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A COMPREHENSIVE REVIEW ON SELF EMULSIFYING MOUTH DISSOLVING FILM

Satyajit Sahoo*, Riya Patel, Mukesh Patel, D B Meshram

***Pioneer Pharmacy College, Vadodara, Gujarat, India - 390019**

*Corresponding Author's E mail: satyajitppdc@gmail.com

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ABSTRACT:

A self-micro-emulsifying mouth dissolving film (SMMDF) is a dosage form which is based on mouth dissolving film integrated with self micro emulsifying components. Stability of self-micro emulsifying drug delivery system is one of the major problems occur in lipid-based drug delivery system is its stability. This can be minimized by converting liquid self micro emulsifying drug delivery system into solid SMMDF. This drug delivery system enjoys both advantages of self micro emulsifying drug delivery system (SMEDDS) along with mouth dissolving film (MDF). SMMDF is an approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs.

KEYWORDS: Mouth dissolving film, Self-micro emulsifying drug delivery system and Self micro-emulsifying mouth dissolving film.

INTRODUCTION

In modern drug discovery techniques, there has been a consistent increase in the number of poorly water-soluble Drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. Self-micro emulsifying drug delivery (SMEDDS) is one of the methods for the improvement of oral bioavailability[1]. SMEDDS are the isotropic mixtures of oils, surfactants, solvents, and co-solvents. A self-micro-emulsifying mouth dissolving film (SMMDF) is a dosage form which is based on mouth dissolving film integrated with self-micro emulsifying components. Stability of self-micro emulsifying drug delivery system is one of major problem of lipid-based drug delivery system. This can be minimized by converting liquid self-micro emulsifying drug delivery system into solid SMMDF. This drug delivery system enjoys both advantages of self-micro emulsifying drug delivery system (SMEDDS) along with mouth dissolving film (MDF). Self-micro-emulsifying mouth dissolving film formulations can be used to improve the oral

bioavailability of hydrophobic drugs due to their efficiency of presenting the hydrophobic drug in solubilized form.

Lipid-based formulation approaches, particularly the SMEDDS, are well known for their potential as alternative strategies for delivery of hydrophobic drugs [2], which are associated with poor water solubility and low oral bioavailability[3]. SMEDDS formulations are isotropic mixtures of an oil, a surfactant, a cosurfactant (or solubilizer), and a drug. The basic principle of this system is its ability to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption.

Self-emulsifying mouth dissolving films, often referred to as SEMDFs, are innovative pharmaceutical dosage forms designed to enhance the bioavailability and effectiveness of orally administered drugs[4,5]. These films are a part of the broader category of oral thin film formulations and they offer several unique advantages for drug delivery. Here is an introduction to self-emulsifying mouth dissolving films:

Oral Thin Films (OTFs): Self-emulsifying mouth dissolving films are a specialized subset of oral thin films. OTFs are flexible, thin, and typically rapidly dissolving drug delivery systems that can be placed on the tongue, where they disintegrate and release the active pharmaceutical ingredient (API). They are particularly beneficial for patients who have difficulty swallowing conventional tablets or capsules [6].

Self-Emulsification: Self-emulsification contains lipids, surfactants, and co-solvents that form an emulsion upon contact with saliva or water. This emulsion enables the encapsulation and improved solubilization of poorly water-soluble drugs, which can lead to enhanced drug absorption and bioavailability [7].

Mouth Dissolving Properties: SEMDFs are engineered to disintegrate or dissolve rapidly in the oral cavity, typically within a matter of seconds. This property ensures that the drug is easily absorbed through the oral mucosa, providing a faster onset of action compared to traditional oral dosage forms [6,7].

Improved Bioavailability: The self-emulsification and mouth dissolving properties of these films enhance the drug's bioavailability. This is particularly advantageous for drugs that have low water solubility and are poorly absorbed in the gastrointestinal tract. The enhanced solubility and absorption lead to more efficient drug delivery [8].

Patient Convenience: SEMDFs offer an excellent patient-friendly dosing option, especially for individuals who have difficulty swallowing pills or capsules. They are convenient, discreet, and don't require the use of water for administration [6,8].

Taste-Masking: To enhance patient acceptability, SEMDFs are often formulated with flavors and sweeteners to mask the taste of the active ingredient. This is important to make the experience more palatable for the patient [7,8].

