IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
March 2022 Vol.:23, Issue:4

Mouth Dissolving Film: Innovations in Formulation and Technology

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An official Publication of Human Journals
ISSN 2349-7203
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Submitted: 23 February 2022
Accepted: 28 February 2022
Published: 30 March 2022

Keywords: Mouth dissolving film, Composition, Evaluation, Casting approaches.

ABSTRACT

The oral route of administration is the preferred route because of its benefits like self-administration, pain turning away, high patient compliance, flexibility in style. A drug can be administered via many different routes to produce a desired pharmacologic effect. As discovery and development of new chemical agents could be a complicated, expensive, and time exhausting method therefore recent trends moving towards designing and developing innovative drug delivery systems for existing medicament. Various approaches are applied for formulating MDF, also they are a good alternate option for those drugs which affects by the stomach environment and first-pass metabolism. This review in short describes the benefits and limitations, provide information regarding formulation technologies creating MDFs, and evaluation parameters for the same. Now a day's MDFs are used as a tool for drug delivery for various treatments.

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INTRODUCTION:

Mouth Dissolving Films (MDFs) is a new technology developed for oral administration of active ingredients, together with the active ingredients it contains numerous excipients such as polymers and other additives like plasticizers, flavors, colors, sweeteners, surfactants, thickening agents, disintegrants[1]. The mouth dissolving film (MDF) is often used for delivering a drug systemically to attained the therapeutic or pharmacological effect. MDF formulations have improved systemic bioavailability because it escapes 1st pass metabolism. [3]When MDFs are placed on the tongue, they quickly disintegrate with secretion, and the requirement of water is not needed. Therefore, they completely have an effect on the bioavailability of the drug, and thus the specified effect starts quicker. [1]The oral mucous membrane is abundant in blood supply and more permeable. The mucous membrane of the mouth is a potential site for an immediate, sustained, and controlled drug delivery system. [7]Available research models suggest that instead of disintegrants we can also use insoluble particles eg. MCC (microcrystalline cellulose), silica as a disintegration enhancer.[15] To beat difficulties related to swallowing of the solid unit dosage form (tablet, capsule.) Oral film technology was invented.[1] In the marketplace, the introduction of MDF was strongly linked with the guidance of patients regarding the suitable administration by giving instructions like ‘‘do not chew/do not swallow’’.[5]A typical ODF is usually equal to the size of a postage stamp. The rapidly dissolving film was initially introduced in the market as mouth fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for the therapeutic benefits of prescription drugs.[4]

Advantages: [3,5,6]

- No need for water to swallow.
- Available in various sizes and shapes.
- Hydrate and dissolve in the oral cavity within a fraction of seconds.
- Fast disintegration or dissolution.
- Taste masking
- Reduced gastrointestinal irritation

- No special training is required for administration.
- Improved oral absorption and bioavailability
- Enhanced stability.
- Improved patient compliance
- Ease of handling and transportation
- No risk of choking.
- Rapid onset of action.
- Minimized first-pass effect.

Disadvantages:[3,5,6]

There are numerous advantages of the MDF but a few disadvantages lead to a main challenging formulation.

- It is hygroscopic in nature so it must be kept in dry places.
- Packaging of films requires special equipment and it is difficult to pack.
- Need special packing has they must be protected from water.
- A high dose cannot be incorporated into the oral film.
- Eating and drinking may become restricted.
- Drugs unstable in oral pH can't be administrated.

METHOD OF PREPARATION:

Mouth dissolving films can be prepared by

- Solvent casting method
- Semisolid casting method
- Hot-melt extrusion
- Solid dispersion extrusion

- Rolling method

1. Solvent Casting Method:

In this method firstly water-soluble ingredients are mixed in water to form a viscous solution. API and remaining ingredients are dissolved in a smaller amount of solution. Both the solutions are combined by using a high shear Process. Vacuum is used to remove the air entrapped. The solution formed is then poured into a glass mold and allowed the solution to dry in the oven at 45-50˚C. Then cut into pieces of desired size and shape.[1]

