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Mouth Dissolving Tablets -An Overview

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ABSTRACT

Mouth dissolving tablets (MDT) have received ever increasing demand during last decade and It is a rapidly a growing area in the pharmaceutical industry. After introduction into the mouth these tablets dissolve or disintegrate in the mouth and leaving an easy to swallow residue. Novel MDTs address the patient and pharmaceutical needs of convenient dosing particularly for busy or traveling patient, pediatric, geriatric and psychiatric patients who have difficulty in swallowing (dysphagia) conventional tablets and capsules. These tablets also have faster onset of action due to buccal absorption of the drug. The popularity and usefulness of the formulation resulted in development of several MDT Technologies. It is expected that this delivery system will get more importance in future as that of conventional delivery systems.

Keywords: Mouth dissolving tablets, disintegrate, residue, conventional delivery system.

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INTRODUCTION

Mouth dissolving tablets are also known as quick dissolve, rapid Dissolve, rapid disintegrate, fast melt, flash melt and mouth dispersing tablet. They are meant to disintegrate instantaneously when put on the tongue and releasing the drug which dissolves or disperses in the saliva. After disintegration some of the drug is absorbed from the mouth, pharynx, and esophagus as the saliva passing down into the stomach. It causes significantly greater bioavailability and faster onset of action of the drug compared to conventional tablet dosage form[1,2.] Table 1 gives details of different MDTs available in Indian market.

Table 1.MDT products available in Indian market[3]

Brand Name	Active Ingredients	Company
Nimulid-MD	Nimesulide	Panacea Biotech
Zyrofmeltab	Rofecoxib	ZydusCadila
MOSID-MD	Mosapride Citrate	Torrent
Feledine Melt	Piroxicam	Pfizer
Maxalt ODT	Famotidine	Merck
Remeron Sol Tab	Mirtazapine	Organon
Romilast	Montelukast	Ranbaxy
Manza BDT	Olanzepine	Orchid
Olanexinstab	Olanzepine	Ranbaxy
Valus	Valdecoxib	Glenmark
Rofaday MT	Rofecoxib	Lupin
Torrox MT	Rofecoxib	Torrent

United States Food and Drug Administration (USFDA), Center for drug Evaluation and Research (CDER) define orally disintegrating tablets in the **' Orange book' as** :- "A solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue".

European Pharmacopoeia describes orally disintegrating tablet as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within **3 minutes**".

Orally disintegrating tablets are appreciated by significant segments of populations particularly who have difficulty in swallowing. It has been reported as dysphagia [4]is common among all age groups or more specific with pediatric, geriatric, psychiatric patients and patients with nausea, vomiting and motion sickness complications[5].

Drug Selection Criteria[6,7]

The ideal characteristics of a drug for oral dispersible tablet include-

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.

- Have the ability to diffuse a partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50mg.
- Short half life and frequent dosing drugs are unsuitable for MDTs.
- Drugs should have good stability in saliva and water.
- Very bitter or unacceptable taste and odour drugs are unsuitable for MDTs.

Table 2 gives a list of drugs that are promising to formulate as MDT.

Table 2.Drugs to be promising to formulate as mouth dissolving tablets[8]

S. No.	Category	Drugs
1	Analgesics and Anti-inflammatory Agents	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Ibuprofen, Indomethacin, Ketoprofen.
2	Anthelmintics	Albendazole, BepheniumHydroxynaphthoate, Cambendazole,
3	Anti-Arrhythmic Agents	Amiodarone, Flecainide Acetate, Disopyramide, Quinidine Sulphate
4	Anti-Epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide
5	Anti-Hypertensive Agents	Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine
6	Anti Protozoal Agents	Benznidazole, Clioquinol, Decoquinate, Diiodohydroxyquinoline,
7	Anxiolytic, Sedatives, Hypnotics and Neuroleptics	Alprazolam, Amyiobarbitone, Baritones, Bentazeparn, Bromazepam

Advantages [9,10,11,12]

- Easy to administer to the patient who cannot swallow such as pediatric, geriatric, bedridden, stroke victim and institutionalized patient specially for mentally retarded and psychiatric patients.
- Pregastric Absorption leading to increased bioavailability/rapid absorption of drugs from mouth, pharynx and esophagus as saliva passes down to stomach also avoids hepatic metabolism.
- Convenient for administration to traveling patients and busy people who do not have excess to water.
- Excellent mouth feels property produced by use of flavors and sweeteners help to change the perception of "medication as bitter pill" especially in pediatric population.
- Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action.
- MDTs offer all the advantages of solid dosage form and liquid dosage forms.

- Convenience of administration and accurate dosing compared of liquids. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunities: product differentiation, line extension and life cycle management, exclusively of product promotion and patent life -extension.

Desired Criteria for MDTs [10,11,13,14]

- MDTs should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
- Effective taste masking Technologies should be adopted for bitter taste drugs.
- Exhibit low sensitivity to environment conditions such as humidity and temperature.
- MDTs should dissolve/ disintegrate in the mouth in matter of seconds without water.
- Have sufficient mechanical strength and good package design.
- The drug excipients property should not affect the orally disintegrating tablets.
- Be portable and without fragility concern.
- It should allow high drug loading.
- It should allow the manufacture of tablet using conventional processing and packaging equipment's.
- It should be cost effective.

Limitations of MDTs [15,16]

- The tablets usually have insufficient mechanical strength.
  Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated property.

