JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON ORAL FAST DISSOLVING SUBLINGUAL FILM FOR AN INNOVATIVE ORAL DRUG DELIVERY SYSTEM

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Abstract:

In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. Fast dissolving oral films are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. These films have a potential to deliver the drug systemically through intra-gastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. Fast dissolving oral films are found to be satisfactory in many situations like allergic conditions, cold and cough, sore throat, nausea, pain, mouth ulcers, CNS disorders and CVS disorders. Oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, film stabilizing agents, plasticizers, sweeteners, flavours, colors, saliva stimulating agents, surfactants etc.

Keywords: Fast dissolving sublingual film, Sublingual absorption, solvent casting method, Drug release, and Fast onset of action.

Introduction (1-8)

Fast Dissolving Drug Delivery Systems serves as a real benefit over the conventional dosage forms since the drugs gets quickly disintegrated & dissolves in the salivation without the utilization of water. The most well known oral solid dosage forms are tablets and containers. Numerous patients find it hard to swallow tablets and hard gelatin capsules especially pediatric and geriatric patients and do not take their medicines as prescribed. Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolves or disintegrates in the mouth within few seconds and eliminates the fear of chocking as an alternative to fast dissolving tablets. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. 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 mucosal 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.

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

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active lifestyle.

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. 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. (9, 10)

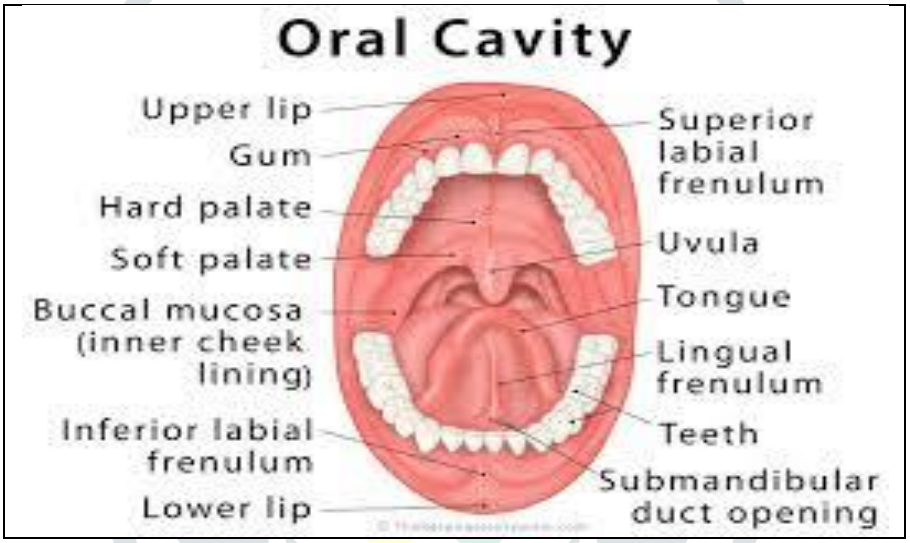

Fig. 1: Figure of Oral Mucosa

Sublingual glands

Salivary glands are available in the floor of the mouth underneath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The inner area of the mouth stays lubricated due to production of the saliva by the glands, which is necessary for chewing and food swallowing. The fluid which is produced by the glands gets blend with the food, so the food gets easily chewed. Due to low secretion of the saliva it can create problem in swallowing the food and potential for food lodge in the throat increases. 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 is like Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can deliver fast onset of action so the drug with short delivery period can be delivered and dose regimen is regulars. The drug gets diluted in the saliva and from there the drug is adsorbed across the oral cavity. (11)

