FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET: REVIEW ARTICLE

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ABSTRACT
Now day’s formulation research is breaking barriers of conventional methods. Recently, MDTs have take over an important position in the market by overcoming previously administration problems and contributing to extension of patient life, which have difficulty in swallowing tablets and capsules. Upon introduction into the mouth, these tablets dissolve/ disintegrate in the mouth without additional water for easy administration of pharmaceutical ingredients. These dosage forms are also used to attain instant a higher concentration of drug in body for immediate actions. These are novel dosage forms which dissolve in mouth cavity within a few seconds. This article attempts at discussing ideal properties, advantages, limitation, choice of drug candidates, need of formulation, approaches for preparation of MDTs, Patented technologies on MDTs and Evaluation tests of MDTs.

KEYWORDS: Mouth dissolving tablets, fast Dissolving Tablets, Superdisintegrants, patented technology, MDT’s, FDT.

INTRODUCTION
In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the mouth dissolving tablet (MDT) is the most widely preferred commercial products.

The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like Tablets, Capsules, Liquid preparations are administered by oral route. During the last decade, mouth dissolving tablet (MDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention.

The MDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All MDTs approved by the Food and Drug Administration (FDA) are
classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients.

The disintegration time for good MDTs varies from several seconds to about a minute. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control.

Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Mouth dissolving of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastric absorption when formulated as MDTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing.

Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

**Mouth dissolving tablet (MDT)**

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3 min. Most of the MDTs include certain super disintegrates and taste masking agents.

**Ideal properties of Mouth Dissolving Tablets**

- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- It should have pleasant mouth feel.
- It Should have an acceptable taste masking property.
- It should have sufficient hardness to withstand rigors during manufacturing processes and post manufacturing handling.
- It should allow high drug loading.
- Should leave minimal or no residue in mouth after disintegration.
- Should exhibit low sensitivity to environmental conditions (temperature and humidity).
- It should allow the manufacture of tablets using conventional processing and packaging equipments.
- It should be cost effective.

**The Need for Development of MDTS**

The requirement of non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes. The paediatrics and geriatric populations are the primary targets, as both the groups found it difficult to swallow conventional tablets.

The **patient related factors** for development of MDTs include the following:

- Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction avoided, thus providing improved safety.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.

The **effectiveness factors** are:

- Increased bioavailability and faster onset of action are a major claim of these formulations.
- Because the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions.
- The pre-gastric drug absorption avoids the first-pass metabolism and drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.
- Safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism.

The **Manufacturing and marketing factors** involving:
Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size.
As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form.
A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation etc.
Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient population.

**Advantages of Mouth Dissolving Tablets**
Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients.
Patient’s compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
Pre-gastric absorption can result in Improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
Good mouth feel property of Mouth Dissolving Drug Delivery System helps to change the basic view of medication drugs.
Drug should have good stability in saliva and water.
More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
Convenience of administration and accurate dosing as compared to liquid formulations.
Benefit of liquid medication in the form of solid preparation.
New business opportunities: product differentiation, line extension and lifecycle management, exclusivity of product promotion and patent-life extension.

**Limitations of Mouth Dissolving Tablets**
The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
The tablets usually have insufficient mechanical strength. Hence, careful handling is required.

**Drug selection criteria**
The ideal characteristics of a drug for Mouth Dissolving tablet include
Ability to permeate the oral mucosa.
At least partially non-ionized at the oral cavity pH.
Have the ability to diffuse and partition into the epithelium of the upper GIT.
Small to moderate molecular weight.
Low dose drugs preferably less than 50 mg.
Short half life and frequent dosing drugs are unsuitable for MDT.
Very bitter or unacceptable taste and odor drugs are unsuitable for MDT.
The role of excipients is important in the formulation of Mouth Dissolving tablets.
These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Binders keep the composition of these Mouth dissolving tablets together during the compression stage.
Important ingredients that are used in the formulation of MDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Disintegration and solubilization of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents.