Structure and secretion of oral cavity:

Epithelial Layer Oral epithelium is to provide a protective surface layer between the oral environment and the deeper tissues. The oral epithelium has a squamous epithelium of tightly packed cells that form distinct layers by a process of maturation from the deeper layers to the surface. The pattern of maturation differs in different regions of the oral mucosa due to the variation in the specific function of the tissues. The surface layer of the hard palate and tongue forms keratin to yield a tough, non-flexible epithelial surface resistant to abrasion, but the epithelium of the cheek, floor of the mouth, and soft palate is non-keratinized and facilitates distensibility.

Vascular System of Oral Cavity The blood supply to the oral cavity is delivered predominantly through the external carotid artery. The maxillary artery supplies the main cheek, hard palate, and the maxillary and mandibular gingiva. The internal jugular vein eventually receives almost all of the blood derived from the mouth and Pharynx.

Salivary Secretions of Oral Cavity

The primary protection of oral cavity is offered by epithelial layer and in order to maintain a moist surface three pairs of salivary gland secretes ‘saliva’.

Salivary secretion is supplied by three pairs of glands, namely,

1. Parotid (under and in front of the ear)
2. Submaxillary (below the jaw)
3. Sublingual (under the tongue)

Blood supply to the salivary glands and their ducts by branches of the external carotid artery and afterwards, travelling through the many branch arteries and capillaries, returns to the systemic circulation via the jugular veins.

Saliva

Saliva is viscous, colourless and opalescent, hypotonic compared to plasma (between 110 and 220 milli Osmoles per litre), with a specific gravity of about 1.003. The pH varies 7.4 to 6.2 (low to high rates of

flow), but the action of bacteria on sugar can reduce the pH to between 3 and 4 around the teeth. Saliva is mainly composed of water, mucus, proteins, mineral salts, and amylase [10].

Advantages of Self-Emulsifying Mouth Dissolving Films [5,11]:

1) Enhanced Bioavailability: Self-emulsifying mouth dissolving films can improve the bioavailability of poorly water-soluble drug into the lipid phase of the self-emulsifying drug delivery system. This leads to better drug absorption.

2) Rapid Onset of Action: These films disintegrate quickly in the oral cavity, allowing for faster drug absorption through the oral mucosa and leading to a rapid onset of action.

3)Improved Patient Compliance: Self-emulsifying mouth dissolving films are convenient for patients who have difficulty swallowing traditional tablets or capsules. They don't require water for administration, making them more patient-friendly.

4)Taste-Masking: These films can be formulated with flavours and sweeteners to mask the taste of the active ingredient, enhancing patient acceptability.

5) Manufacturing: Ease of manufacture and scale- up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposome, etc.

Disadvantages of Self-Emulsifying Mouth Dissolving Films [6,12]:

1)Complex Formulation: The formulation of self-emulsifying mouth dissolving films can be complex, involving the use of specific excipients, including lipids, surfactants, and co-solvents, which can make the manufacturing process more challenging.

2) Stability Concerns: The stability of self-emulsifying formulations, especially in terms of emulsion formation and drug degradation over time, may be a concern and require careful formulation and packaging considerations.

3) **Regulatory Challenges:** Regulatory approvals for novel drug delivery systems can be challenging, and manufacturers may need to provide extensive safety and efficacy data to gain regulatory clearance for these formulations.

4) Variable Performance: The performance of self-emulsifying mouth dissolving films can vary with factors such as individual patient characteristics and differences in saliva pH, which can affect the self-emulsification process.

APPLICATIONS OF FAST DISSOLVING FILM [13]

1) Topical applications: The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other topical conditions.

2) Gastro retentive dosage systems: Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract and could potentially be used to treat gastrointestinal disorders.

3) Diagnostic devices: Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

4) Oral Drug Delivery: Pharmaceutical companies can use SEMFs to deliver drugs with poor solubility, enhancing the bioavailability of the drug. The self-emulsifying system helps solubilize lipophilic drugs, making them more bioavailable.

5) Pediatric and Geriatric Patients:

SEMFs are especially useful for pediatric and geriatric patients who may have difficulty swallowing conventional oral dosage forms. The rapid dissolution and ease of administration make them a suitable choice for these populations.

