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# Mouth Dissolving Film: A Novel Approach for Oral Dosage Form

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**ABSTRACT:** Oral route is the most convenient route of drug administration among all other routes, but still it is challenging for paediatrics and geriatrics due to swallowing issue. Thus, to overcome this problem MDFs are used. This novel and safer approach; gives rapid systemic action by avoiding first pass metabolism. There are more several advantages like rapid disintegration, no need of water for administration, prevent degradation from acidic environment of stomach. This review work is useful to give an idea about various ideal characteristics, advantages, formulation aspects of MDFs selection involves API, polymers used, plasticizers, sweetening agents, saliva stimulating agents, surfactants, flavouring agents. Formulation Methods used of MDFs solvent casting method, hot melt extrusion method, semisolid dispersion method, solid dispersion method and rolling method. Among all the methods, solvent casting method should be preferred. The MDFs can be evaluated using various evaluation parameters like thickness, folding endurance, tensile strength, tear resistance, drug content, surface pH, Young's module, disintegration time, dissolution test, transparency, etc. MDFs have received extensive interest due to a distinct set of its properties and advantages compared to traditional oral dosage form. The aim of this review work is to summarize formulation, advantages, and disadvantages, method of preparation, various evaluation parameters and examples of API used for preparing MDFs along with the polymers used in its formulation.

**KEY WORDS**: Mouth dissolving film, Rapid disintegration, Geriatrics patients.

## I. INRODUCTION:

Among, all the routes of drug administration, the most preferred one is oral route because of its convenient, cost effective and ease of administration that is highly convenient for both paediatrics and geriatrics. Although, it is still a challenging route for swallowing in both paediatrics and geriatrics. So to overcome it, the novel and safer drug delivery such as buccal film, oral strips have been developed. These systems were developed in1970,s as a novel dosage form to overcome the problem of swallowing for both paediatrics and geriatrics and for the systemic drug delivery the film was launched in 2004 [1,41].The ideal characteristics of that it should be Easy to handle and transport. It should have high stability and ease of administration. It should be easily ionized at oral cavity pH and pleasant in taste. Upto 40% of dose is incorporated in the formulation. It should have high tensile strength and does not stick to packaging material [3].The advantages of it such as, there is no need of water for administration, accurate dose can be delivered, easy to swallow for both geriatrics and paediatrics, acidic environment of stomach should be avoided. It also gives site specific and local action and provides rapid disintegration and dissolution in oral cavity, due to large surface area. [4, 5].The disadvantages are that it is not suitable for high dose, the packaging required is expensive, the dose uniformity is a technical challenge and the drugs which are unstable and irritate at buccal pH are not suitable. In addition, restriction of drinking and eating after consumption of oral film for required period of time. [2, 5, 6]

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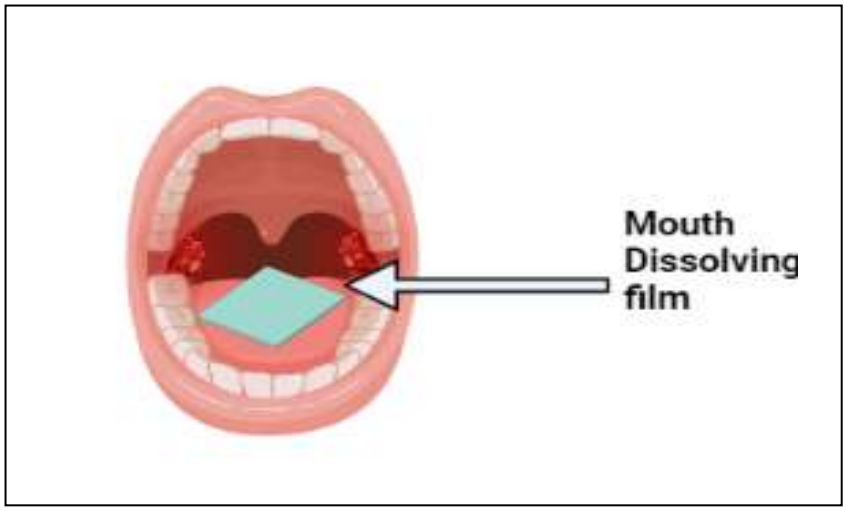


**Fig.1 Mouth dissolving film.**

**Classification of oral film:**

Three types of oral films are there:

1. Flash release
2. Mucoadhesive melt away wafer
3. Mucoadhesive

Types of oral films with their different properties are summarized in the below table.1

**Table 1.Types of film and their properties** [7]

| **Property** | **Flash Release Water.** | **Mucoadhesive melt away wafers** | **Mucoadhesive sustained release** |
|---|---|---|---|
| Area($cm^2$) | 2-8 | 2-7 | 2-4 |
| Thickness(µm) | 20-70 | 50-500 | 50-250 |
| Structure | Film; single layer | Single or multilayer system | Multilayer system |
| Excipients | Soluble, highly hydrophilic polymers | Soluble, Hydrophilic polymers | Low/Non soluble polymers |
| Drug phase | Solid solution | Solid solution or suspended drug particles | Suspension and/or solid solution |
| Site of action | Systemic or local | Systemic or local | Systemic or local |
| Dissolution | Maximum 60 seconds | Disintegration in few minutes, forming gel. | Maximum 8-10 hours. |
| Application | Tongue(upper plate) | Gingival or buccal region | Gingival |

## II. FORMULATION OF MOUTH DISSOLVING FILM:

➢ **Active pharmaceutical ingredient:**

MDFs can be suitable for various APIs can be for mouth dissolving films. For improving dissolution and uniformity of MDFs; micronized drug can be effective(less than 20mg/day).For drug that is water soluble, there will be no issue of uniformity of distribution. But in water insoluble drug the uniformity may variate, thus to overcome it and for homogeneous distribution for better drug content uniformity, the water insoluble drug is added in milled, micronized form or nanocrystal or microcapsule to get smooth texture of the film. The examples of APIs includes antiasthmatics(e.g., salbutamol), antiulcer(e.g.,omeprazole),NSAIDS(e.g.,paracetamol,meloxican,valdecoxib),cough(e.g,dextrometrophan),menstrualpain(ketoprofen), smoking cessation (e.g., nicotine), allergic reaction(e.g., cetrizine, azatadine maleate). [2,8, 9, 10]

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➢ **Film forming polymer:**

For the formation of the film, the polymers play an important role. Hydrophilic polymers can be used for the preparation of various films. The amount of polymer added should affect the robustness of the film. Minimum 45% w/w of polymer should be present based on total weight of dry film. [60].Alone as well as in combination the polymer is used, to obtain desired properties of film.

The polymers used must be non irritant, non toxic, and should be inexpensive. It must have good spreadibility and wetting property. Polymer must have adequate tensile strength. The polymer must have good half life and it does not cause any secondary infection in oral mucosa or in dental site. Both natural and synthetic polymers are used for the preparation [2, 11, and 60].List of such polymers given below in table.2

**Table 2.Examples of Natural and synthetic polymers:** [3]

| **Natural polymers:** | **Synthetic polymers:** |
|---|---|
| Pectin | Polyvinyl alcohol |
| Starch | Hydroxy propyl cellulose |
| Guar gum | Polyvinyl pyrrolidone |
| Gelatine | Hydroxy propyl methyl cellulose |
| Pullulan gum | Sodium carboxy methyl cellulose |
| Carrageenan gum | Polyethylene oxide |
| Xanthan gum | Pyroli vinyl pyrollidine |

Examples of various polymers with their various properties are described in below table.3

**Table 3. List of properties of various films forming polymer: [**60]

| **Name of Polymer** | **Molecular weight** | **Solubility** | **Film forming ability** | **pH** | **Melting point** |
|---|---|---|---|---|---|
| Hydroxy propyl methyl cellulose | 10,000-1,500,000 | Soluble-cold water, Insoluble-chloroform and ethanol | It has film forming ability | 5-8 | 190-200ºc |
| Pullulan | 8000-2,000,000 | It is soluble in both hot and cold water | Having high adhesion and film forming capacity | 5-7 | 107ºC |
| Gelatin | 15000-250,000 | It is soluble in acid, glycerine and alkali-swell in water | Very good film forming capacity | 3.8-6.0 | - |
| Starch and modified starch | 50,000-1,60,000 | Insoluble in cold water and ethanol. At 37ºC swells in water about 5-10% | Modified starch is having property to form a fast dissolving film | - | 250ºC |
| Kollicoat | About 45000 | ≥50% in water | Good film forming property | 6-7 | - |

