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Mouth Dissolving Tablet: a novel approach for better patient compliance

Umesh D. Laddha*[1], Rasika V. Zilpelwar[2],

[1]Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule-425405, (MS) India.
[2]Asentech India PVT LTD, Pune-411041, (MS) India.

Abstract: Mouth dissolving tablet (MDT) is novel dosage form which disintegrates within 3 minutes. MDTs are found more effective in paediatric and geriatric patient who refused to take medicine as well as in bedridden patient having fear of chocking of tablet in throat. MDTs are uncoated tablets that are formulated by using one or more superdisintegrants which help the tablets to disintegrate in mouth within few minutes in presence of saliva. MDTs can be evaluated for various parameter like general appearance, tablet hardness and friability, weight variation test, uniformity of thickness, wetting time, water absorption ratio, *in vitro* disintegration time and *in vitro* dissolution study.
Keywords: Mouth dissolving tablets, orodispersible tablet, superdisintigrants, MDT technology.

Introduction

The oral route of administration is considered as the most widely accepted route for systemic effect of drugs. Most commonly used oral dosage forms like tablets and capsules are suffers from several drawbacks like difficulty in swallowing, risk of chocking, need of water and first pass metabolic effect which results in poor patient compliance particularly in case of pediatric and geriatric patients [1]. Drawbacks of conventional oral dosage forms can be overcome by formulating Mouth Dissolving Tablets (MDT's) [2].

As per European Pharmacopeia, MDT is also known as orodispersible tablets (ODT's) [3]. MDT's can be defined as uncoated tablet, intended to be placed in the mouth where it rapidly disperses within 15 secs to 3 min. MDTs are formulated by using one or more superdisintegrants, which helps the tablet to disintegrate in mouth within few minute in the presence of saliva [4,5]. The target population for MDT is pediatric, geriatric and bedridden or developmentally disabled patients [6].

Ideal properties for MDT's[5, 7]

MDTs should posses the following ideal properties:

- Disintegrates within 3 minutes.
- No requirement of water for administration.
- Have a pleasing mouth feel.
- Acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablets by using conventional processing and packaging equipments.

Advantages[7,8]

- Administration to the patients who have difficulty in swallowing or who refuse to swallow like psychiatric, pediatrics and geriatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
- Convenient for traveler patient who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- Avoid the risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction.

Limitations of MDT's[9,10]

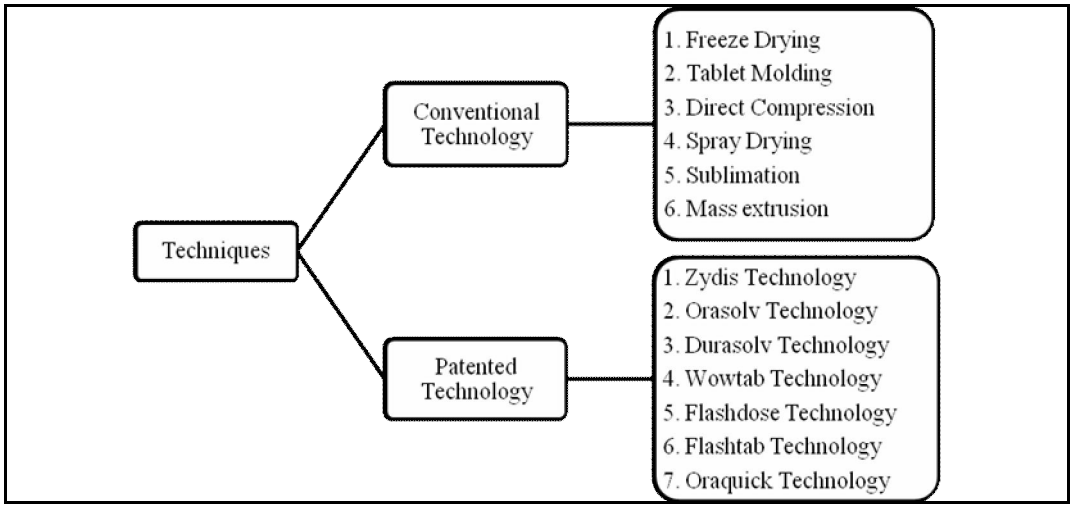
- The tablets usually have insufficient mechanical strength due to superdisintegrant. Hence; required careful handling.
- The tablets may leave unpleasant taste and/or grittiness in mouth after disintegration.
- MDT's required specific packaging.

