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REVIEW ON MOUTH DISSOLVING FILMS

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ABSTRACT

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric, geriatric and bedridden patients who experience difficulties swallowing traditional oral solid- dosage forms. Fast dissolving films have become a novel approach to oral drug delivery system as it provides convenience and ease of use over other dosage forms such as orally disintegrating tablets, buccal tablets and sublingual tablets, so mouth dissolving films are gaining the interest of large number of pharmaceutical industries. It was developed on the basis of technology of transdermal patch. Mouth dissolving films are thin solid dosage forms which when placed in the oral cavity; dissolve within few seconds without chewing and intake of water. The oral buccal mucosa being highly vascularized, drugs can absorb directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing and enhance the efficacy and safety profile of medicament. Present review provides an account of various formulation methods and their evaluation used in film formulations.

KEYWORDS: mouth dissolving films, materials, preparation methods, evaluation.

INTRODUCTION[1-5]

The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. The conventional oral solid dosage forms are tablets and capsules. Lots of patient find it difficult to swallow tablets and capsules particularly pediatric and geriatric noncompliant or nauseous patients and do not receive their medicine as prescribed.[1]

Various bio adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and sub mucosa by an undulating basement membrane. It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine. Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration. The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 μm layer. These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but are extremely sensitive to environmental moisture.[2]

Fast dissolving oral film, a novel drug delivery system for the oral delivery of the drugs is an ultra thin film prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity**.** It is an ultrathin strip (50- 150 microns thick) of postage stamp size with an active agent and other excipients developed on the basis of transdermal patch technology.[3] This delivery system consists of a thin film, is prepared using hydrophilic polymers which dissolving film is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva[4] the film rapidly disintegrates and dissolves to release the medication for oral mucosal absorption. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to themoistoral environment.[5]

IDEAL CHARACTERSTICS OF FILM[6-8]

The ideal requirements are summarized below

- ODF should be thin and flexible, but stable to guarantee a robust manufacturing and packaging process and ease of handling and administration.
- The films should be transportable, not tacky and keep a plane form without rolling up.
- Ease of administration for patients who are mentally ill disabled and uncooperative.[6]
- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.

- ❖ They should exhibit low sensitivity to environmental conditions such as temperature and humidity.[7]
- ❖ Size of a unit FDF should not be too large that it will affect the patient's compliance.[6]
- ❖ Un obstructive
- ❖ Excellent mucoadhesion.[8]

Ideal characteristics of drug candidate[9, 1]

- ➢ The incorporating APIs should have a low dose of up to 40 mg.
- ➢ Drugs with low molecular weight are preferable.[9]
- ➢ The drug should possess pleasant taste.
- ➢ The drug should have good solubility and stability both in water and saliva.
- ➢ It should have the ability to permeate oral mucosal tissue.[1]

ADVANTAGES[10,9]

1) Due to larger surface area, provides rapid disintegration and dissolution in the oral cavity.
2) Dose accuracy.
3) Acidic environment of stomach can be avoided.
4) Site specific action and local action.
5) Flexible and portable in nature so provides ease in transportation during consumer handling and storage.[10]
6) No risk of choking and obstruction.
7) No need of water has led to better acceptability amongst the dysphagic patients
8) Improved oral bioavailability of drugs
9) Taste masking
10) Enhanced stability
11) Reduction in first pass metabolism may lead to reduction in the dose
12) 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.[9]

DISADVANTAGES.[8]

1) High doses cannot be incorporated.
2) Excessive bitter drugs are not feasible.
3) Dose uniformity is a technical challenge.
4) They require special packaging for the products stability and safety.

5) Drugs which irritate the oral mucosa cannot be administered by this route.

FORMULATION

The area of drug loaded FDF should be between 1-20cm2. The drug can be loaded up to a single dose of 30mg.

All excipients in the fast dissolving film should be generally regarded as safe (GRAS-listed) and authorized for use in oral strip. Formulation considerations have been reported as important factors which affected mechanical properties of the films.

Table 1: Composition of the films.