6) Fast-Acting Medications:

SEMFs can be used to formulate fast-acting medications, allowing for rapid onset of action. This is crucial for drugs that require quick relief, such as pain relievers, antiemetics, and anti-allergy medications.

7) Nutraceuticals and Dietary Supplements:

SEMFs can be employed for the delivery of lipophilic nutraceuticals and dietary supplements, making it easier for individuals to take these compounds, especially if they have difficulty swallowing pills or capsules.

8) Enhanced Absorption:

These films can enhance the absorption of certain drugs by promoting emulsification in the gastrointestinal tract. This can lead to improved therapeutic outcomes for specific medications.

9) Controlled Release:

SEMFs can be designed to offer controlled release of drugs, allowing for prolonged therapeutic effects. This can be advantageous for drugs that require sustained release profiles.

10) Taste-Masking:

They can be used to mask the bitter or unpleasant taste of certain drugs, making them more palatable for patients.

SEMFs in drug delivery and aim to develop novel dosage forms to address various therapeutic challenges.

Ideal characteristics of mouth dissolving film [14]

1. **Rapid Dissolution**: MDFs should disintegrate or dissolve quickly in the mouth, ideally within seconds to a minute, without the need for water or chewing. This allows for convenient and easy administration, making them suitable for patients who have difficulty swallowing pills or tablets.
2. **Good Palatability:** MDFs should have a pleasant taste, as the patient will be able to taste the formulation while it dissolves in their mouth. An acceptable taste helps improve patient compliance and acceptability.
3. **Thin and Flexible:** The film should be thin and flexible, typically in the range of 25 to 100 micrometers, to ensure comfortable placement on the tongue or oral mucosa. It should not feel bulky or uncomfortable when in the mouth.
4. **Uniform Drug Distribution:** The active ingredient or drug should be uniformly distributed within the film to ensure consistent dosing and effectiveness.
5. **Stability:** MDFs should have a good shelf life and remain stable over time. They should be protected from factors that can degrade the active ingredient or the film itself, such as moisture, light, and temperature.

Components of SMEDDS

1) Drugs:

Mainly drugs from BCS II class are used in formulation of the SEDDS.

2) Oils:

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient selfmicro emulsify-cation markedly reduces their use in SMEDDS. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound, suchas, GELUCIRE Other suitable oil phases are digestible or nondigestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil and animal fats etc [20] .

3) Surfactant:

Non-ionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc. The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid

spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules [21].

4) Cosurfactant:

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion [21].

5) Cosolvent Organic:

Solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid, base[20,22], Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents.

6) Consistency builder:

Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and /or beeswax etc [23].

7) Polymers:

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc [24].

FACTORS AFFECTING SMEDDS

1. **Drug Dose:**

Drugs which are administered at very high dose are not suitable for SEDDS, unless they exhibit extremely good solubility in at least one of the components of SMEDDS; preferably lipophillic phases the drugs exhibit limited solubility in water and lipid (typically with log P values approximately 2) are most difficult to deliver by SEDDS.

2. Solubility of the Drug in Oily Phase:

The ability of SEDDS to maintain the drug in solubilized form is generally influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent for drug solubilization, and then there could be a risk of precipitation, as dilution of SEDDS will leads to lowering of solvent capacity of surfactant or co-surfactant.

3. Equilibrium Solubility:

Equilibrium solubility measurement can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in solubilizing and colloidal stabilizing environment of the gut. Pouton's study reveals that such formulation can take up to 5 days to reach equilibrium and that the drug can remain in a supersaturated state up to 24 hours after the intestinal emulsification events.

4. Polarity of Oil Droplets:

The polarity of lipid phase is one of the factors that govern the release from the microemulsion. HLB chain length and degree of unsaturarion of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of process involved. The high polarity will promote rapid rate of release of the drug in to the aqueous phase. This is confirmed by the observation of sang-cheol et al.[25], who observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had phase with highest polarity.

Formulation Consideration For Mouth Dissolving Film

Formulation of mouth dissolving film involves the careful selection of excipients to impart aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, and mouth-feel etc.