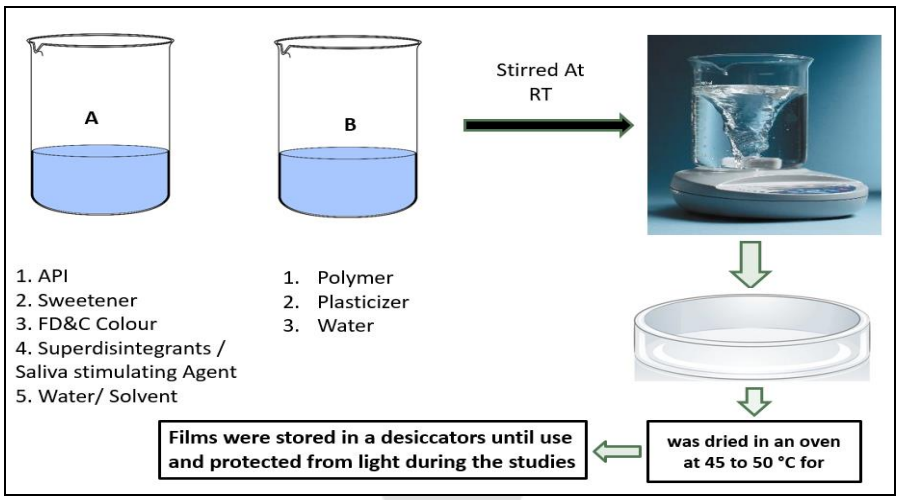

Fig. No. 1: Solvent Casting

2. Semisolid casting method:

If film formulations contain some acid-insoluble polymers, then this system is acceptable. In this method initially prepared water-soluble polymeric solution. Then this solution was added to the solution containing acid-insoluble polymer (Examples: cellulose acetate phthalate, cellulose acetate butyrate, etc.). The plasticizer is added in applicable quantity in order that a gel mask is created. It is then cast into the films or ribbons by exploitation heat management drums. The ratio of the acid-insoluble polymer and film-forming polymer keep as 1:4. [2,4,5]

3. Hot-melt extrusion:

the rug is mixed with carrier in the solid form so that Granular material is formed. These granules are then dried and then introduced into the extruder. The speed of the screw should be around 15rpm so that the granules reside inside the extruder for about 3-4 min. The

processing temperature should be 100˚C. The extrudate is then pressed into a cylindrical calendar to obtain a film.[2,20,21]

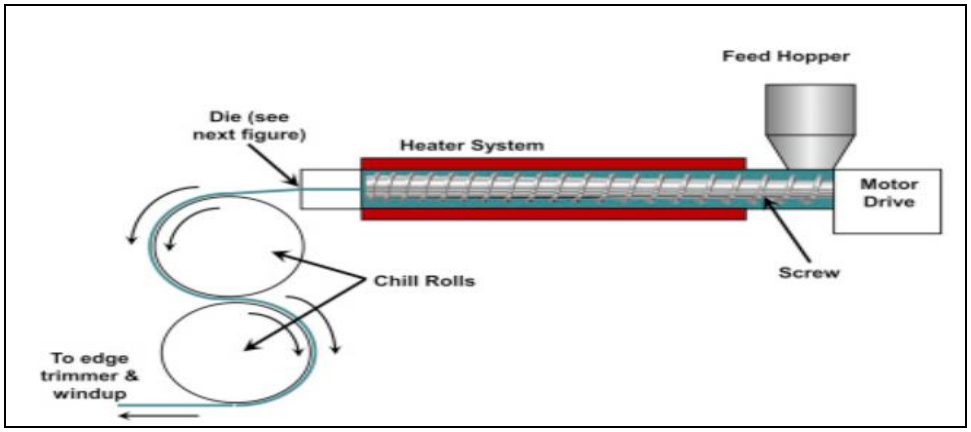

Fig. No. 2: Hot melt extrusion [22]

4. Solid Dispersion Extrusion:

This method is also used to improve the solubility of the poorly water-soluble drug. The term solid dispersion is used for the dispersion of one or additional active ingredients in a very inert carrier in a solid-state within the presence of amorphous hydrophilic polymers.[2]The drug is dissolved in an appropriate liquid solvent and obtained resultant mixture is further added to the previously dissolved polymeric solution available below 70°C while not removing the liquid solvent to get the solid dispersion. Finally, the obtained solid dispersions are formed into films by using dyes. [4]