S.NO	INGREDIENTS	AMOUNT(W/W)
1	Drug	1 – 30 %
2	Film forming polymer	40-50 %
3	Plasticizer	0 – 20 %
4	Saliva stimulating agent	2 – 6 %
5	Sweetening agent	3 – 6 %
6	Flavoring agent	q.s
7	Surfactant	q.s
8	Colour, Filler	q.s

ACTIVE PHARMACEUTICAL INGREDIENTS[5, 11]

The market for thin film (strips) is mainly for the vitamins, minerals and supplements (VMS) and OTC areas. Active ingredients which appear to be suitable are vitamins, supplements such as melatonin and Coenzyme Q10 (CoQ10), and some OTC ingredients. A class of molecules that can be incorporated into this delivery system, includes cough/cold remedies (antitussives, expectorants), sore throat, erectile dysfunction drugs, antihistamines, antiasthmatics, gastrointestinal disorders, nausea, pain, CNS drugs (Anti-Parkinson), caffeine strips, snoring aid, multivitamins, sleeping aid etc. The MDFs technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in MDFs.[5] The main disadvantage of oral strip/ film is the size of the dosage form due to which high dose could not be loaded. We incorporate 5% w/w to 30% w/w of active pharmaceutical ingredients for multi vitamins, up to 10% w/w of dry film weight was loaded. APIs can be milled, micronized or loaded in the form of nanocrystals or particles depending upon the ultimate release profile desired. For bitter drugs taste required to be masked before incorporating APIs in the OS. To enhance the taste different techniques are used but the simplest method includes mixing and co-processing

of bitter testing API with excipients with good pleasant taste called as ob-scuration technique.[11]

Table 2: Drugs that can be formulated as mouth dissolving films.

Molecule	Therapeutic category	Dose
Nicotine	Smoking Cessation	1.0–15.0 mg
Nitroglycerin derivatives	Vasodilator	0.3–0.6 mg
Zolmitriptan	Anti migraine	2.5 mg
Loratidine	Antihistaminic	5–10 mg
Desloratidine	Antihistaminic	5.0 mg

FILM FORMING POLYMERS[12-15]

Polymers are used in formulation to obtain the desired film and nano fiber properties either alone or in combination. The water-soluble polymers result in rapid disintegration, good mouth feel and mechanical properties to the films and nanofibers. The type and quantity of the polymer could affect the strength of the dosage. As the molecular weight of polymer formulation bases increase the rate of disintegration of the polymer decreases. Currently, both natural and synthetic polymers are employed in preparation of fast dissolving oral film.[12]

The polymers employed in the oral film preparation should be.[13]

1) Non-Toxic and Non-Irritant
2) Devoid of leachable impurities
3) Should not retard disintegration time of film
4) Tasteless.
5) Should exhibit sufficient peel, shear and tensile strength
6) Readily available
7) Inexpensive
8) Should have sufficient shelf life
9) Should not aid in causing secondary infections in the oral mucosa or dental region.

Examples include: Glycerol, Propylene glycol, Low molecular weight polyethylene glycols, Phthalate derivatives like dimethyl, diethyl, dibutyl derivatives, Citrate derivatives like triacetin acetyl citrate, etc.[15]

PLASTICIZER[16]

Plasticizer is an important ingredient of the OS formulation. It assists in improving the flexibility of the strip and decreases the brittleness of the strip. Plasticizer significantly

reduces the glass transition temperature of the polymer therefore polymer chains can slide over each other at lower temperature, thus improves the strip properties. Plasticizer due to its properties improves the flow of polymer and enhances the strength of the polymer. The compatibility of plasticizer with the polymer and type of solvent used in the casting of strip determines the selection of plasticizer. Some of the frequently used plasticizer excipients are glycerol, propylene glycol, low molecular weight PEGs, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil. Usually plasticizers should be used in the concentration of 0–20%w/w of dry polymer weight otherwise inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid. Glycerol acts as a better plasticizer for PVA while diethylene glycol can be used for both HPMC as well as PVA films.

SALIVA STIMULATING AGENTS[17]

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.

SWEETENING AGENTS[18]

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving. Suitable sweeteners include.

(a) Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc

(b) Water soluble artificial sweetener: sodium or calcium saccharin salts, cyclamate salts, acesulfame-k etc.

(c) Dipeptide based sweetener: aspartame.

(d) Protein based sweeteners: thaumatin I and II.