➢ **Plasticizer:**

Plasticizers should be used improve the flexibility as well as the mechanical properties of film like tensile strength and elongation and reduce the breakability of the film. A plasticizer selected should be compatible with APIs as well as with the other ingredients. For improving the strip property of plasticizers, the glass transition temperature of polymer for non-aqeous solvent system reduced in the range of 40-60 and for aqeous system the glass transition temperature of polymer is reduced below 75. Examples of some plasticizer are castor oil, polyethylene glycol, citrate derivatives. Etc [2, 12].Various examples of APIs along with the plasticizers used is described in below table.4

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**Table.4 Examples of API with plasticizer used:** [2, 50, 51, and 55]

| API | Name of Plasticizer |
|---|---|
| Triclozan | PEG |
| Montelukast sodium | Glycerine |
| Sertraline | PEG |
| Loperamide | PEG |
| Famotidine | PEG |
| Ropinirole hydrochloride | PEG |
| Cetrizine | PEG |
| Telmisartan | PEG |
| Dicyclomine hydrochloride | PEG |
| Metachlopramide hydrochloride | Glycerol |

- **Sweetening agents:**

Sweetening agents should be used for masking the bitter taste of the APIs. Approximately 3 to 6% w/w concentration of sweeteners should be used in the preparation, either alone or in combination. In the formulation, both natural and artificial sweeteners may be used. Natural sweeteners like sorbitol, mannitol, and isomalt and artificial sweeteners include sucrose neotame, alitame, aspartame, cyclamate may ne incorporate in the films. However, artificial sweeteners are mostly preferable, because natural sugars are restricted for diabetic patients as well as in people who are on diet. [13]

- **Saliva stimulating agents:**

Saliva stimulating agents should be used to increase saliva secretion that helps in faster disintegration of the film. Various acids may be used in the preparation of food can be used as saliva stimulant, such as ascorbic acid, citric acid, lactic acid, tartaric acid and malic acid. Among all the examples the most widely saliva stimulating agent used is citric acid. [9]

- **Flavouring agents:**

Flavouring agents are used to impart flavour to any formulation. Flavouring agents should be compatible with drugs as well as with excipients. Flavours can be extracted from different parts of the plants like flowers, leaves, fruits. Flavours used are natural as well as artificial. Examples are peppermint oil, spearmint oil, cinnamon oil, vanillin, chocolate, apple, pineapple, cherry, and raspberry [8]. Flavouring agents used for masking different taste is descried below in table.5.

**Table. 5 Flavouring agents used for masking of different tastes is described as under: [**18]

| Taste | Flavouring agent used |
|---|---|
| Bitter | Mint, anise, walnut, chocolate, wild cherry |
| Salty | Peach, butterscotch, vanilla, apricot, maple, winter green |
| Sweet | Vanilla, fruit, berry |
| Sour | Raspberry, citrus, liquorice root |

- **Surfactants:**

Used as wetting or dispersing or solubilising agent. It is used to dissolve film within seconds and thus immediately release active ingredient. Examples are sodium lauryl sulphate, benzalkonium chloride, tweens, spans, polaxamer 407.Among various examples, mostly Polaxamar 407 is used as wetting, dispersing and solubilising agent [14].Other adjuvant like antioxidants, stabilizers, chelating agent, etc can be used as per need of formulation.

## III. MANUFACTURING METHODS:

MDFs can be formulated by different methods:-

- Solvent casting method.
- Semisolid casting method.
- Hot melt extrusion.
- Solid dispersion technique.
- Rolling method.

- **Solvent casting method.**

This method is most commonly used for manufacturing of fast dissolving oral film. In solvent casting method, the water soluble polymers are mixed in water to form homogeneous solution. Then, the API and remaining excipients are

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dissolved in smaller amount of other suitable solvent. Both the solutions are combined by stirring and mixing, the air entrapped is removed by sonification. Finally solution is poured in petridish and then dried in the oven. [15]