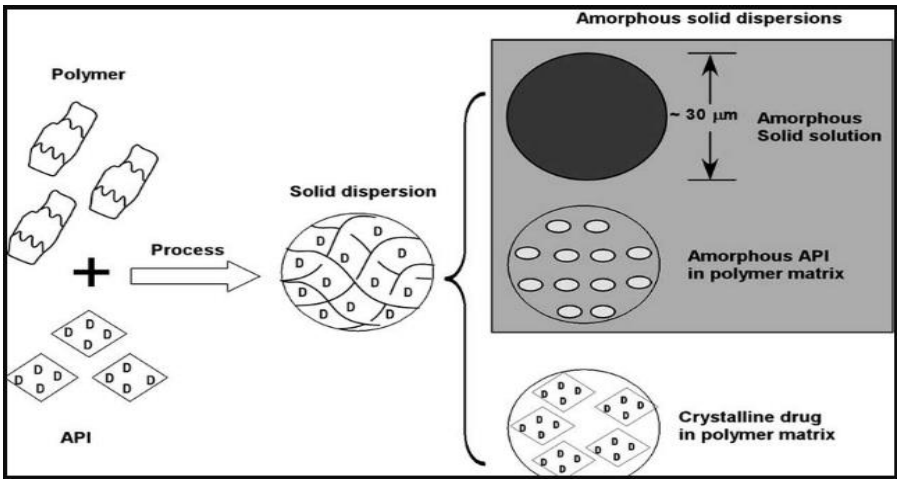

Fig. No. 3: Solid dispersion technique.

One of the **examples** of film formation by means of solid dispersion method is as follows: Solid dispersion of domperidone using beta-cyclodextrin, PEG400, and HPMC E15 was successfully prepared and films were cast using solid dispersion extrusion method. [5,16,17]

5. Rolling method:

In this method, suspension or solution containing API is prepared. Then this solution is completely mixed with the solution of film-forming polymer. The prepared solution was placed on a carrier and allowed to move onto it. Certain rheological properties of the solution should take into consideration. Films are dried on the rollers and cut into desired shapes and sizes. [4,5,13,]

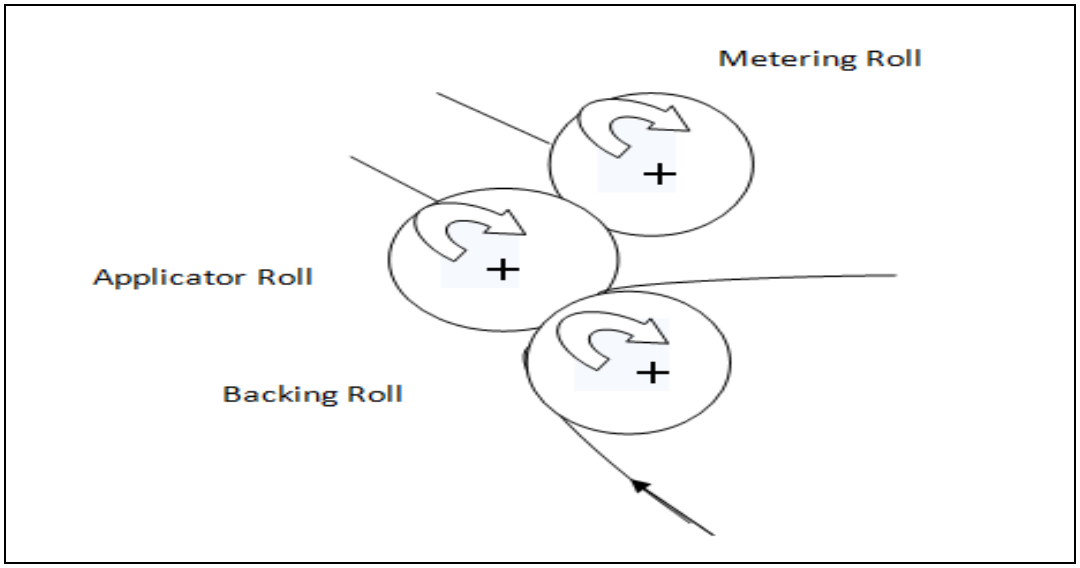

Fig. No. 4: Rolling Method.

Table No. 1: Comparison between ODT and ODF[2,3,19]

ORAL DISSOLVING TABLETS	ORAL DISSOLVING FILMS
Lesser dissolution due to less surface area	Greater dissolution due to large surface area
Less durable as compared with oral films	Better durable than oral disintegrating tablets
Less patient compliance than films	More patient compliance
High dose can be incorporated	A low dose can only be incorporated
It has fear of chocking	No risk of chocking

COMPOSITION OF MDF:

DRUG (ACTIVE PHARMACEUTICAL INGREDIENT):

Different types of API can be successfully incorporated in the mouth dissolving film. Micronized API can improve the texture of the film and also the dissolution and uniformity of the oral fast-dissolving film. Taste of bitter drug need to be masked for that bitter mask is used they prevent the direct contact of API with the saliva. Usually, API should have a pleasant taste, low dose ≤ 40 mg, stable, and permeable through the oral mucous membrane.[3]. Sonication is the method to load high doses in the film. [23]

It includes-

- Cough/Cold Remedies (antitussive, Expectorants)- Ambroxol HCL.
- CVS Agent- Valsartan, Verapamil.
- Antihistamines- Levocetirizine HCL.
- Antiasthmatic- Salbutamol sulfate, Montelukast sodium.
- Nausea- Domperidone.
- Pain- NSAIDS (Paracetamol, Tramadol, Ibuprofen, Nimusulide)

FILM-FORMING POLYMER:

Polymers play an important role in film formation. Hydrophilic polymers are used in the preparation. Now a day's both natural and synthetic polymers are used in the oral cavity. Natural polymers are safe, effective, and devoid of side effects so more preferred than synthetic polymers. The robustness of the film depends on the type and the amount of polymer used. [3, 4, 5, 13]

Ideal properties-

- It should be inexpensive and readily available.
- It should have good wetting and spreadability property.

