e-ISSN: 2248-9126
Vol7|Issue 2| 2017 |43-49. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

AN OVERVIEW ON: ORALLY FAST DISSOLVING SUBLINGUAL FILM

Utkarsha C. Tope[1*], S.B.Gondakar[2], R.B. Saudager[3]

[1*]Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.
[2]Department of Quality Assurance, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.
[3]Department of Pharmaceutical Chemistry, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik- 422213, Maharashtra, India.

ABSTRACT

Sublingual route is a useful when rapid onset of action is desired with better patient compliance. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolism processes giving acceptable bioavailability. Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology, which aim to enhance safety and efficacy of a drug molecule to achieve better patient compliance. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients with fear of choking. Overthecounter films for pain management and motion sickness are commercialized in the US markets. Many companies are utilizing transdermal drug delivery technology to develop thin film formats. Fast dissolving oral films are useful in patients such as paediatric, geriatric, bedridden or developmentally disabled who face difficulty in swallowing conventional tablets or capsules and liquid orals or syrups leading to ineffective therapy. The delivery system consists of a very thin oral strip, which 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.

Keywords: Paediatric, Bioavailability, Geriatric.

INTRODUCTION

Fast dissolving films (FDF), a type of oral drug delivery system for the oral delivery of the drug, was developed based on the technology of the transdermal patch. 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 [1]. The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology [2]. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self administration even without water or chewing. An ideal fast dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a

Corresponding Author:- **Utkarshachintaman Tope** Email: utkarshatope712@gmail.com

pleasant taste.

Fast dissolving oral films (FDOFs) or Oral wafers or Oral strips (OS) or sublingual strips or oral thin films (OTF) are the most advanced form of oral solid dosage form due to more flexibility and comfort1. It improves 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 and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [3, 4].

Within the oral cavity, delivery of drugs via the membranes of the oral cavity is classified into three categories:

i)Sublingual delivery which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation;

ii) Buccal delivery which is drug administration through the mucosal membranes lining the cheeks and the area between the gums and upper and lower lips to the systemic circulation.

iii) Local delivery which is drug delivery to periodontal, gingival, delivery for the local treatment of ulcers, bacterial and fungal infections and periodontal disease. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through ventral surface of the tongue and floor of the mouth. The 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 then drained in to systemic circulation [5].

Sublingual glands

Salivary glands which 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 interior area of the mouth remains 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 mix 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 follows in this way Sublingual >Buccal> Gingival > Palatal.

The Mechanism of Sublingual Absorption

The absorption potential of the buccal mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the molecular weight of the substances. For example, absorption of some drugs via the buccal mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline). The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if by hollowly wrapping itself around it. These engulfed particles are usually too large to diffuse through its wall). It is unlikely that this mechanism is used across the entire stratified epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is believed that acidic stimulation and uptake into the circulatory system.

The 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 Sub mandibular and the Sublingual which lies on the floor of the mouth. The more acid the taste the greater the stimulation of salivary output, serving also to avoid potential harm to acid sensitive tooth enamel by bathing the mouth in copious neutralizing fluid.

CLASSIFICATION OF FAST DISSOLVING TECHNOLOGY

For ease of description, fast dissolve technologies can be divided in to three broad groups [6].

- Lyophilized systems.
- Compressed tablet‑based systems.
- OTF.

Lyophilized systems

The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet‑shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. The units are capable of incorporating a range of taste masked materials and have more rapid disintegration than tablet‑based systems.

Compressed tablet‑based systems

Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard high density polyethylene (HDPE) bottles or blisters through to more specialists pack designs for product protection, for example, CIMA Labs, PackSolv. The speed of disintegration for fast dissolving tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or superdisintegrate or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is BiovailFuisz Technology [6]. It uses the proprietary Shearform system to produce drug loaded

candy floss, which is then used for tableting with other excipients.

OTF

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable OTF or OS have evolved over the past few years from confection and oral care markets in the form of breath strips and become a novel and widely accepted form by consumers for delivering vitamins and personal care products. Today, OTF are a proven and accepted technology for systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs.

Salivary glands

Saliva is produced by three pairs of major salivary glands:

- The parotid
- The sublingual
- The submandibular

And numerous minor accessory glands scattered throughout the oral mucosa. Saliva is a hypnotic, watery secretion containing variable amounts of mucus, enzymes (principally amylase and anti-bacterial enzyme lysozyme), antibodies and inorganic ions.