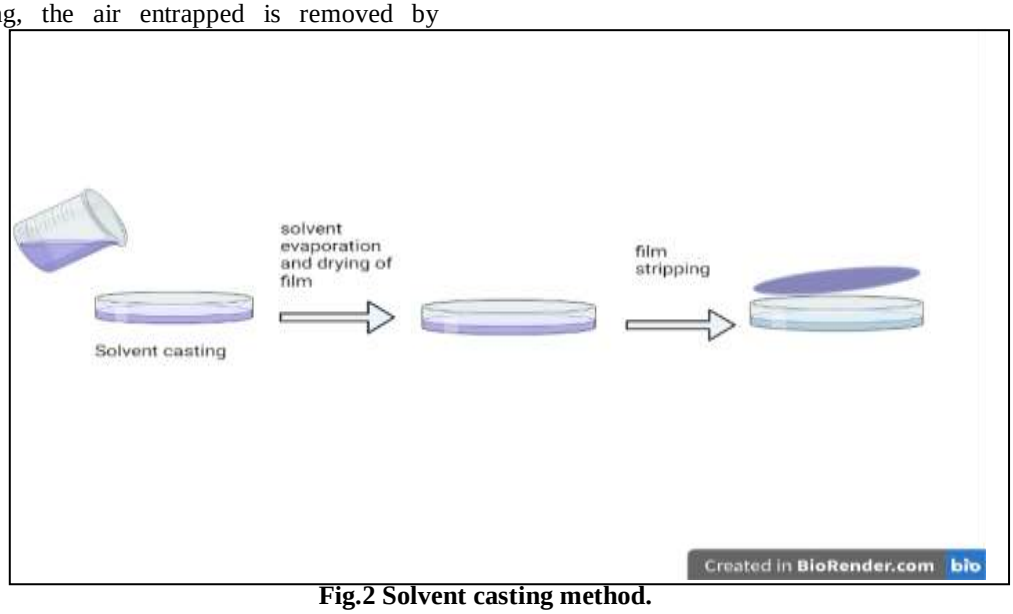


**Fig.2 Solvent casting method.**

Advantages:

- Films have good physical properties as well as flexibility.
- It is low-cost method.
- It does not cause any changes to API when exposed to high temperature.
- Films have better clarity and gloss.
- Films are free from any damage such as die lines.

Disadvantages:

- The polymer should be dissolved in water or volatile solvent.
- Stable solution should be obtained with moderate viscosity.
- The film formed should be homogeneous.[18]

➢ **Semisolid casting method:**

This method is preferred when acid insoluble polymers are used for the preparation of film. Firstly in this method, the solution of water soluble film forming polymer is prepared. The prepared solution is than added to a solution of acid insoluble polymer. Then plasticizer is added in appropriate amount to obtain gel mass. Finally the obtained gel mass is casted in the films or ribbons using heat controlled drums. The ratio of acid insoluble polymer to film forming polymer used should be in 1:4. [16]

➢ **Hot melt extrusion method:**

This method is mostly used for preparation of granules, transdermal drug delivery system, transmucosal drug delivery system and sustained release tablets. This method includes shaping of polymers through heating. In this method, the drug along with other excipients are combined in dry state, without use of any solvent and then subjected to extruder. Then the extruders having heaters that melt the mixture. The molten mass obtained is shaped in to the films. [17]

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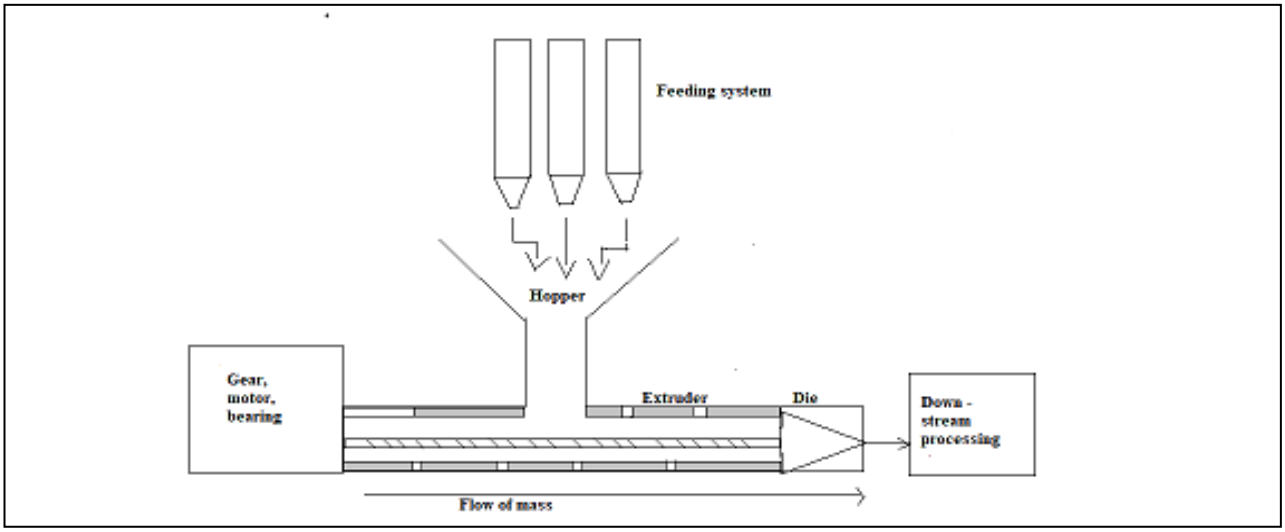


