shapes and sizes [16].

Various Technologies used in Oral Film Formulation

XGel: XGel film technology developed by Bio-progress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

Soluleaves: This is applied to flavour-release products such as mouth fresheners, confectionery and vitamin products. SOLULEAVES technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form.

Wafertab: WAFERTAB is a patented delivery system that uses a unique process to prepare drug loaded thin film which can be used in topical or oral application. Active ingredients are incorporated into the film after casting.

Foamburst: FOAMBURST is a new patent granted in September 2004 which is for capsule made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The Light honeycombed structure results in capsule that dissolve rapidly, causing a melt-in-the mouth sensation.

Micap: Micap plc signed an option agreement in 2004 to combine its experts in micro encapsulation technology with the Bio progress water-soluble films. The development will be aimed at providing new delivery mechanism for the \$1.4bn global market for smoking sensation products (SCPs) [17].

EVALUATION OF THE FILM

1) Thickness

The thickness of a film can be measured by micrometer or screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

2) Folding endurance test

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

3) Moisture uptake

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner. The films were placed in the desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 % R.H. After 3 days the films were taken and weighed the percentage moisture absorption of the films was found.

4) Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks [16]. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given [16]. In the equation below

$$\text{Tensile stress (S)} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m \cdot g}{b \cdot t}$$

Where, S = tensile stress in 980 dynes/cm²

m = mass in grams

g = acceleration due to gravity (980 dynes/cm²)

b = breadth of strip in centimeters

t = thickness of strip in centimeters

5) Percent elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases [17].

$$\text{Strain (E)} = \frac{\text{Total elongation}}{\text{Original length}} \times 100 = \frac{L - L_0}{L_0} \times 100$$

Where, L = length after force was applied

L₀ = original length

6) Weight variation

Ten films were randomly selected and their average weight was obtained. Individual films were weighed and compared with the average weight for the deviation.

7) Drug content

The film of area 2x2 cm² was cut and dissolved in distilled water. Then solvent ethanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with distilled water to 100ml in 100ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10ml. The absorbance of the solution was taken at relevant

nm and concentration was calculated. By correcting dilution factor, the drug content was calculated

8) Disintegration test

To find out actual time required for disintegration of the film. For this dissolve the prepared film in a suitable buffer and note down the time required to breakdown of the films.

9) In vitro dissolution test

The dissolution studies using three media such as, distilled water, simulated saliva consisting of phosphate buffer (pH 6.8) and simulated gastric fluid (pH 1.8) to ascertain dissolution behavior of the film.

RATIONALE IN THE SELECTION OF THE DRUG

Ideal characteristics of a drug for formulation as fast dissolving films

- Should be potent and have less therapeutic dose.
- Should be compatible with excipients.

All the above ideal characteristics are fulfilled by, a 5HT₃ antagonist and hence it is selected for our study.

8. Rationale in the selection of the dosage form

Fast dissolving films are the novel approach to get quick onset of action and to get immediate relief of the symptoms. Moreover in geriatric patients have difficulty of swallowing. Hence, fast dissolving films are the best formulations as they are soluble in saliva with in 1 minute releasing the drug and inactive ingredients. Most of the

drug is swallowed with saliva where subsequent absorption takes place in gastrointestinal tract

PACKAGING TECHNIQUES

SoluStrip™

SoluStrip™ with its soluble film strip(s) in a pouch is an ideal delivery format for OTC and Rx drugs, whether oral, mucosal, or topical, and may even offer extended patent protection for your brand. Soluble films strips are well known for their oral care applications such as tooth whiteners, and can also deliver vitamins and nutraceuticals, flavors or fragrances. Soluble film is not just limited to edible or oral applications — soluble film is also appropriate for topical skin care treatments, cosmetics, and numerous general household applications.

Soluble film may be a standalone product or as an additive to other products to deliver visible value. Film with unique ingredients including vitamins, minerals, special flavors or colors can be cut into various shapes or sizes and added to gels, lotions, creams or other products to deliver ingredients that can be easily “seen and appreciated by consumers.”