Technology for MDT's [5,11,12]

The performance of MDT's depends on the technology used in manufacturing. Orally disintegrating property of MDTs is imparted by quick permeation of water into the tablet matrix, which creates porous structure and results in rapid disintegration.
The basic approaches to develop MDTs include,

- Maximizing the porous structure of the tablet matrix.
- Incorporating the effective quantity of superdisintegrating agent/agents.
- Using highly water-soluble excipients.

Various approaches used for manufacturing of MDT's are summarized in flow chart



Freeze Drying:

In this process water is sublimated from the product after freezing. Freeze dried product gives more rapid dissolution than other solid products. The lyophilization process imparts glossy amorphous structure to bulking agent and sometimes to the drug, which results in high dissolution characteristics to the formulation. However, use of freeze drying is limited due to high equipment and processing cost [3].

Ahmed et al. developed MDT's by using freeze-drying process with aqueous dispersion of Meloxicam, containing matrix former, sugar alcohol and collapse protectant. Optimised Meloxicam MDT's were disintegrated within 5 sec[15].

Moulding:

Tablets produced by moulding are solid dispersions. Physical form of drug in tablets depend whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier and remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on dispersion or dissolution of tablet. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs[3,14].

Abdelbery et al. formulated MDT's by using hydrophilic waxy binder. Optimized tablet showed 40 sec. disintegration time[15].

Sublimation:

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water. Porous tablets that exhibit good mechanical strength and dissolve quickly. Inert solid ingredients (e.g., urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. Prepared tablets dissolve within 10-20 seconds[16].

Ahmed et al. developed MDT's by using sublimation process different subliming agents like camphor, menthol and thymol were used with Ac-Di-Sol as a superdisintegrant. Optimised Meloxicam MDT's were disintegrated within 47 sec[13].

Jain et al. formulated MDT's by using sublimating method using Camphor as sublimating agent and it shown 92.13% releases in 12 min[1].

Spray Drying:

Spray drying can be used to prepare MDT's. This technique is based upon a particulate support matrix that is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredient and compressed into tablet. Allen and Wang have employed spray drying technique to prepare MDT's[17].

Mass Extrusion:

This technology involves softening the active blend using suitable solvent, mixture of polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blend to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and there by masking their bitter taste[18].

Direct Compression:

This technology is commonly use to manufacture tablets. In direct compression, conventional equipment, commonly available excipients and a limited number of processing steps are involved. Tablets containing high doses can be compressed.

Disintegrant's efficacy strongly affects tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. Products with optimal disintegration properties often have medium to small size and high friability and low hardness [1].

Bhardwaj et al. developed Aceclofenac MDT's by using direct compression method with various superdisintegrant. Optimized Aceclofenac MDT was disintegrate within 12 to 27 sec[19].

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 materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength to obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of Zydis unit during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

ZYDIS (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of Orally Disintegrating dosage forms. There are approximately 12 marketed ZYDIS products, including lorazepam, piroxicam, loperamide, loratidine, enalapril and selegiline. These formulations are freeze-dried products prepared from combination of water-soluble matrix material with drug, which is preformed in blister pockets and freeze dried to remove the water by sublimation[20].

Shearform Technology:

The shearform technology is based on preparation of floss that is also known as 'shearform matrix', which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystallized by various techniques to provide uniform flow properties and thus facilitate blending. The recrystallized matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallization. The shearform floss, when blended with the coated or uncoated microspheres is compressed into Flashdose or EZ chew tablets on standard tableting equipment [21,22].

Ceform Technology:

In ceform technology microspheres containing active drug ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds and excipients into a precision engineered and rapidly-spinning machine. The centrifugal force of the rotating head of ceform machine throws the drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquefies the drug blend to form a sphere without adversely affecting drug stability. The microspheres are then blended and compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipients generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microspheres can be incorporated into a wide range of fast dissolving tablets such as Flashdose, EZ chew, Spoon Dose, as well as conventional tablets [18].

Durasolv Technology:

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients[23].

Orasolv Technology:

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked and also contains effervescent agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system [24].

Wowtab Technology:

Wowtab Technology is patented by Yamanouchi Pharmaceutical Company WOW means "without water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with low mouldability saccharides and granulated with high mouldability saccharides and compressed into tablet[25,].