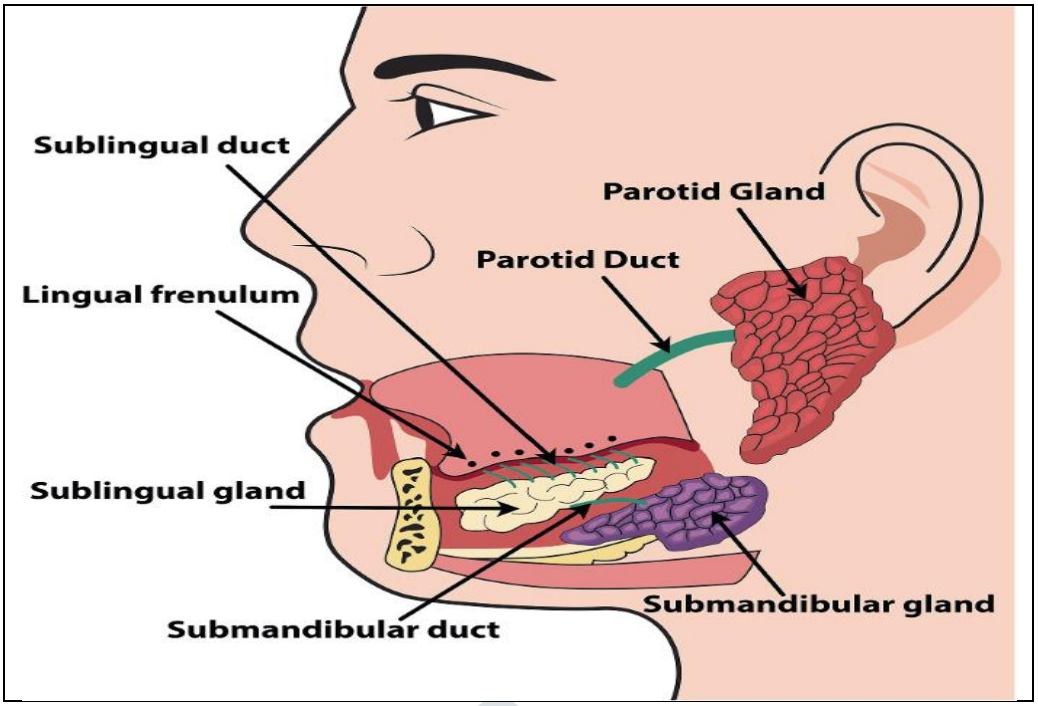

Fig. 2: Figure of sublingual gland

Mechanism Of Absorption

Salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acid the taste,the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighboring muscles and to the mucous membranes of the mouth, tongue and gums.

Two symmetricalbranches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the submental branches of the facial artery. The sublingual artery stems from the lingual artery the body's main blood supply to the tongue and the floor of the mouth which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere.(12, 13)

Special Features (14, 15)

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

Factors Affecting the Sublingual Absorption (16, 17)

- **Lipophilicity of 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.
- **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.

- **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.
- **Binding to oral mucosa**: Systemic availability of drugs that bind to oral mucosa is poor.
- **Thickness of 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.
- **Oiltowater partition coefficient:** Compounds with favorable oil-to-water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Advantages of Films (18, 19)

- No risk of choking and obstruction.
- No need of water has led to better acceptability amongst the dysphagic patients
- Improved oral bioavailability of drugs
- Taste masking
- Enhanced stability
- Improved patient compliance
- Oral films are flexible and they are not as fragile as most of the ODTs
- Reduction in first pass metabolism may lead to reduction in the dose
- The oral or buccal mucosa is highly vascularized, hence drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract
- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma.

Disadvantages of Films (20)

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- These films are moisture sensitive and expensive packing of oral film is required.
- Limitations: Most bitter drugs should be avoided or taste masking is required. Proteinaceous drugs should be avoided if used then co-administration of enzyme inhibitors such as aprotinin, bestatin, puromicin and bile salts required for the inhibition of proteolytic enzymes present in saliva.

Ideal Characteristics of A Drug To Be Selected (21)

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 20 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

FORMULATION OF FAST DISSOLVING FILMS (22-28)

Table 1: Composition of fast dissolving oral sublingual film

S.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.	Colouring agent	1%

1. Active pharmaceutical agent

A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in OFDFs. Multivitamins upto 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 OFDFs. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste.

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 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 non animal 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. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Examples of salivary stimulants are citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. Among these the most preferred one is citric acid.

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, sweet mint, 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 (29, 30)

Following processes can be used to manufacture fast dissolving films:

1. Solvent casting method
2. Semi solid casting method
3. Hot melt extrusion method
4. Solid dispersion extrusion method
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 into the Petri plate dried and cut in to uniform dimensions.