Oral Soluble Film:

1. Keep the film in the foil pouch until ready to use. Use the film right away, after you take it from the pouch.
2. Make sure your hands are dry.
3. Fold the pouch along the dotted line to expose the tear notch. See Figure A.

Table 1. differences between ODF's and ODT's

Orally dissolving Films	Oral disintegrating Tablets
It is a film	It is a tablet
Greater dissolution due to the larger surface area	Lesser dissolution due to less surface area
Better durable action than oral disintegrating tablets	Less durable as compared with oral films
More patient compliance	Less patient compliance than films
Low dose can only be incorporated	High dose can be incorporated
No risk of choking	It has a fear of choking

Table 2. Different API's used in preparation of films

Drug	Action	Dose (mg)
Salbutamol	Antiasthamatic	4
Levocetizine	Antihistaminic	15
Chlorohexidine	Antiseptic	12
Ondonsetron	Antiemetic	2.5

Table 3. A typical composition of FDF contains the following

CONTENTS	PERCENTAGE
Drug	5% to30% w/w
Water soluble polymer	45% w/w
Plasticizers	0-20% w/w
Surfactants	q. s.
Sweetening agent	3 to 6 % w/w
Saliva stimulating agent	2 to 6% w/w
Fillers, colors, flavors etc.	q. s.

Table 4. Examples of marketed oral thin films

Brand name	Manufacturer/ distributor	API (strength)	Uses
Klonopin Wafers	Solvay Pharmaceuticals	Clonazepam (in five strengths: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg and 2 mg.)	Treatment of anxiety
Listerine Cool Mint Pocket Packs	Pfizer, Inc.	Cool mint	Mouth fresheners
Sudafed PE	Walters Lower Health, Inc.	Phenylephrine	Relieving congestion
Suppress®	InnoZen®, Inc.	Menthol (2.5 mg)	cough suppressants
Triaminic	Novartis	Diphenhydramine HCL (12.5 mg)	Anti allergic
Theraflu	Novartis	Dextromethorphan HBR (15 mg)	Cough suppressant
Orajel	Del	Menthol/pectin (2 mg/30 mg)	Mouth ulcer
Gas-X	Novartis	Simethicone (62.5 mg)	Anti Flatuating
Chloraseptic	Prestige	Benzocaine/menthol (3 mg/3 mg)	Sore throat

Table 5. Excipients generally used in preparation of fast dissolving films

Ingredient/ Purpose	Examples	% (w/w)
Water soluble polymers	Cellulose ethers(HPMC, HEC, HPC, and MC), PVC, PVA, gelatin, Pullulan, kollicoat IR, PEG, tragacanth gum, guar gum, chitin, etc.,	40-50
Plasticizers	Glycerol, PG, PEG	0-20
Disintegrants	Pregelatinised starch, MCC, croscopolidone, soluble starch	0-40
Preservatives	Salts of edetate (disodium EDTA)	0.01-1
Saliva stimulating agents	Citric Acid, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acid	2.5-6
Cooling agents	Monomethyl succinate	0.2-0.4
Surfactants	Mono & diglycerides of FA, polyoxy ethylene sorbitol esters	0.5-15
Stabilizing agents	Xanthan gum, locust Bean gum and carrageenan	0.1-2
Emulsifying agents	Triethanolamine Stearate, Qt. Ammonium Cpds, Acacia, gelatin	0-01-0.7
Thickening agents	MC, carboxy methyl cellulose	0.01-5
Sweetening agents	Sucralose, aspartame, Acesulfame K, Neotame	0-2