Flashtab Technology:

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared using the conventional technique like coacervation, microencapsulation, and extrusion spheronization. All these processes utilized conventional tableting technology. Nowadays orodispersible tablets are gaining more and more importance in the market. Currently, these tablets are available in the market for many diseases; more is concentrated on analgesics and anti-pyretic. Research is in progress for anti-hypertensive's, anti-emetics and anti-asthmatics[26,27].

Mechanism of superdisintegrants

Use of disintegrants is play major role in development of MDTs. It is important to choose a suitable disintegrant, in an optimum concentration so as to ensure fast disintegration and high dissolution rates. Superdisintegrants provide fast disintegration due to combined effect of two mechanism that is swelling and water absorption by the formulation. Due to swelling of superdisintegrants the surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant[14,28].
Tablets are disintegrate in to mouth by various mechanism which is listed bellow

1. By capillary action
2. By swelling
3. Because of heat of wetting
4. Due to release of gases
5. By enzymatic action
6. Due to disintegrating particle/particle repulsive forces.

Evaluation of fast dissolving Tablets

Tablets are subjected to following quality control test.

1. General appearance:

The general appearance of a tablet, its visual identity and overall elegance is important for patients acceptance. It includes size, shape, colour, odour and surface texture of the tablets.

a. Size and shape:

The size and shape of the tablet can be dimensionally monitored by scalper scale.

b. **Tablet Thickness:**

The thickness is measure by placing tablet in Varnier caliper. 5 tablets are use for measurement of thickness[1].

2. **Tablet hardness:**

The tablet hardness measure by using hardness tester like Monsanto or Evesta hardness tester. Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness is expressed in Kg/cm^2. Three tablets are randomly evaluated from each formulation and the mean and standard deviation values has been calculated[29].

3. **Friability test**

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets has determined by using Friabilator. It is expressed in percentage (%). Twenty tablets are initially weighed and transferred into friabilator. The friabilator is operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets weighed again[31]. The percentage friability is calculated by,

$$F = \frac{Wi - Wf}{Wi} \times 100$$

Where; F= friability
Wi= initial weight
Wf= final weight

4. Weight variation test

Tablets are selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia and Indian Pharmacopoeia allows a little variation in the weight of a tablet[29]. Allowed percentage deviation in weight variation is shown in table no. 1

Table No. 1. Percentage deviation in weight variation

Average weight of a tablet		Percentage deviation
USP	IP	
130 mg or less	80 mg or less	10
More than 130 mg and less than 324 mg	More than 80 mg but less that 250 mg	7.5
324 mg or more	250 mg or more	5

5. Uniformity of thickness

The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing five or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge[29].

6. Wetting time

The method is applied to measure tablet wetting time. A piece of tissue paper folded twice is placed in a small petri dish (i.d. = 6.5 cm) containing 6 ml of water in which small quantity of amaranth red color is added. A tablet is placed on the paper and the time for complete wetting is measured[31,32]. Procedure for wetting time measurement in presence of amaranth red is shown in fig. no. 1

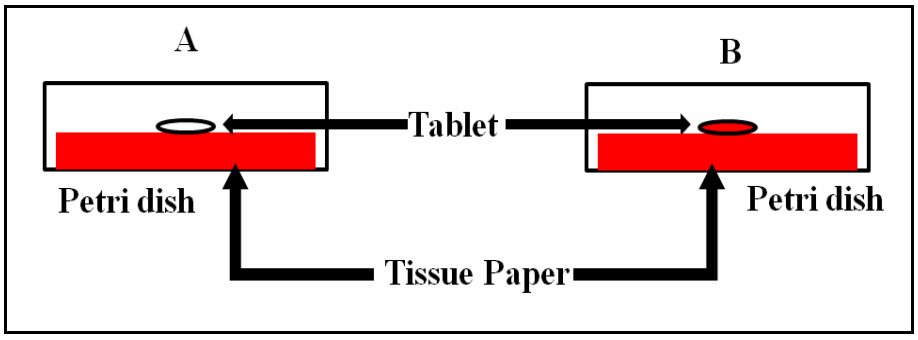


Fig. No. 1 Wetting time measurement A) before absorbance of water, B) after absorbance of water

7. Water absorption ratio

A piece of tissue paper folded twice is placed in a small Petri dish containing 6 ml of water. A tablet is put on the paper and time required for complete wetting is measured. The wetted tablet is weighed. Water absorption ratio (R) is determined by using following equation[32]. Procedure for water absorption is shown in fig. no.2