The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Aspartame was used for the preparation of oral strips of valdecoxib. For the oral strip of piroxicam, maltodextrin was employed as sweetening agent Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

SURFACTANTS[19]

Surfactants are used as solublising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

FLAVORING AGENTS[20]

Itwas observed that age plays a significant role in the tastefondness. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, oil of nutmeg are examples of flavor oils 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.

COLORING AGENTS[21]

FD & C approved coloring agents are used (not exceeding concentration levels of 1% w/w) in the manufacturing of orally fast dissolving films. E.g. Titanium dioxide.

METHOD OF PREPARATION OF MOUTH DISSOLVING FILMS[22]

One or a combination of the following processes can be used to manufacture the Mouth dissolving film.

1. Solvent casting method
2. Hot-melt extrusion

3. Semisolid casting
4. Solid dispersion extrusion
5. Rolling

SOLVENT CASTING METHOD[22]

Fast dissolving films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in a suitable solvent then both the solutions are mixed and stirred and finally casted into the Petri plate and dried.

Advantage[23]

- Greater uniformity of thickness and great clarity than extrusion.
- Films have fine gloss and freedom from defect such a die lines.
- Films have more flexibility and better physical properties.

Disadvantages

- The polymer must be soluble in a volatile solvent or water.
- The stable solution with reasonable minimum solid content and viscosity should be formed.

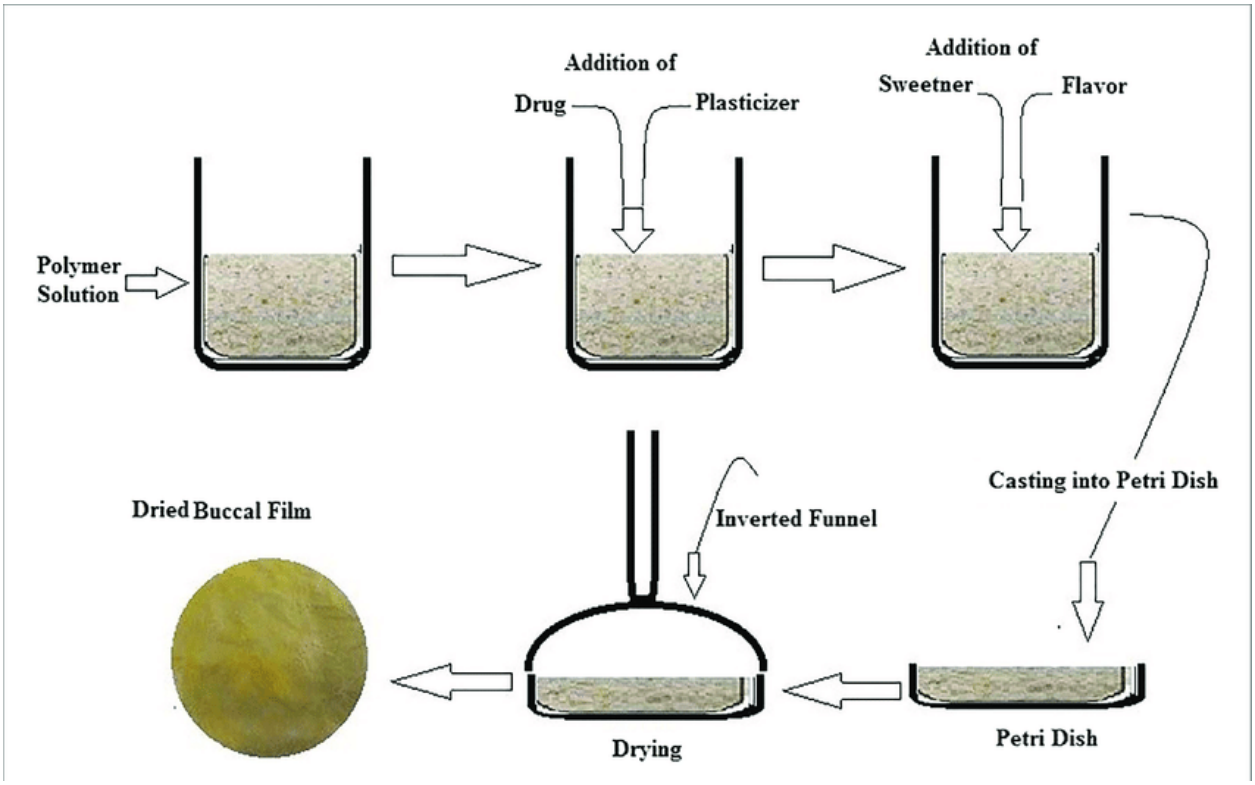

Figure 1: Procedure for solvent casting method

HOT MELT EXTRUSION[24]

Hot melt extrusion is a technique where drug, polymer and excipients are mixed together and extruded under high temperature to form a homogenous liquid mass which is cast on the drying tunnel and finally slitting of mass to form smooth film. The films are punched, pouched and sealed.