1. Active Pharmaceutical Ingredients

The active pharmaceutical ingredient used in the formulation can belong to any class but should fulfil the requirements. Some of the examples of various classes of drugs that can be incorporated into MDFs include anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, antiemetic, etc some e.g of drug incorporated into MDF are salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin [26].

2. Water soluble polymer

A variety of water-soluble polymers can be used in the preparation of mouth dissolving films. The polymers can be used alone or in combination to achieve the desired film properties[27]. There are several characteristic properties of the oral film can be controlled with type or grade of polymer include mucoadhesiveness, disintegration time, drug loading capacity, mechanical strength, elasticity, handling properties[28].

The choice of the polymer should be made based on the following criteria.

1. The polymer should be nontoxic and non-irritating.
2. It should be inert and tasteless.
3. It should not have impurities which could leach into the product.

4. It should readily disintegrate.

5. It should have good wettability and spreadability.

6.The polymer should form a film has good shear and tensile strength so that it can be manufactured on a large scale on machines.

Some examples of the water-soluble polymers used as film former include various grades of HPMC, methyl cellulose, pullulan, carboxymethyl cellulose, polymerized resin polyvinyl pyrollidone PVP K-90, pectin, gelatin, sodium alginate, hyroxy propyl cellulose, polyvinyl alcohol, maltodextrins and eudragit RD10 [28].

3. Plasticizer

The plasticizer is a vital ingredient that helps to improve the film flexibility and reduce brittleness. Use of inappropriate plasticizer may result in film cracking, splitting and peeling. The plasticizer is added to the formulation in 0-20% concentration range to modify the mechanical properties of the film such tensile strength and percent elongation. Some examples of plasticizer include PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate [29].

4. Surfactants

Surfactants are added to solubilise the poorly soluble drug and also to solubilise or wet and disperse the film and release the active ingredients easily. Examples include poloxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzethonium chloride, tweens and spans [29].

5. Sweetening agent

The mouth dissolving films need to have good taste for patient acceptance and compliance as the films are to be taken without water and they are not swallowed but are required to disintegrate and dissolve in the oral cavity [30].

6. Saliva Stimulating agents

These agents are added to stimulate saliva production in oral cavity which promotes faster disintegration of mouth dissolving films. Examples include citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid. Citric acid is one of the most preferred ingredients [30].

7. Flavoring agents

These are added for patient acceptance and compliance. The selection of flavors depends on the age of the patients, type of drug and the taste of drug to be masked. Flavoring agents can be selected from the synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers [31].

8. Coloring agents

Colors approved by FD &C are used for improving the appearance of film incase the drug is insoluble or for aesthetic appeal. Pigments like titanium dioxide can be used for coloring. The concentration of coloring agent should not exceed 1% w/w [31].

Technologies for manufacturing thin film

1) Solvent casting:

Solvent casting is feasible, preferable and undoubtedly widely used method mainly due to the straightforward manufacturing process and low cost of processing.

Steps of preparation:

1. Preparation of solvent suspention (viscosity of the solution /suspention, temperature)
2. Casting of polymeric solution /suspention (Air entrapment, Viscosity of the solution)
3. Drying of the solution / suspention (drying temperature, moisture control, control of thickness)

4 Film stripping and packing (moisture control, selection of packing container)

The rheological properties of the polymeric mixture should be taken into account since they affect the drying rate, the film thickness, the morphology as well the content uniformity of the films [32]. The mixing process could introduce the air bubbles into the liquid inadvertently; therefore, de-aeration is a pre-requisite to obtain a homogeneous product [33]. After casting the solution into a suitable substrate, they are left for drying to allow the solvent to evaporate that just leaves a polymeric film with a drug on it [34].

After the complete drying of the film, it is cut into suitable shape and size depending upon the required dosage of the formed strip. In the majority of the cases, the strips are rolled and stored for a certain time before cutting, which is known as ‘rollstock’ in an industry. However, a film should not be exposed for too long time since it is prone for being damaged. If possible, it should be cut and packed immediately after the preparation to keep its stability [33]. Several advantages such as better physical properties, easy and low-cost processing, and excellent uniformity of thickness are observed with the film obtained by solvent-casting [35].

Translating the production of films from a bench scale to production scale is one of the biggest challenges because many factors such as heating, mixing speed, and temperature could bring variability in quality and consistent formation of films in commercial scale may not be possible.