Two types of secretary cells are found in the salivary glands: serous cells and mucosa cells. The parotid glands consist almost exclusively of serous cells and produce a thin, watery secretion rich in enzymes and antibodies. The sublingual glands have predominantly mucous secretory cells and produce a viscid mucous secretion.

The submandibular glands contain both serous and mucous secretory cells and produce a secretion of intermediate consistency. The overall composition of saliva varies according to the degree of activity of each of the major glands types. The watery component of saliva moistens and lubricates the masticatory process. Salivary mucous is helps to bind the food bolus ready for swallowing. The surface coating of mucous also serves to protect the epithelium from potentially harmful substances. Enzymes present in the saliva initiate the digestive process.

SPECIAL FEATURES OF FAST DISSOLVING FILMS

- Film should be thin and elegant.
- Available in various size and shapes.
- Unobstructive.
- It should adhere to the oral cavity easily.
- Should processes fast disintegration without water.
- Rapid release [7].

Advantages

Relatively large surface area

The oral cavity offers a relatively large surface area (the total area of the buccal cavity is approximately 100 cm^2) for, both from the application and relatively drug absorption.

Accessibility

The oral cavity offers a very accessible surface for drug delivery, both for the application and removal of drug delivery systems. This accessibility omits the need for complex delivery devices to enable the drug to reach its absorption site. Thus devices for an oral delivery are simpler in design than those intended to deliver drugs to, for instance, the alveolar region of the lun**g.**

Ease of use

Oral transmucosal devices, such as sprays, tablets or patches, are also simple for the patient to use and might be expected to be more acceptable to the patient than use of pessaries or suppositories for the intravaginal and rectal delivery routes respectively.

Rich blood supply

The highly vascular surface of the oral mucosa ensures rapid absorption and onset of action, as well as the maintenance of sink conditions. In particular, the sublingual route is characterised by rapid onset of action. The buccal offers the combined advantages of relatively rapid onset of action, with the potential for sustained delivery over several hours.

Low metabolic activity

The metabolic activity of the oral cavity is thought to be less than that of the GI tract, which making this route an attractive alternative to the oral delivery of the enzymatically labile drugs such as therapeutic peptides and proteins. Furthermore, this route avoids first-pass effects of degradation in the intestinal wall or the liver(Hepatic metabolism), prior to the drug reaching the systemic circulation.

Low variability

This route has less variability than, for example, the oral route, where factors such as intestinal motility, presence of food and extremes of pH combine to make oral drug delivery highly variable. However, factors such as salivary flow and certain diseases states can contribute to a degree of variability associated with this route.

Robust

The oral mucosa is routinely exposed to a multitude of different foreign compounds and is relatively robust and less prone to irritation than the nasal mucosa.

Prolonged retention

Prolonged retention of the drug is possible in the buccal cavity, if the appropriate delivery is used. This allows a lowering of the dosing frequency.

Intestinal alternatives

The buccal cavity is a useful alternative to the intestinal route for drug absorption in situations where the gastrointestinal route is unfeasible.

Examples include:

- patients with nausea and vomiting ;
- patients with swallowing difficulties;
- for drugs that cause gastric irritation;
- for drugs that are unstable in the gastrointestinal fluid

Zero-order controlled release

Buccal drug delivery offers the potentive to achieve zero-order controlled release.

Zero-order controlled release offers advantages of: Avoiding the peaks that is (risk of toxicity) and troughs (risk of ineffectiveness) of conventional therapy; reducing the dosing frequency; increasing patient compliance.

Disadvantages

Limited to potent molecules

For drugs of a high molecular weight (weight thus are poorly absorbed), the route is limited only to potent drug molecules, typically those with effective plasma concentrations within or below the ng mL^{-1} range [8-11].

Adverse reaction

Locally irritating or sensitizing drugs must be used with caution in this route. However as per overview, the oral epithelium is relatively robust and this factor is not a limiting as in other highly sensitive mucosal sites, such as nasal cavity.

Metabolic activity

While the metabolic activity of the oral cavity towards peptides and proteins is less than that of the GI tract, it should be recognized that the oral mucosa secretions do have the ability to degrade drugs and that measures might be necessary to overcome this.