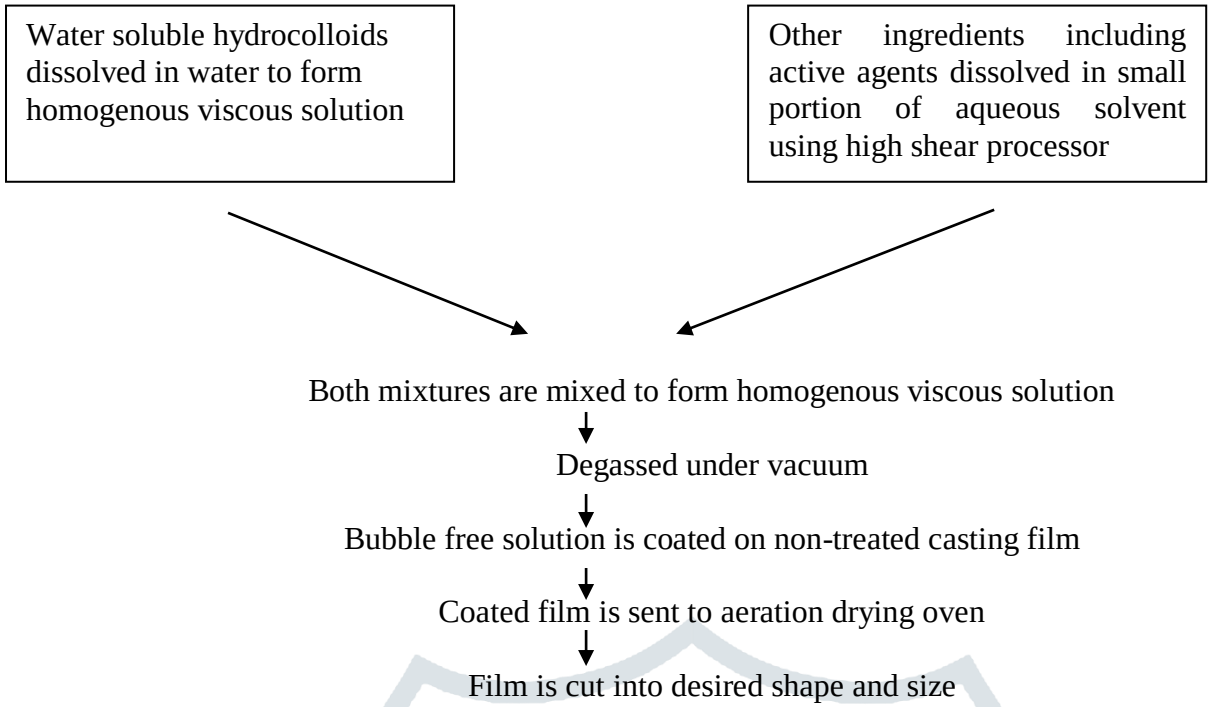

Fig. 3: Process for solvent casting method

Advantages:

1. Great uniformity of thickness and great clarity then extrusion a typical relative standard deviation (RSD) for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1.2% RSD.
2. Film has fine gloss and freedom from defects such as die lines.
3. Films have more flexibility and better physical properties.
4. The preferred finished film thickness is typically 10-100µm, although various thicknesses are possible 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.

2) Semisolid casting method

This technique is ideally embraced when acid insoluble polymers are to be used in the preparation of the films. Acid-insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

Solution of water soluble film forming polymer is prepared.
↓
Resulting solution is added to a solution of acid insoluble polymer
↓
Appropriate amount of plasticizer is added so that gels mass is obtained.
↓
Finally the gel mass is casted into the films or ribbons using heat controlled drums.

3) Hot melt extrusion

Hot melt extrusion method has various benefits; those are fewer operation units, minimum product wastage, better content uniformity, an anhydrous process, absence of organic solvents.

In hot melt extrusion method-
Drug is mixed with carriers in solid form.
↓
The extruder having heaters melts the mixture
↓
Finally the melt is shaped in films by the dies

Advantages:

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.
- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages:

- Thermal process so drug/polymer stability problem
- Flow properties of the polymer are essential to processing
- Limited number of available polymers.

4) Solid dispersion extrusion method

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Precautions while preparing solid dispersions: The selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol and polymeric form of drug precipitated in the solid dispersions may get affected by the liquid solvent used.

Drug is dissolved in a suitable liquid solvent.
↓
Then solution is incorporated into melt of polyethylene glycol, obtainable below 700C.
↓
Finally the solid dispersions are shaped into the films by means of dies.

5) Rolling method

In this method the film is prepared by preparation of a pre-mix, the addition of an active and subsequent formation of a film.

Prepare pre-mix with film forming polymer, polar solvent and other additives except a drug.

↓

Add pre mix to master batch feed tank.

↓

Fed it via a 1st metering pump and control valve to either or both of the 1st and 2nd mixer.

↓

Add required amount of drug to the desired mixer.

↓

Blend the drug with master batch pre mix to give a uniform matrix.

↓

Then a specific amount of uniform matrix is then fed to the pan through 2nd metering pumps.

↓

The film is finally formed on the substrate and carried away via the support roller.

↓

The wet film is then dried using controlled bottom drying

Packaging (31, 32)

In the pharmaceutical industry it is vital that the package selected adequately 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, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement
- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product tastes or odors.

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. The pouches can be single pouches or aluminum pouches.

2. Single pouch and Aluminium pouch

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.

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 semirigid 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.

Conclusion

It can be concluded that the oral thin film is a potential new dosage form for pediatrics, geriatrics and bedridden patient experience difficulties in swallowing the conventional oral dosage form. To overcome this problem a novel formulation was developed i.e. oral fast dissolving films.This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.

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