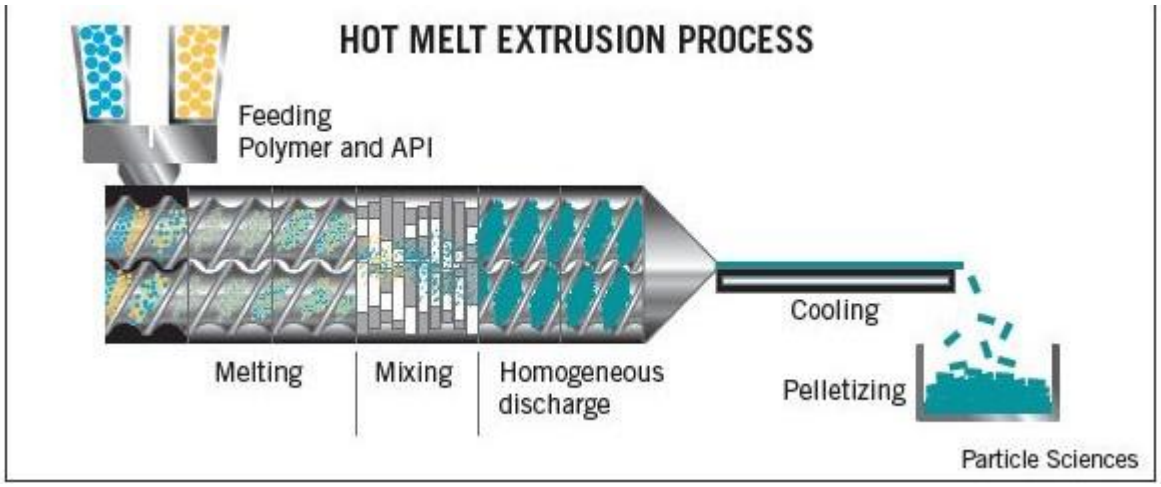

Figure 2: Process of hot melt extrusion.

Advantages[25]

- Improved bioavailability of poorly soluble compounds.
- Cost effective process with reduced production time and reduced number of unit operation.
- Capability of sustained, modified and targeted release.
- Better content uniformity.
- Have stability at varying pH and moisture levels.

Disadvantages

- Thermal process. So, requires drug and polymer stability.
- Require high power input Binders with low melting point are at the risk of melting or softening of the binder during handling and storage of the agglomerates.
- Binders with high melting point require high melting temperatures and can contribute to volatility problems especially for heat labile materials.

SEMISOLID CASTING METHOD[26]

Semisolid casting method is generally used when acid insoluble polymers are used. In this method a solution of water soluble film forming polymer is made then this solution is poured

in the solution of acid insoluble polymer, which is prepared in sodium or ammonium hydroxide. After this plasticizer is added to form the gel mass. Amount of plasticizer added affect the property of gel mass formed. The gel mass formed is then casted into film or ribbons using heat controlled rollers/drums. The ratio of acid insoluble polymer and film forming polymer should be 1:4. The films thickness formed by this method is about 0.015-0.05 inches.

SOLID DISPERSION EXTRUSION[27]

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. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70◦ C. Finally the solid dispersions are shaped into the films by means of dies.

Advantages

- Low shear method.
- Uniform dispersion of fine particles.
- Less processing steps

ROLLING METHOD[28]

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 cutted in to desired shapes and sizes. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

EVALUATION OF MOUTH DISSOLVING FILMS[28]

Mechanical properties

- Thickness
- Dryness/tack test
- Tensile strength
- Percent elongation
- Young’s modulus
- Tear resistance
- Folding endurance

- Palatability test
- Orangoleptic test
- Swelling test
- Surface pH test
- Contact angle
- Transparency
- Assay/ content uniformity
- Disintegration test
- In-vitro dissolution test

Thickness[29]

A thickness of film should be measured with the help of micrometer screw gauge or calibrated digital vernier callipers. Film should be measured at five points i.e. from the centre and from all the four corners and then mean thickness is calculated. It is necessary to determine the uniformity of thickness as it is directly related to accuracy of dose in the film.