Mucus and salivary clearance

Mucus and salivary clearance reduces the retention time of drugs within the oral cavity and thus the opportunity for absorption. This may be overcome by the use of mucoadhesive systems.

Mucus barrier

Drug diffusion may be limited by the physical barrier of the mucus layer and also the specific or non-specific binding of the drugs to the mucus layer.

GENERAL METHODS USED FOR PREPARATION OF FILMS

1. Solvent casting
2. Hot melt extrusion
3. Rolling
4. Solid dispersion extrusion
5. Semisolid casting

Solvent Casting Method

In this method, water soluble polymer is completely dissolved in water to form uniform clear viscous solution; all other ingredients including API are dissolved in a small portion of suitable solvent by using a high shear processor. This viscous solution is degassed under the vacuum to remove the air bubbles. This bubble free solution is poured into a suitable glass mold and kept in oven at 40 º-50 º C.

Hot melt extrusion (HME)

Now a day, this method is commonly used to prepare granules and sustained release tablets; also transdermal and transmucosal drug delivery system. By this technique, preparation of film involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting technique. Hot melt extrusion process based on polymer with a high glass transition temperature such as PVP.

Advantages of Hot melt extrusion

- Neither solvent nor water is used in the process
- Only few processing steps are needed; time consuming drying steps are eliminated
- No requirement on the compressibility of the active ingredients
- The bioavailability of the drug gist can be improved when it is dispersed at the molecular level in hot melt extruded dosage forms.
- Uniform dispersion of the fine particles is more due to intense mixing and agitation causing suspended drug particles to deaggregate in the molten polymer

Equipment used

- The equipment used for hot melt extrusion consists of extruded, downstream auxiliary equipment and monitoring tools.
- Extruder comprises of a feeding hopper, the barrel, screw, die, screw-driving unit and heating/cooling device.
- Producing thin films for transdermal/transmucosal drug delivery and wound care is via film casting from aqueous or organic solvents. Repka et al studied the influence of Chlorpheniramine maleate on topical HPC films by hot melt extrusion technique.
- Chlorpheniramine has been reported to function as an effective plasticizer, which is increasing percent elongation and decreasing tensile strength in concentration dependent manner. Whereas Chlorpheniramine also acted as a processing aid in the extrusion of hot melt films and

allowing film processing at lower temperature.

Rolling Method

In this method, suspension or solution containing drug is rolled on a carrier. The solvent is mainly water or mixture of water and alcohol. The solution or suspension should have a specific rheological consideration. Film is dried on the rollers and cut into desired shapes and sizes .Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

Solid Dispersion Extrusion

In solid dispersion extrusion method all immiscible components is extrude with drugs and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.

Semisolid Casting Method

In this method, at first homogenous solution of water soluble film forming polymer is prepared. Then this prepared solution is added to a solution of acid insoluble polymer. Then approximate amount of plasticizer is added so that a gel mass is obtain. At last the gel mass is casted into the films or ribbon by using heat controlled drums. The thickness of film is about 0.015- 0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be kept as 1:4[12].

Patented approaches

Xgel

XGel™ film provides unique product benefits for healthcare and pharmaceutical products: It is nonanimal derived, approved on religious grounds, and is suitable for vegetarians; the film is genetically modified organism (GMO) free and continuous production processing provides an economic and competitive manufacturing platform. XGel™ film can be taste masked, colored, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGel™ film systems can be made to encapsulate any oral dosage form and can be soluble in either cold or hot water. XGel™ film is comprised of a range of different water soluble polymers, specifically optimized for the intended use [13].

Soluleaves

This technology is used to produce a range of oral delivery films that can incorporate active ingredients, colors, and flavors. Soluleaves™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients, and flavors. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses, this method of administration is especially useful for pediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal, and pain therapeutic areas as well as delivering nutritional products. Soluleaves™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 min.

Wafertab

Wafertab™ is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The Wafertab™ filmstrip can be flavored for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a premanufacturedXGel™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The Wafertab™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. Wafertab™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty in swallowing.

Foamburst

It is a special variant of the Soluleaves™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. Foamburst™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavors.

Micap

Micapplc signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress water soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4 billion global market for smoking cessation products (SCPs).