2) Hot-melt extrusion (HME)

HME is a versatile method adopted for the manufacture of granules, tablets, pellets [36]
and also, thin films [37]. HME is a process of shaping a mixture of polymers, drug substance, and other excipients into a film by melting all the components [38]. Eventually, the films are cut into a particular

shape and dimensions[39]. In this method, a mixture of pharmaceutical ingredients is molten and then charged through an orifice (the die) to obtain homogeneous matrices [40]. Since APIs are subjected to operation at high-temperature with complete absence of solvents, this method is not suitable for thermos-labile APIs [33]. The practical steps of HME are outlined as follows (I) Feeding of the components to the extruder through a hopper, (ii) Mixing, grinding, and kneading, (iii) Flowing the molten and blended mass to the die, and (iv) Extruding the mass through the die and further downstream processing The equipment for the process of HME is illustrated in Fig. 1, which consists of the hopper, extruder, film die, and roller. The extruder contains one or two rotating screws (co rotating or counter rotating) inside a static cylindrical barrel.

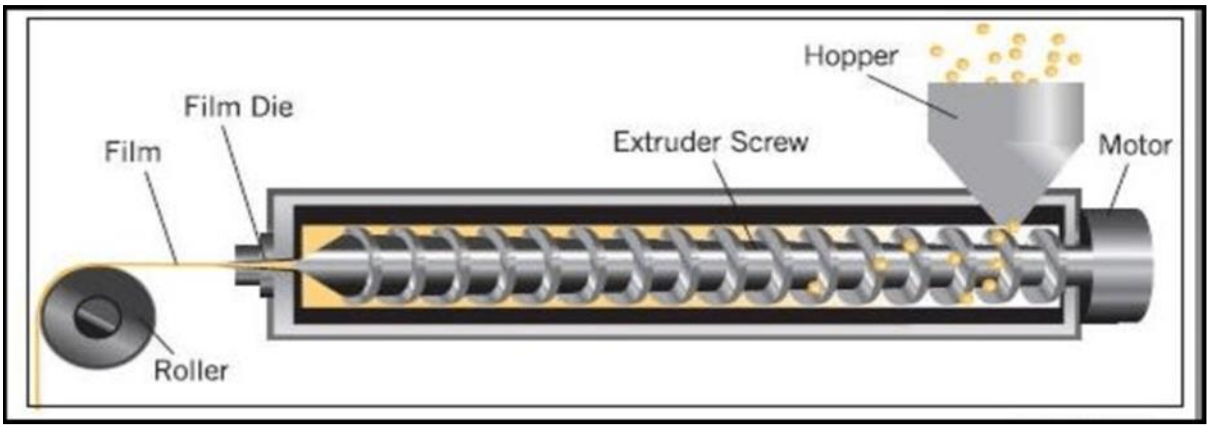
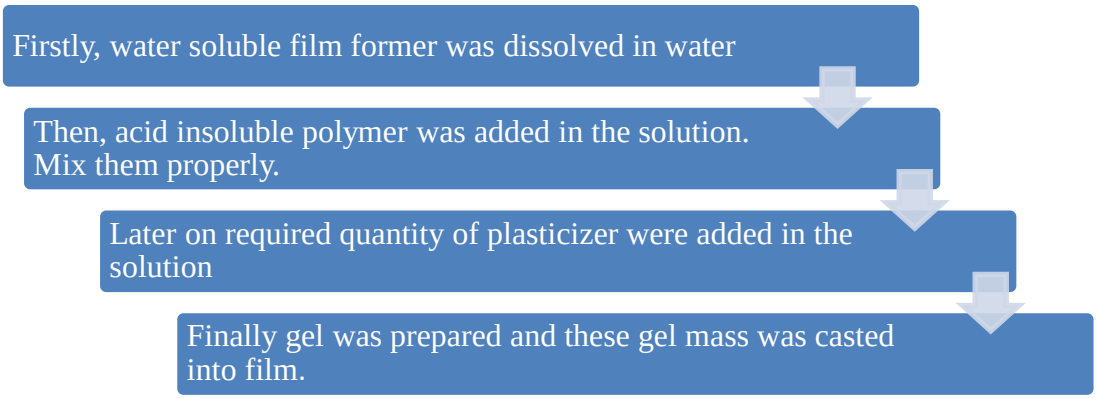


Figure 1: Diagram of a film extrusion system

4) Semisolid Casting Method:

The water soluble polymer was dissolved in suitable solvent. The acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate) was added in the solution. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Appropriate amount of plasticizer was added to obtained gel mass. Gel mass was casted into the films or ribbons using heat controlled drums [44].