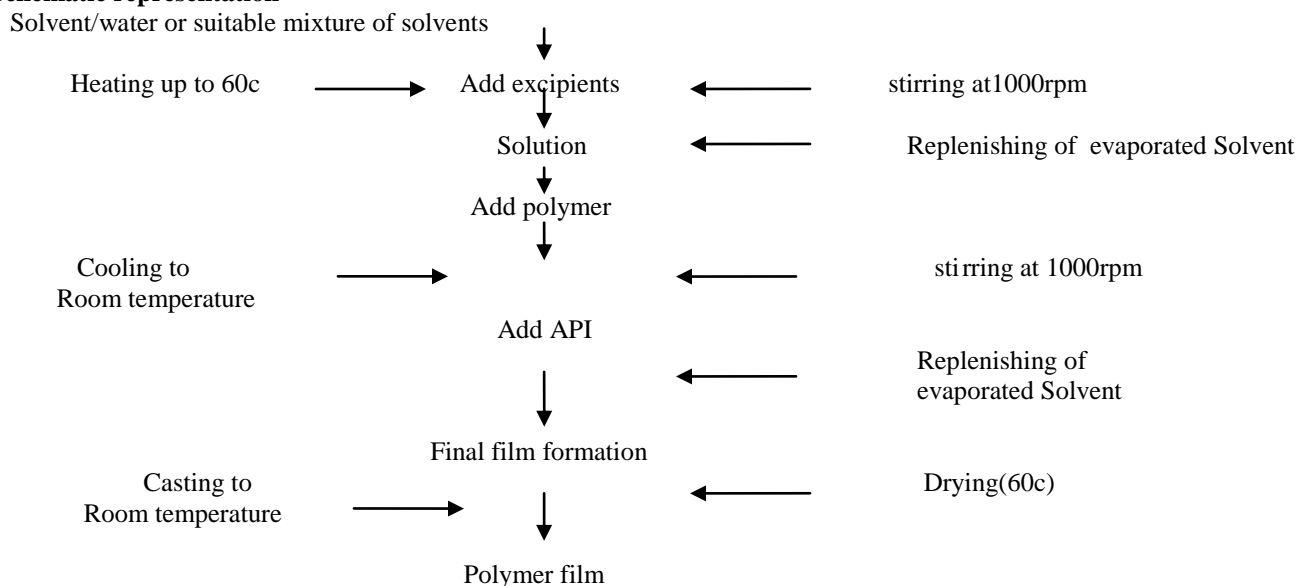
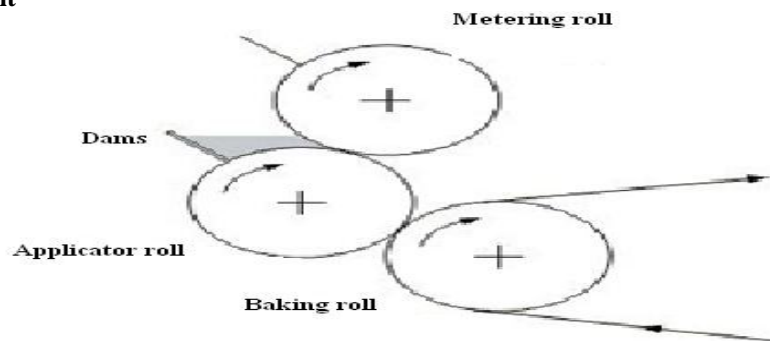
Fig 3. Flow chart for solvent cast evaporation method**Schematic representation**

Fig 4. Three roll coating unit**Oral Soluble Film:**

1. Keep the film in the foil pouch until ready to use. Use the film right away, after you take it from the pouch.
2. Make sure your hands are dry.
3. Fold the pouch along the dotted line to expose the tear notch. See Figure A.

**Figure A**

4. While still folded, tear the pouch carefully along the edge. See Figure B

**Figure B**

5. Take the ZUPLENZ film strip from the pouch. See Figure C.

**Figure C**

6. Put the ZUPLENZ film on top of your tongue, where it will dissolve in 4 to 20 seconds. See Figure D



Figure D

7. Do not chew or swallow the film whole.
8. Swallow after the film dissolves. You may swallow the dissolved film with or without liquid.
9. Wash your hands after taking ZUPLENZ.

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