**Fig.3 Hot melt extrusion method**

Advantages:

- Processing steps are less.
- Solvent or water is not used in this method.
- It is more suitable for poorly soluble drugs.
- Energy needed is less than high shear methods.

Disadvantages:

- Thermoliable drugs are not suitable for this method.
- For processing the polymer must have good flow properties.
- It is difficult to maintain dose uniformity.
- Packaging require is expensive.[18]

➢ **Solid dispersion method:**

Solid dispersion method is dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Using suitable liquid solvent, the drug is dissolved. Incorporate solution into the melt of polyethylene glycol, below 70ºC. Atlast the solid dispersions are shaped into the films by means of dies. [1]

➢ **Rolling method:**

In this method, the solvent mainly used are water and mixture of water and alcohol. In small portion of aqueous solvent, the active agent and other ingredients are dissolved by means of high shear processor. Then to prepare homogeneous viscous solution water soluble hydrocolloids is dissolved in water. The solution containing drug is then rolled on a carrier. The films are dried on roller and cutted in desired shape and sizes. [19]

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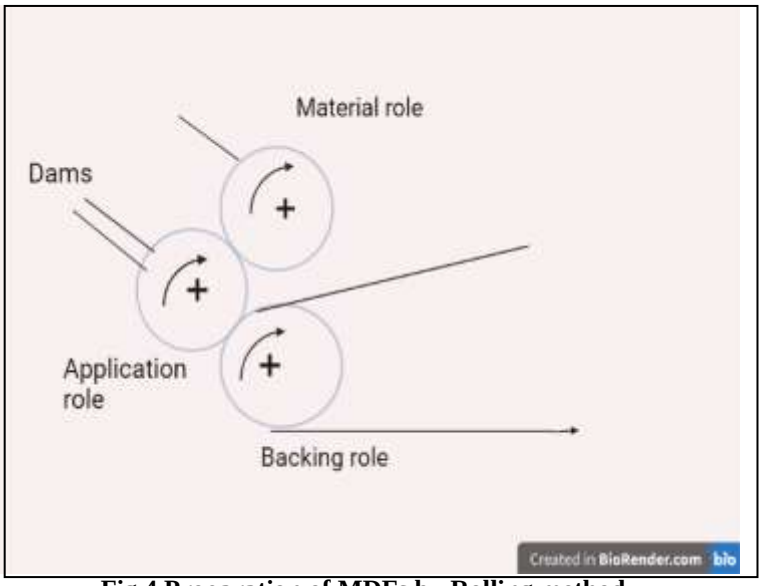


**Fig.4 Preparation of MDFs by Rolling method.**

## IV. EVALUATION PARAMETERS:

➢ **Thickness:**

The thickness of film strip is measured by using micrometer screw gauge. The thickness of film must not be more than 5% from 5 different locations. The thickness of film is measured to obtain uniformity of film. This step is important because uniformity in the film thickness is related to the dose accuracy in the film strip. [20, 22]

➢ **Folding endurance:**

To study the film elasticity, is essential to do folding endurance of film during its handling as well as during its storage. The folding endurance is obtained by cutting a strip of film and continuously folding the film at the same point till it breaks. The number of times, film is folded without breaking considered as folding endurance value.Folding endurance of film is must between 100-150.

➢ **Swelling study:**

The film swelling studies is determined using simulated saliva solution. Each film sample is weighed and placed in a pre-weighed stainless steel wire mesh. In a plastic container containing 15 ml of simulated saliva solution, the mesh containing film samples is merged. At each time interval, the increase in weight of film is measured constant weight is obtained. And percentage elongation is calculated by following equation. [20]

The degree of swelling was calculated by below equation:

W=Wt-Wo/Wo

Wt=It is the weight of film at time t.