Steps involved in semi solid casting method:



5) Solid Dispersion Extrusion:

Drug in a suitable liquid solvent was dissolved. The drug solution was incorporated into the melt of polyethylene glycol, below 70^0 C. Solid dispersions was passed through suitable extruder to form films [45].

6) Rolling Method:

Roll a suspension containing drug on a carrier. The solvent is mainly water and mixture of water and alcohol. Dry the film on the rollers and shape as desire [45]. The active agent, polar solvent, film forming polymer, and necessary excipients are combined together in a tank to create the premixed solution. To achieve the correct thickness, a controlled valve pump feeds the fluid with the intended dose.

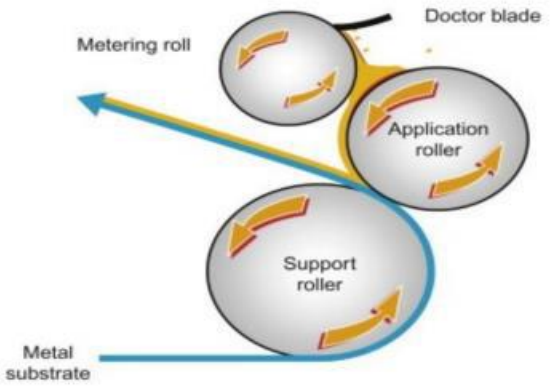


Figure 2: Rolling method

EVALUATION OF MOUTH DISSOLVING FILMS [46,47]

1)Tensile strength of films

It was determined using an apparatus fabricated in laboratory. A small film strip (3×2 cm^2) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly. Measurements were done in triplicate

for each batch. The mechanical properties tensile strength and % elongation was calculated for the mouth dissolving film from the above measurements. Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the cross-sectional area of the fractured film as a mean of three measurements and described in the equation

Tensile strength = Force at break (N)/ Initial cross-sectional area of the film (mm^2)

Percentage elongation was calculated by the following equation

% Elongation = (Increase in length / Original length) × 100

2)Folding Endurance

This test was performed by cutting the mouth dissolving film of size 3 × 2 cm^2. The films were folded at same place until it breaks apart [48].

3)In-vitro disintegration studies

Disintegration time study was slightly modified to mimic the in-vitro and in-vivo conditions. For the study, film as per the dimensions (3 x 2 cm^2) required for dose delivery were placed on a stainless-steel wire mesh containing 10 mL distilled water. Time required for the film to break and disintegrate was noted as in-vitro disintegration time. Since, the film is expected to disintegrate in the mouth in presence of saliva; only 10 mL of medium was used [49].

4)Weight variation

test 3 × 2 cm2 film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation observed [50].

5) Surface pH Measurement

The surface pH of Mouth dissolving film is determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to neutral as possible. A combined pH electrode is used for this purpose. Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation and mean ± S.D calculated [51].

6) Thickness Test

The thickness of the film can be measured by micrometer screw gauge at different 5 strategic locations. This is helpful in determination of uniformity in the thickness of the film & this is directly related to the accuracy of dose in the film [52].

7) Uniformity of drug content

A film of size 3 × 2 cm2 is cut and put in 30 mL of volumetric flask containing solvent. This is then shaken in a mechanical shaker for 1 hr to get a homogeneous solution and filtered. The drug is determined spectroscopically after appropriate dilution [53].

8) Taste evaluation

Taste acceptability was measured by a taste panel (n=5) with 3 mg drug and subsequently film sample containing 3 mg drug held in mouth until disintegration, then spat out and the bitterness level was then recorded. The volunteers were asked to gargle with distilled water between the drug and film sample administration. The scale for the bitterness study was as follows [49].