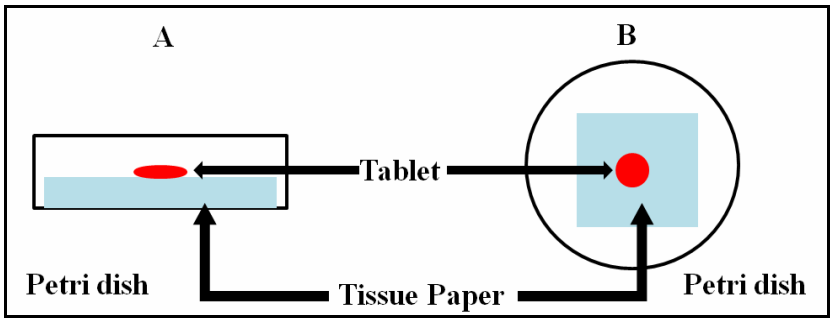


Fig. No. 2 Water absorption measurement A) Frontal view, B) Central view

$R = 100 (W_a - W_b)/ W_b$

Where; W_b = weight of tablet before absorption.

W_a = weight of tablet after absorption.

8. *In vitro* disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus measured and recorded [31,32].

9. *In vitro* dissolution studies

Dissolution rate is studied by using USP type-II apparatus and 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium is maintained at 37±0.5°C, aliquot of dissolution medium is withdrawn at fixed time interval and filtered. The absorbance of filtered solution is measured by UV spectrophotometric or HPLC method and concentration of the drug is determined from standard calibration curve[31,32].

Suitable drug candidates: Table No.2 contain promising drug categories for preparation of MDT's

Table No. 2: Suitable drug candidates[33]

Sr. No.	Drug Category	Examples
1	**Antibacterial agents**	Ciprofloxacin, Erythromycin, Tetracycline, Rifampicin, Penicillin, Doxycyclin, Nalidixic acid, Trimethoprim, Sulphadiazine, Sulphacetamide
2.	**Anthelmintics**	Mebendazole, Albendazole, Thiabendazole, Livermectin, Pyrantel Embonate, Praziquantel, Dichlorophen.
3.	**Antidepressants**	Trimipramine Maleate, Trazodone HCl, Nortriptyline HCl, Mianserin HCl, Amoxapine.
4.	**Antidiabetics**	Glipizide, Glibenclamide, Tolbutamide, Tolazamide, Chlorpropamide, Gliclazide
5.	**Analgesics/Anti-Inflammatory Agents**	Ibuprofen, Diclofenac sodium, Ketoprofen, Mefenamic acid, Naproxen, Indomethacin, Oxyphenbutazone, Piroxicam, Phenylbutazone
6.	**Antihypertensives**	Amlodipine, Diltiazem, Carvedilol, Felodipine, Minoxidil, Nifedipine, Nimodipine, Prazosin HCl, Terazosin

7.	**Antiarrhythmics**	Disopyramide, Quinidine sulphate, Amiodarone HCl
8.	**Antihistamines**	Cetrizine, Acrivastine, Cinnarizine, Loratadine, Triprolidine, Fexofenadine
9.	**Anxiolytics, Sedatives Hypnotics and Neuroleptics**	Alprazolam, Diazepam, Amylobarbitone, Clozapine, Haloperidol, Lorazepam, Nitrazepam, Thioridazine, phenobarbitone, Oxazepam, Midazolam
10.	**Diuretics**	Acetazolamide, Amiloride, Clorthiazide, Furosemide, Bumetanide, Spironolactone.
11.	**Gastro-Intestinal Agents**	Ranitidine HCl, Cimetidine, Famotidine, Domperidone, Omeprazole, Granisetron HCl, Ondansetron HCl

Conclusion

In recent decades, a variety of pharmaceutical researches have been conducted to develop novel dosage forms targeting patient compliance. Among all these dosage forms mouth dissolving tablet (MDT) is most preferred because of its ease of administration specially in case of geriatric and paediatric patients. The oral cavity is an attractive site for administration of drugs because various dosage forms like tablets, capsules, liquid preparations are administered by this route. During last decade, mouth dissolving tablet (MDT) technologies that make tablet disintegrate in mouth without additional intake of water and avoiding chewing have drawn a great deal of attention.

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