Wo=It is the weight if film at time zero.

➢ **Percentage elongation:**

When the stress is applied to the sample of film strip, it stretches that is referred as strain. Increase in concentration of plasticizer causes increase in elongation of strip. Percentage elongation of film is calculated by following equation:

Percentage elongation= $\frac{\text{Increase in length of strip}}{\text{Initial strength of strip}}$ *10

➢ **Young's modulus:**

Stiffness of strip is measured by young's modulus.Young's modulus is the ratio of applied stress over strain in the region of elastic deformation. The equation is as under:

Young's modulus=slope*100/strip thickness*cross head speed.

As per Young's modulus, the value for film is to be obtained 0.30±0.07Mpa. [17]

➢ **Tensile strength:**

The meachanical strength of the film is measured tensile strength measurement. The point at which maximum stress is applied to break a film is termed as tensile strength. Tensile testing machine like Instron and Monsanto tester is use for testing tensile strength of the film. It can be calculated by the load applied divided by cross sectional area of the film as described in the following equation:

Tensile strength= (load at failure/strip thickness*strip width)*100. [17]

➢ **Surface pH:**

It is important to determine the surface pH of the film to avoid risk of any side effects by placing film in vivo on the surface of 1.5%w/v agar

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gel followed by placing pH paper(pH range 1-11) on films. The colour change of pH paper is determined and reported. The surface pH value for film must be 7 or near to neutral value.

Another method to measure surface pH of film is by using buffer. Cut a film put it in to petridish than add o.5 ml of buffer solution and measure the surface Ph of film by using Digital pH meter. [1, 21]

- **Tear resistance:**

In this method, very low rate of loading 51mm (2 in)/min is employed to plastic film and the force that initiate tearing is measured. The force or maximum stress needed to tear the specimen is referred as tear resistance value in Newton (or pound-force).

- **Assay/drug content and content uniformity:**

For this test standard pharmacopeia is referred, for any particular API, the standard assay method is preferred to determine its content uniformity.Drug content uniformity of the film is measured by UV-Visible spectrophotometer or specify as per pharmacopoeia. In different volumetric flask of 100ml, place films of each formulation and using pH buffer it can be dissolved. The sample of 5ml is withdrawn after 30 minutes and taken into volumetric flask of 10ml and the volume was made up to the mark. If UV spectroscopy is applied the absorbance is taken, than the value of absorbance is compared against blank in UV spectrophotometer. Using the standard graph, the percentage drug content is determined. [21, 22]

- **Contact angle:**

Goniometer is used to measure the contact angle at room temperature. On the surface of the dry film place a drop of distilled water and within 10 seconds of deposition the image of water droplet are recorded by means of digital camera. The contact angle can be measured on both side of drop and average is taken.

- **Transparency:**

By using a simple UV spectrophotometer the transparency of the films can be determined. In rectangular shape cut the film and put it inside the spectrophotometer cell. Now determine the film transparency at 600nm. The transparency of film can be calculated by following equation. [23]

Transparency= (log T600)/b = c

- **Invitro dissolution test:**

The standard basket or paddle apparatus or specify as per pharmacopoeia is used to perform this test as described in any of the pharmacopeia. As per the dose of API and sink condition, the essential dissolution apparatus should be selected. When the paddle apparatus is used, it will be difficult to perform dissolution test due to floating of strip on dissolution medium. Thus, appropriate dissolution apparatus must be used to get accurate results.

- **Disintegration time:**

For orally disintegrating tablets, the disintegrating time limit is 30 seconds or less that is described in CDER guidance and can be used at development stage or for the quality test as a qualitative guideline. For this study pharmacopeia disintegration test apparatus may be used. Strips have typical disintegration time between 5-30seconds. [24]

Few examples of MDFs along with the APIs and polymers used for its preparation are described in below table.