- **Table No. 2: Types of Polymers**

Natural polymer	**Synthetic polymer**
Pullulan	Hydroxypropyl methylcellulose (HPMC)
Starch	Polyvinyl pyrrolidone (PVP)
Pectin	Kollicoat
Sodium alginate	Hydroxypropyl cellulose
Maltodextrin	Carboxymethyl cellulose (CMC)
Lycoat NG 73	Poly ethylene

PLASTICIZERS:

Plasticizers are the important excipient of the film formulation. It improves the flexibility and mechanical property of the film like tensile strength, folding capacity, elongation and reduces the brittleness of the strip. A plasticizer should be selected in such a way that it must be compatible with the drug.

Examples of plasticizers include glycerine, sorbitol, propylene glycol, polyethylene glycol, tri-acetin, dibutyl phthalate, tri-ethyl-citrate, acetyl tri-ethyl-citrate, and other citrate esters. [3,5,13]

SALIVA STIMULATING AGENT:

These are used to increase the secretion of saliva so that the oral film disintegrates and dissolves faster in the oral cavity. The acids that are employed in the preparation of food are typically used as saliva stimulators. Citric acid, malic acid, lactic acid, ascorbic acid, tartaric acid are the saliva stimulating agent. [13.24]

SWEETENING AGENT:

Sweeteners are used for the taste masking of bitter drugs so that drugs are palatable. Natural as well as artificial sweeteners are used in the preparation of the oral film.

- **Natural sweeteners**: xylose, ribose, glucose, sucrose, maltose, sativosides, dextrose, fructose, liq. Glucose.

- **Artificial sweeteners:** sodium or calcium saccharin salts. [5,13]

FLAVOURING AGENT:

Flavoring agents are those ingredients that impart flavor to any formulation. Any US-FDA-approved flavor can be added to the formulation according to the choice of individuals of different age groups. It should be compatible with the drug and other excipients. Eg: Peach, Vanilla, Wall-nut, chocolate, Mint, Raspberry, Peppermint oil, Spearmint oil, cinnamon oil. [2,6]

SURFACTANT

Surfactants are added as a solubilizing or wetting or dispersing agent in order that the film gets dissolved inside the mouth within seconds and let out the API instantly. Some of the commonly used surfactants are sodium lauryl sulfate, poloxamer, and tweens. [5,6]

COLORING AGENTS:

Only TiO2, FD&C-approved coloring agents are used in the formulation. It should not be more than a concentration of 1% w/w. E.g., Quinoline yellow, sunset yellow, etc. [3,6]

EVALUATION PARAMETERS:

1. Uniformity of mass: Twenty MDFs were randomly selected. They were then weighed individually on an electronic balance and the average weight was calculated. (As per European Pharmacopeia 9th edition).[1]

2. Film thickness: Ten MDFs were randomly selected and their thickness was measured by a micrometer with five different points at the corners and in the middle. [3,25,26]

3. Surface pH of films: Six randomly selected MDFs were slightly moistened with distilled water. The pH electrode was contacted to the MDF surface and the measurements were recorded. It was reported that saliva pH is in the range of 5.8–8.4. Surface pH for the MDFs close to neutral pH.[2,5]

4. Mechanical properties:

A. Tensile strength: The maximum force applied to the point where the film is broken.

$$\text{Tensile strength} = \frac{\text{Load at break}}{\text{Strip thickness x Strip width}} \times 100$$

B. Young's modulus: It defines the hardness of the film. [13]

$$\text{Young's modulus} = \frac{\text{Force at corresponding strain x 1}}{\text{Cross-sectional area x Corresponding strain}}$$

C. Elongation at break: This parameter is used to express the elongation percentage of the film. When stress is applied deformation of the films occurs by means of stretching or elongation of the sample. Generally, the elongation of the film increases as the plasticizer content increases. [3,5]

$$\% \text{ Elongation} = \text{Increase in length} \times 100 / \text{Original length}$$

D. Folding endurance: It measures by manually repeated folding the film at the same place until it breaks and the fold is recorded. Typical folding endurance for a film ranges between 100- 200. [1,3]

5. Uniformity of content: It is determined by measuring the drug content in the individual film. MDFs were randomly selected and 10 ml of artificial saliva (pH 5.7) was added. The content was mixed on a magnetic stirrer until the drug dissolves, and then, the mixture was filtered through filters. After dilution with artificial saliva, it was analyzed by UV Spectrophotometer. [1]

6. Disintegration Time:

The disintegration time should be about ≤30 for MDF. Mostly, the USP disintegration apparatus is used for this test.