Dryness Test/Tack Tests[30]

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack- free (surface dry), Dry-to-touch, dry-hard, dry-through (dryto-handle), dry to-recoat and dry print free. Although these tests are primarily used for paint films, most of the studies can be adapted intricately to evaluate pharmaceutical OS as well. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper)that has been pressed into contact with the strip. Instruments are also available for this study.

Tensile strength[29]

It is the maximum stress applied to a point of a film at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross section area of the stripes given in the equation,

Tensile strength= Load at failure*100/ strip thickness* strip width

Percent elongation[31]

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.

Strain [E] = total elongation / original elongation * 100

= $L - L_0 / L_0 * 100$

Where, L = length after force was applied.

L0 = original length.

Young's modulus[32]

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows.

Young's modulus = Slope × 100/Strip thickness × Cross head speed

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Tear resistance[33]

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. The maximum stress or force (that is generally found near the Onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds-force).

Folding endurance[33]

To determine folding endurance, a strip of film is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Typical folding endurance for film is between100-150.

Palatability test[34]

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade it would be the very good formulation. Grades: A= very good, B= good, C=poor

Organoleptic test[32]

The desired organoleptic properties a fast dissolving formulation should have are color, flavor, and taste. As the formulation will disintegrate in the oral cavity so it should provide acceptable organoleptic palatable characteristics. Color makes a formulation acceptable among the patients and moreover, oral films should have attractive color as they are

administered to children. Hence, color of formulation should be uniform and attractive. Color can be evaluated by visual inspection. The other organoleptic property is the odor. The flavor used in the formulation should provide good odor to the formulation. The odor of the polymer, drug and any other excipient should be masked with use of flavoring agent. Taste is also an important factor which has to be evaluated. To evaluate the taste, special human taste panels are used. Experiments using electronic tongue measurements have also been reported to distinguish between sweetness levels in taste masking formulation. Electronic tongue technique works on the principle of potentiometric titration method.

Swelling index[34]

The studies for swelling index of the film are conducted in stimulated salivary fluid. The film sample is weighed and placed in a pre-weighed stainless steel wire sieve. The mesh containing the film is submerged into 50 ml of stimulated salivary medium contained in a mortar. Increase in weight of the film is determined at each interval until a constant weight is observed. The degree of swelling is calculated using the formula.

SI = wt – wo /wo

Where SI is the swelling index,

wt is the weight of the film at time "t",

wo is the weight of film at t = 0

Surface pH test[35]

Surface pH of the film is determined by placing the film on the surface of 1.5% w/v agar gel and consequently placing a pH paper (pH range 1-11) on film. The change in the color of pH paper is noticed and document.

Contact Angle[35]

Contact angle is measured by using Goniometer at room temperature. Place a drop of distilled water on the surface of the dry film. Then the images of water droplet are recorded within 10 sec of deposition with the digital camera. The contact angle is measured on both side of drop and average is taken.

Transparency[36]

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell.

The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows.

Transparency = (logT600)/b = - €c

Where T600 is transmittance at 600 nm and b the film thickness (mm) and c is concentration.

Assay/ Content uniformity[36]

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.

Disintegration[37]

In vitro disintegration time was determined visually in a petridish containing 25 ml of pH 7.2 artificial saliva with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

In-vitro dissolution[37]

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 7.2 artificial saliva maintained at 37 °C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 7.2 artificial saliva maintained at 37°C.

CONCLUSION

Recently mouth dissolving films has gained popularity as dosage form and is most acceptable and accurate oral dosage form which avoid the first pass metabolism and show more therapeutic response. The pharmaceutical companies prefer this dosage form due to acceptability in patients like pediatric and geriatric and also in pharmaceutical industries. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Oral films can replace the over-the counter drug, generic and brand name from market due to lower cost and consumer preference. These dosage forms increases in bioavability of drugs.

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