**Table 7. Examples of MDFs prepared using different APIs and polymers:** [1]

| Sr. No | API | Polymer | Uses | References |
|---|---|---|---|---|
| 1 | Montelukast sodium | HPMC, PVA, SSG | Asthma | 25 |
| 2 | Rizatriptan benzoate | HPMC E5 AND 15, Pullulan gum | Arthritis | 26 |
| 3 | Diazepam | HPMC E3, E5, E15. | Antiepileptic | 27 |
| 4 | Domperidone | B Cyclodextrin, HPMC E15 | Antiemetic | 28 |
| 5 | Paracetamol | HPMC, SLS | Antipyretic | 29 |
| 6 | Amphotericin B | Maltodextrin, Avicel 200 | Antifungal | 30 |
| 7 | Dicyclomine | HPMC PVA | Antispasmodic | 31 |
| 8 | Rofecoxib | HPMC | Osteoarthritis | 32 |
| 9 | Aceclofenac | Cyclodextrin, HPMC E5 AND HPMC | Anti-inflammatory | 33 |

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| | | | | |
|---|---|---|---|---|
| | | E15LV | | |
| 10 | Losartan potassium | HPMC, NA-CMC, Gelatin, Na Alginate | Hypertension | 34 |
| 11 | Amlodipine Besylate | HPMC E3, E5, E15 | Angina pectoris and hypertension | 35 |
| 12 | Sumatriptan Succintae | HPMC E5, E15, PVP K30 | Migrane | 36 |
| 13 | Metoprolol Tartrate | HPMC E5 | Hypertension, angina pectoris and arrhythmia | 37 |
| 14 | Phenobarbital | METHOCEL- E15, HPC (LV), SSG, Croscarmellose sodium. | Epilepsy | 38 |
| 15 | Piroxicam | Sodium CMC, chitosan, crospovidone | NSAID | 39 |
| 16 | Nicotine | HPMC | Smoking cessation | 42 |
| 17 | Propranolol hcl | HPMC E15 | Hypertension | 40 |
| 18 | Lercanidipine HCL | HPMC E5, E15 and PVA | Hypertension and angina pectoris | 43 |
| 19 | Zolmitriptan | Sodium alginate, gelatine, pectin | Migrane | 44 |
| 20 | Ketorolac tromethamine | HPMC E15 LV ,PVP | Pain management | 45 |
| 21 | Meloxicam | HPMC K50, PVPK30, Poloxamer 127 | NSAID | 46 |
| 22 | Levocetirizine di hydochloride | HPMC, PVA | Anti-inflammatory | 47 |
| 23 | Etoricoxib | HPMC | Anti-inflammatory, Analgesic and antipyretic | 48 |
| 24 | Loratadine | HPMC E5, HPMC E15 | Anti-allergic | 49 |
| 25 | Famotidine | HPMC, Carbopol-934 P and Polyvinyl pyrrolidone | Anti-ulcerative | 50 |
| 26 | Loperamide | HPMC E5 AND HPMC E50 | Irritable bowl syndrome | 51 |
| 27 | Quetiapine | PVP | Major depressive disorder | 52 |
| 28 | Chlorpheniramine maleate | HPMC E3, HPMC E5, HPMC E15 | Anti-histamine | 53 |
| 29 | Omeprazole | HPMC 15cps | Proton pump inhibitor | 54 |
| 30 | Cetrizine | HPMC E5 | Anti-allergic | 55 |
| 31 | Ketoprofen | Sodium alginate, PVP K30, Gelatin | Anti-inflammatory | 56 |

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| | | | | |
|---|---|---|---|---|
| | | | and analgesic | |
| 32 | Ropinirole Hydrochloride | Pullulan | Parkinson's disease | 57 |
| 33 | Telmisartan | HPMC | Hypertension | 58 |
| 34 | Phenylephrine Hydrochloride | HPMC | Relieving congestion | 59 |

## V. CONCLUSION:

Mouth dissolving film is more convenient than other oral dosage forms due to its rapid disintegration. It gives rapid action by avoiding first pass metabolism and by directly reaching in systemic circulation. It is thus more suitable for geriatric as well as for paediatric patients as it avoids swallowing. It is ease to administer and low in cost, thus more convenient for patients. And it also has several advantages over conventional dosage form. And thus, mouth dissolving film is unique, useful and selective dosage form. Various methods used to formulate MDFs such as solvent casting method, Hot melt extrusion method, semisolid casting method, solid dispersion technique and rolling method. There may be quite challenging to produce film in large scale production for commercialisation, although various evaluation parameters such as thickness, folding endurance, drug content, dissolution test, disintegration test, transparency, contact angle, tensile strength, young's modulus,etc used to characterize the film.

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