THE TECHNOLOGY BEHIND THE FAST DISSOLVING FILM /MOUTH DISSOLVING FILM (FDF/MDF)

The Peroral application is an effective and inexpensive way for drugs that can be absorbed in the gastrointestinal tract. However, in some case the application of tablets or solution is a problem. A tablet has to disintegrate in the gastrointestinal tract in order to dissolve the drug. The Process extends the absorption of drug to some extent, which is undesirable in some diseases, like pain, vomiting. In gastrointestinal diseases, the patient is often unable to swallow a solid dosage form due to nausea. That problem was solved in the past by the

application of the drug in the form of drop or syrup. However, the regimen of the amount of drop or the use of metering spoon needs and it is not precise. Furthermore not all drugs are stable in aqueous – alcoholic solution. Children very often fight against oral medicine; they may spit out tablet or not consume the entire dose. Fast dissolving Films have all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability). The film dissolves immediately after application in the mouth and releases the drug. Depending on the physicochemical parameters, absorption can begin in the mouth itself, through the oral mucosa. The resulting drug suspension or solution can be swallowed quickly; the plasma levels are increasing at least as rapidly as an immediate release tablet. The patient swallowing the drug solution or suspension has no sense of a foreign body. The system ensures an excellent patient compliance even in cases of nausea. Children cannot spit the drug out because the film adheres to the upper gum after dissolution. Therefore, safe application is increased in children as a single dose application, the precision of the dose can be ensured, which is not the case with drops or syrups. The Fast Dissolving Film Technology also has clear advantages over Oral DissolvingTablets (ODT) which, unlike FDFs/ OTFs, do not require water for administration, whereas ODTs are sometimes difficult to carry, store and handle (fragility and friability); Many ODTs are produced using the expensive lyophilization process; FDFs/OTFs can be packed using various options, such as pouches, blister cards dispensers and Rapid Card.

FILM FORMING POLYMERS

A variety of polymers are available for preparation of fast dissolving oral films [13]. The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of film forming polymers, is one of the most important and critical parameter for the successful development of film formulation. The polymers can be used alone or in combination to provide desired film properties. The polymers used in oral film formulation should be:

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spread ability property.
- Should have sufficient peel, shear, and tensile strength.
- Readily available.
- Inexpensive.
- Sufficient shelf life.
- Should not aid in causing secondary infections in oral mucosa.

Presently, both natural and synthetic polymers are used for the preparation of orally dissolving films. Table 4 represent various natural and synthetic polymers used for preparation of fast dissolving films. Tables 5 and 6 represent the quality parameters of natural and synthetic polymers, respectively.

Polymers used in the formulation fast dissolving film

Polymer Examples

Natural polymer : Pullulan, starch, gelatin, pectin, sodium alginate, maltodextrins, polymerized rosin

Synthetic polymer : Hydroxypropyl methylcellulose, sodium carboxymethylcellulose, polyethylene oxide, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, ethyl cellulose

EVALUATION PARAMETERS FOR FAST DISSOLVING SUBLINGUAL FILM:

Several evaluation parameters used for a FDSF is as follows;

Mechanical properties

Mechanical properties of the films are evaluated using Instron TA.XT2 texture analyzer equipment equipped with a 5 kg load cell. Films are held between two clamps positioned between 3 cm. During measurement the strips were pulled at the rate of 2mm/sec. The force and elongation are measured when film breaks. Three mechanical properties namely tensile strength, elastic modulus and % elongation are calculated.

Tensile strength

Tensile strength is calculated by Formula;

Tensile strength= force at break / initial cross sectional area of film in mm^2

% Elongation: It is calculated as:

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \text{ X } 100$$

Folding endurance

Is determined by folding the films of uniform cross sectional area and thickness until breaks.

Morphology study

The morphology of the films is studied using scanning electron microscopy (SEM), at a definite magnification.

Thickness of the Film

The thickness of the drug loaded films is measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each film. Mean SD is calculated. The standard range for film thickness should not be less than *5 %*. This is essential to assure uniformity in the thickness of the film as this was directly related to the accuracy of dose.

Weight variation of the film

Weight variation is studied byindividually

weighing 10 randomly selected filmstrips and calculating the average weight should not deviate significantly from average weight.

***In vitro* disintegration time**

In vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate.