There are two methods for determining disintegration time:

a. Petri dish method: Two ml of distilled water was taken into a Petri dish and kept the film in it without shaking. The time is taken to disintegrate film as well as wetting time is recorded.

b. Drop Method: One drop of distilled water let fall on the film using a pipette and record the time that caused a cavity in the film. [1,3]

7. In Vitro Dissolution Studies: Dissolution studies of films are performed by U.S.P. type II apparatus in 6.8 phosphate buffer at various time intervals by maintaining below conditions. [1,6]

- Temp: 37°±0.5 C
- Speed: 50-75 rpm
- Aliquot: 5 ml
- Sink conditions: maintained with 5 ml.
- Analyzed: UV Spectrophotometer.

8. DRUG EXCIPIENT INTERACTION STUDIES [1]

A. Differential scanning calorimetry (DSC)

The thermal properties were evaluated using DSC. It offers the physiochemical state of the drug in the formulation by detecting shifts in melting endotherm and exotherm.

B. X-ray diffractometer analysis (XRD):

This is used to discover the crystalline structure of the drug in the formulation and the effect of the preparation method. XRD analysis in order to determine the crystallographic properties of the compound in MDFs.

C. Scanning electron microscopy (SEM):

The surface morphology was examined via a scanning microscope. Additionally, these results confirmed that optimum MDF formulation had the graceful texture of film surface, which could be a fascinating aesthetic property of MDFs.

9. Stability studies:

These are carried out as per ICH guidelines to check the effect of temperature and humidity on the formulation. Selected MDF formulations were stored in an aluminum package in a chamber controlled at 40 °C and 75% humidity for 4 weeks. Samples taken at periodic intervals (0, 15, and 30. days) were characterized in terms of drug content and other parameters (appearance, weight, thickness, surface pH, moisture content, and disintegration time). [1,3.27]

Table No. 3: List of Marketed Product

Brand name/ designation	Originator company	Patent(s)	Partner/ distributor	Product	Drug substance	Phase/ Status	Oral Film Type
Rapid Dissolving Film	Kyukyu Pharmaceutical Co Ltd	WO-2005117803; WO-2011108643; WO-09917753	Biomedix.Co. , Ltd	Amlodipine OD Film	Amlodipine Besylate	Launched	Dispersible
Rapid Dissolving Film		WO-2010023874			Loperamide	Launched	Dispersible
Schmelzfilm	Hexal Pharmaceuticals	WO- 2007009801	-	Olanzapin HEXAL® SF Schmelzfilm	Olanzapine	Launched	Orodispersible
			Hexal Sandoz	Risperidone HEXAL® SF	Risperidon	Launched	Orodispersible
Rapidfilm	Labtec Gmbh / APR Applied Pharma Research	WO-2008040534; WO-2009043588	Sciclone Pharmaceutical, Takeda Canada	Ondansetron Rapidfilm®/ Ondissolve	Ondansetron Hydrochloride	Launched	Dispersible
Smartfilm	Seoul Pharma Co Ltd	WO- 2013129889	Pfizer Inc	Vultis®	Sildenafil Citrate	Launched	Dispersible
Pharmfilm	Monosol Rx LLC	WO-2012177326	Midatech Midasol Therapeutics		Insulin Nanoparticles (Midaform Insulin)	Phase 1 Clinical	Buccal

CONCLUSION:

The present review reveals that Mouth dissolving films are novel approaches in the field of the pharmaceutical industry. Nowadays this technology is used to improve the patent life of the existing product in various pharmaceutical organizations and companies. There are various approaches for the preparation of MDF. The major concept behind the formulation of MDFs was to deal with the issue of swallowing typical oral dose forms among medical specialty, geriatric, and psychiatric patients with dysphasia. The formulation delivers the drug directly into systemic circulation hence bioavailability gets improved and minimizes adverse effects with higher safety. This dosage form is cost-effective and travel-friendly as no water is needed for administration. Therefore, mouth dissolving film becomes distinctive, elegant, selective, and required dosage form.

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