Material used in preparation of mouth dissolving tablet

<table>
<thead>
<tr>
<th>Drug and Excipients</th>
<th>Supplied by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan</td>
<td>A gift sample from Glenmark Pvt Ltd, Nashik.</td>
</tr>
<tr>
<td>Tulsion 671</td>
<td>A gift sample from Glenmark Pvt Ltd, Nashik</td>
</tr>
<tr>
<td>Crossprovidone</td>
<td>Molychem, Mumbai</td>
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<tr>
<td>Talc</td>
<td>Molychem, Mumbai</td>
</tr>
<tr>
<td>Peppermint</td>
<td>Molychem, Mumbai</td>
</tr>
</tbody>
</table>

METHODS FOR PREPARING MOUTH DISSOLVING TABLETS
The basic approaches to developing Mouth dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation. Various technologies used in the manufacture of Mouth dissolving tablets include

I. Conventional Technologies

1. Sublimation
In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Granules containing nimusulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure. Conventional methods like dry granulation, wet granulation and direct compression with highly soluble excipients, superdisintegrants and/or effervescent systems can also be used.

2. Molding

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as compression molding.) Then the solvent can be removed by airdrying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Recently, the molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as heat molding) or by evaporating the solvent from a drug solution or suspension at ambient pressure (novacuum lyophilization).

3. Lyophilization or Freeze drying method

A process in which water is sublimated from the product after freezing is called as lyophilization. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, and which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolves rapidly but also improved the bioavailability of several drugs such as spironolactone and troleandomycin. Corveleyn and Remon studied various formulation and
process parameters by using hydrochlorothiazide as a model drug on the basis of which US Patent 6,010,719 was granted. Tablets prepared by lyophilization, are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions.

4. Spray drying
Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen et al. have reported applying this process to the production of fast dissolving tablets. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatine as a support agent for sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 second in an aqueous medium.

5. Mass extrusion
In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

6. Direct compression
Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Effective Superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water
absorption capacity. Studies revealed that the water insoluble Superdisintegrants like sodium starch glycolate and Croscarmellose sodium show better disintegration property than the slightly water soluble agents like Crospovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants.

II. Patented Technologies for Mouth Dissolving Tablets

1. Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginites are incorporated. These form a glossy amorphous structure, which imparts strength.

2. Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

3. Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine 100 is used to produce the tablets. The tablets produced are soft and friable.

4. Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product
launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

5. Wow tab Technology
Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water”. In this process, combination of low mouldability saccharides and high saccharides is used to obtain a rapidly melting strong tablet.

The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, glucose, and mannitol), granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides) and then compressed into tablet.

6. Flash tab Technology
Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tabletting technology.

EVALUATION OF MOUTH DISSOLVING TABLETS

1. Tablet thickness
Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using micrometer.

2. Hardness (Crushing strength)
Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of MDTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation.

3. Friability
Friability Attempts for decreasing the disintegration time increase the friability of MDTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are
placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

\[
\% \text{ Friability} = 1 - \left( \frac{\text{loss in weight}}{\text{Initial weight}} \right) \times 100
\]

4. Weight variation
Standard procedures are followed as described in the official books.

5. Wetting time and water absorption ratio
Wetting time of dosage form is related to the contact angle. Wetting time of the MDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. Five circular tissue papers of 10cm diameter are placed in a petri dish. Ten milliliters of water soluble dye solution is added to petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petri dish noted (Wb). The wetted tablet from petri dish is taken and reweighed (Wa). The water absorption ratio, R can be determined according to the following equation.

\[
R = 100 \left( \frac{Wa - Wb}{Wb} \right)
\]

6. Disintegration time
According to the European pharmacopoeia the fast disintegrating or Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. However it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. To overcome these problems, several new methods have been proposed. One of these methods uses a Charge Couple Device (CCD) camera or texture analyzer to evaluate the disintegration time of tablets. In another method, a modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature...
at 37°C and a magnetic stirrer. DT is noted at 25 rpm. One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted.

7. **In vivo disintegration time**

In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth.

8. **Dissolution test**

The dissolution study is performed by use of USP 2 (paddle speed of 50 rpm) apparatus which is most suitable for MDTs.

The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets.

9. **Stability study (Temperature dependent)**

The mouth dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C
(ii) 50 ± 1°C
(iii) 37 ±1 °C and RH 75% ± 5%

The tablets were withdrawn after 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

**CONCLUSION**

The popularity of MDTs has increased tremendously over the last decade because of better patient acceptance and compliance and may offer improved biopharmaceutical properties, For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules improved efficacy, and better safety compared with conventional oral dosage forms. The clinical studies also showed that MDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. There are about 40 drugs that have been formulated into marketed MDTs using various technologies. The key to MDT formulations is fast disintegration, dissolution, or melting in the mouth and this can be achieved by producing the porous structure of the tablet matrix or adding superdisintegrant and/or effervescent excipients.
REFERENCES


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