***In vitro* dissolution studies**

The in vitro dissolution study is carried out in simulated saliva solution pH 6.8 phosphate buffer using USP paddle apparatus at 37±0.5^{o}C.Samples were withdrawn at regular time interval and analysed by UV-Visible spectrophotometer.

Surface pH

The film formulation has to be kept in the oral cavity, pH of saliva ranging from 5.5-7.5. So, to dissolve and solubilise drug in the saliva present in the oral cavity the pH of film should kept near to neutral. If it is acidic one leads to irritation of the buccal mucosa.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

No Interest

Fig 1. The Anatomy and Physiology of Oral Mucosa

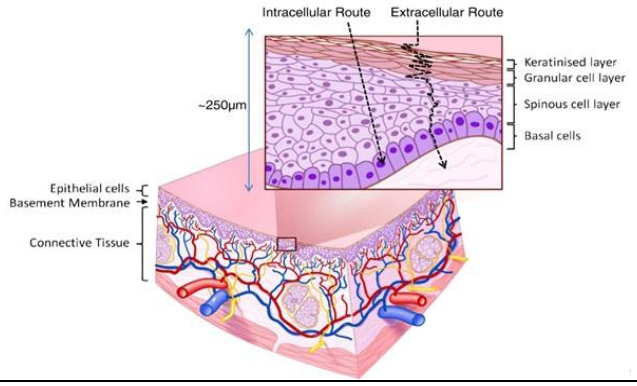
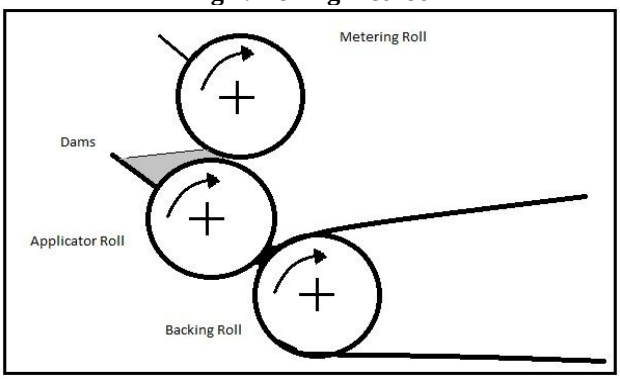


Fig 2. Rolling method



REFERENCES

1. Nishi T, *et al.* Overview A Novel Approach of Fast Dissolving Films and Their Patients Advan. *Biol. Res*, 7(2), 2013, 50-8.
2. Farhana S, Mohammad A, Saiful IP. Preparation and Evaluation of Fast Dissolving Oral Thin Film Of Caffeine Int. *J. Pharm. Bio. Sci*, 3(1), 2013, 153-61.
3. Rajni B, Pravin P, Sushi K and Sandeep A. Orally dissolving strips: A new approach to oral drug delivery system. *International Journal of Pharmaceutical Investigations*, 3, 2013, 67-76.
4. Ishikawa T, Koizumi N and Mukai B, Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PHM06) and spherical sugar granules. *Chem Pharm Bull*, 49, 2002, 230-32.
5. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. *Int J Chem Tech Re*, 2, 2010, 576‑83.
6. Chemical Market Reporter. Fuisz sign deal for drug delivery. *Chem Mark Report*, 253, 1998, 17.
7. Sublingual mucosa as a route for systemic drug delivery. *International Journal of Pharmacy and Pharmaceutical Sciences*, 3, 2011, 32.
8. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. *Int J Chem Tech Res*, 2, 2010, 576‑83.
9. Chemical Market Reporter. Fuisz sign deal for drug delivery. *Chem Mark Report*, 253, 998, 17.
10. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. *Int J Pharm Sci Rev Res*, 9, 2011, 50‑6.
11. Sudhakar Y, Kuotsu K, Bandopadhyay AK. Buccalbioadhesive drug delivery; a promising option for orally less efficient drugs. *Journal of Control Release*, 114, 2006, 15-40.
12. Sharma S and Lewis S. Taste Masking Technologies: A Review. *International Journal of Pharmacy and Pharmaceutical Scienc*es, 2(2), 2010, 6-7.
13. Indian pharmacopoeia. Published by The Indian Pharmacopeia Commission Ghaziabad, 2, 2014, 1897-1899.