+ = very bitter

++ = moderate to bitter

+++ = slightly bitter

++++ = tasteless/taste masked

+++++ = excellent taste masking

9) In-vitro dissolution studies

The in-vitro dissolution studies were conducted using simulated saliva (300 mL). The dissolution studies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37 ± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (3 x 2 cm^2) was placed on a stainless-steel wire mesh with sieve opening 700μm. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 0, 15, 30 and 60 sec. time intervals and filtered through 0.45μm whatman filter paper and were analyzed spectrophotometrically at 250 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches [49].

10) Scanning electron microscopy (SEM)

The surface morphology of the film was observed using Scanning electron microscope (Philips, XL 30, The Netherlands). The film sample was placed in the sample holder and the photomicrographs were taken using tungsten filament as electron source and GSE detector at 65x and 350x magnification [49].

Storage:

Keep them in their original packaging: MDFs typically come in blister packs or sealed pouches. It's essential to keep them in their original packaging to protect them from moisture, light, and external contaminants[50].

Store in a cool and dry place: Avoid exposing MDFs to high temperatures, humidity, or direct sunlight. Store them in a cool, dry place with a controlled temperature and relative humidity. Room temperature[51] is generally suitable for most MDFs.

Check the expiration date: Pay attention to the expiration date on the packaging. Do not use MDFs that have expired, as they may have lost their effectiveness or could be unsafe to consume.

Keep them away from moisture: Moisture can cause MDFs to degrade and lose their structural integrity. Ensure that the storage area is dry, and do not expose the MDFs to excessive moisture or damp conditions.

Avoid extreme temperature fluctuations: Rapid changes in temperature can impact the stability of mouth dissolving films. Avoid storing them in places where temperatures fluctuate significantly, such as in the bathroom or near heating sources.

Keep out of reach of children and pets: MDFs should be stored in a location inaccessible to children and pets to prevent accidental ingestion or tampering.

Follow specific instructions: Some MDFs may come with specific storage instructions provided by the manufacturer or pharmacist. It's essential to follow these instructions for optimal storage conditions.

Packaging:

The material selected for packaging must have the following characteristics:

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

1) **Foil, paper or plastic pouches:** The flexible pouch is a packaging concept capable of providing not only a package that is temper- resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling or sealing equipment. The pouches can be single pouches or aluminum pouches [52].

2) **Single pouch and Aluminium pouch:** Soluble film drug delivery pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2D structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and

moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminium pouch is the most commonly used pouch [53].

3) **Blister card with multiple units**: The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mold. After cooling the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally, the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture [54].

Figure 3: Blister card

Stability:

The stability of mouth dissolving films (MDFs) is an important consideration when developing and manufacturing these pharmaceutical dosage forms. Moth dissolving films are thin, water-soluble films that disintegrate or dissolve rapidly in the oral cavity, delivering the active ingredient for systemic absorption. To ensure the effectiveness and safety of MDFs, stability studies are crucial, and they typically include several aspects:

Chemical Stability: This aspect involves monitoring the degradation of the active pharmaceutical ingredient (API) and other components within the film. Factors such as temperature, humidity, and light exposure can accelerate the degradation of the API. Stability testing assesses the API's chemical integrity over time.

Physical Stability: Physical stability encompasses the changes in the film's appearance, texture, and mechanical properties over time. This includes attributes like color, transparency, flexibility, and

brittleness. Any changes in these characteristics can affect the patient's experience and the efficacy of the product.

Microbiological Stability: MDFs should remain free from microbial contamination during their shelf life. Microbiological stability testing evaluates the ability of the film to resist microbial growth and contamination.

Disintegration and Dissolution: One of the primary characteristics of MDFs is their ability to disintegrate and dissolve quickly in the oral cavity. Stability studies assess whether the films maintain their disintegration and dissolution properties throughout their shelf life.

Packaging Compatibility: The packaging material should not interact with the MDFs, which could lead to changes in the film's quality or the degradation of the API. Compatibility studies evaluate the interaction between the MDF and its packaging materials.

Shelf-Life Determination: Stability studies aim to determine the product's shelf life by subjecting it to various storage conditions, including accelerated aging conditions. These studies help establish appropriate storage recommendations and expiration dates for the product.

List of marketed MDF [55,56]

Product Name	**Manufacturer**	**Active Product Ingredient (API)**	**Dosage form**	**Use of the Product**
Listerine	Pfizer	Cool mint	Film strip	Mouth freshner
Benadryl	Pfizer	Diphenylhydramine HCl	Film strip	Anti-allergic
Orajel	Del	Menthol/Pectin	Film strip	Mouth ulcer
Theraflu	Novartis	Dextromethorphan HBR	Thin Film strip	Cough suppressant
Theraflu	Novartis	Diphenylhydramine HCl	Thin Film strip	Cough suppressant
Theraflu	Novartis	Phenylephrine HCl/Dextromethorphan HBR	Thin Film strip	Cough suppressant
Theraflu	Novartis	Phenylephrine HCl/ Diphenylephrine HCl	Thin Film strip	Cough suppressant
Sudafed PE	Wolters Kluvers Healthcare inc.	Phenylephrine	Film strip	Relieving congestion
Triaminic	Novartis	Dextromethorphan HBR	Thin Film strip	Antiallergic
Triaminic	Novartis	Diphenylhydramine HCl	Thin Film strip	Antiallergic
Triaminic	Novartis	Phenylephrine HCl/Dextromethorphan HBR	Thin Film strip	Antiallergic

Triaminic	Novartis	Phenylephrine HCl/ Diphenylephrine HCl	Thin Film strip	Antiallergic
Chloraseptic	Prestige	Benzocaine / menthol	Film strip	Sore throat
Klonopin Wafers	Solvay Pharmaceuticals	Clonazipam	Wafers	Treatment of anxiety
Supress	Inno. Zen Inclusive	Menthol	Film	Cough suppressant
Gas-X	Novartis	Simethicone	Film	Antiflatuating
Zuplenz	Galena Biopharma	Ondansetron	Film	Nausea and vomiting
Zofran	GSK	Ondansetron	Film	Nausea and vomiting

Future trends of mouth dissolving film [3]

Mouth dissolving films (MDFs) were a relatively new and innovative drug delivery system. These are thin, water-soluble films which are designed to dissolve medications or active ingredients rapidly in the mouth without the need for water or swallowing. According to literature review the future trends of mouth dissolving may be as follows:

Personalized Medicine: One potential trend is the customization of MDFs for individual patients. With advancements in 3D printing and pharmaceutical compounding, MDFs could be tailored to a patient's specific needs, such as the required dosage and the rate of drug release.

Improved Drug Delivery: Ongoing research may lead to the development of MDFs that can deliver a wider range of drugs, including biologics and large molecules. This could expand the scope of conditions that can be treated using this delivery method.

Enhanced Taste-Masking: Improving the taste of MDFs will be important, especially for pediatric and geriatric patients. Future trends may involve the development of better taste-masking techniques to make MDFs more palatable.

Biodegradable Materials: The use of biodegradable materials for MDFs could become more prevalent, aligning with sustainability trends in pharmaceuticals and healthcare. Biodegradable MDFs would dissolve completely without leaving any waste.

IoT Integration: Smart MDFs could incorporate IoT (Internet of Things) technology to track patient adherence, monitor drug release, and transmit data to healthcare providers. This could improve patient management and treatment outcomes.

Combination Therapies: MDFs may be developed for combination therapies, allowing for the simultaneous delivery of multiple drugs or active ingredients, which could be beneficial in treating complex health conditions

Regulatory Approval: The regulatory environment for MDFs is likely to evolve, with clearer guidelines and standards for the development, testing, and approval of these products.

Prolonged Release: Future MDFs might be designed to provide prolonged drug release, addressing chronic conditions more effectively. This could be achieved through modifications in film composition or manufacturing techniques.

Enhanced Bioavailability: Ongoing research may lead to MDFs with improved bioavailability, ensuring a higher percentage of the drug reaches the bloodstream, leading to more effective treatments.

Theranostic Films: MDFs could be developed to not only deliver medications but also provide diagnostic information or monitor patient health in real-time. This convergence of therapeutic and diagnostic capabilities is an exciting possibility.

CONCLUSION:

Self-emulsifying mouth dissolving film is promising approach for the formulation of drugs with poor aqueous solubility, high molecular weight, pre systemic first pass effect, enzymatic degradation, gastric irritation, limited dissolution rate and low bioavailability. SMMDF is economic as it requires less quantity of drug and less sophisticated machineries. Moreover, SMMDF is an approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs.

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