TECHNOLOGIES USED FOR MANUFACTURING OF ORALLY DISINTEGRATING TABLETS:

Conventional Technologies

Freeze drying or lyophilization

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze- dried forms offer more rapid dissolution than other available solid products. The lyophilization processes imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristic of the formulation. The entire freeze drying process is done at non-elevated temperature to eliminate adverse thermal effects that may affect drug stability. The major disadvantages of lyophilization technique are that it is expensive

and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions and their limited ability to accommodate adequate concentration of drugs.[17,18]

Direct Compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. The disintegration and solubilization of directly compressed tablets depends on single or combined action of disintegrants, water soluble excipients and effervescent agents used. Breakage of tablet edges during handling and tablet crack during the opening of blister alveolus, all result from insufficient physical resistance. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can promote improved dissolution or disintegration properties. But the main problem of using effervescent excipients is that they are highly hygroscopic in nature [19].

Molding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution [20].

Patented Technologies[21,22]

Flashtab Technology

This technology has been patented by Prographarm laboratories. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug microgranules may be prepared by using the conventional techniques like co-acervation, micro encapsulation, and extrusion spheronization. All the processing utilized conventional tableting technology.

Wowtab Technology

Wowtab Technology is patented by "Yamanouchi Pharmaceutical Corporation “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 a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablets.

Zydis Technology:

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

Superdisintegrants[23]

The basic approach used in the development of the fast–dissolving tablet is the use of superdisintegrants, which permit the tablets for rapid disintegration. Superdisintegrants are generally used at low concentration, typically 1-10% by weight relative to total weight of dosage unit.

Different types of Super disintegrants used in mouth dissolving tablets are as follows[24, 25]

- Crosspovidone
- Microcrystalline cellulose
- Sodium starch glycollate
- Sodium carboxy methyl cellulose or cross carmelose sodium
- Pregelatinzed starch
- Calcium carboxy methyl cellulose
- Modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium.

Factors to be considered for selection of superdisintegrants:

- It should help the tablet to disintegrate fast when tablet meets saliva in the mouth.
- It should be compactable enough to produce less-friable tablets.
- It can able to produce good mouth feel to the patient.
- Thus, small particle size is preferred to achieve patient compliance.
- It should have good flow since it improve the flowability of the total blend.

Taste masking agents[26,27]

Along with fast disintegration the taste masking is also very important for the formulation of MDT, to achieve patient`s compliance. Two approaches commonly utilized for taste masking; firstly by reducing solubility of the drug in the pH of saliva (5.6-6.8), secondly by altering the affinity and nature of drug which will interact with the taste receptor[26] Number of natural and artificial taste masking agents has been evolved in the formulation of oro-dispersible tablet

formulation. Mostly sweetening agent Aspartame (Quarrechin, France) is used as sweetening agent [27].

EVALUATION OF MDTs

Pre-compression characterization

Bulk Density [28,29]

Apparent bulk density was determined by pouring the 5 gram of powder into a 100 ml granulated cylinder. The bulk volume (V) poured drug was determined. The bulk density was calculated using the formula.

$$\rho b = M / V$$

Where: ρb -bulk density, M- is the weight of powder, V- is the volume of powder.

Tapped Density [28,29]

Weight 5g of powder and placed in a measuring cylinder. Measuring cylinder containing known mass (5gm) of powder was tapped for 100 times or fixed time. The minimum volume (Vt) occupied was measured. The tapped density was calculated using following formula.

$$\rho t = M / V$$

Compressibility Index [29,30]

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by Compressibility Index. The value below 15% indicates a powder with give rice to good flow properties, whereas above 25% indicate poor flowability. This is calculated as follow

$$\% \text{ C.I.} = \rho t - \rho b / \rho t \times 100$$

Hausner ratio [29]

Hausner ratio is an indirect index of ease of powder flow. Hausner ratio is the ratio of tapped density to bulk density. Lower the value of Hausner ratio better is the flow property. Powder with Hausner ratio less than 1.18, 1.19, 1.25, 1.3- 1.5 and greater the 1.5 indicate excellent, good, passable, and very poor, respectively. It is calculated by following formula.

$$\text{Hausner ratio} = -\rho t / \rho b$$

Porosity [28,31]

Percent relative porosity (ε) was obtained using the relationship between apparent density (ρapp) and true density (ρtrue) which is calculated by following formula.

$$\varepsilon = (1 - \rho app / \rho true) \times 100$$

Void Volume[28]

Void volume (V) was obtained by difference between bulk volume (Vb) and tapped volume (Vp). Void volume can be calculated by following formula.

$$V = Vb - Vp$$

Angle of repose [29,31]

The angle of repose was determined using funnel method. Funnel can be fit vertically with stand at 6.3 cm. height. The opening end of funnel is closed with thumb until drugs are poured. The 5 gm. of powder was poured into funnel that can be raised vertically until a maximum cone hight (h) was obtained. Radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula.

$$\Theta = \text{Tan-1}(h / r)$$

POST- COMPRESSION CHARACTERIZATION[32]

Hardness

The test is done as per the standard methods. The hardness of three randomly selected tablets from each formulation is determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale is noted down in kg/cm^2

Thickness

The thickness of three randomly selected tablets from each formulation is determined in mm using a vernier caliper. The average values are calculated.

Uniformity of Weight

Weight variation test is done as per standard procedure. Twenty tablets from each formulation are weighed using an electronic balance and the average weigh are calculated. The permissible limits according to I.P. and U.S.P. are given in Table 3 [33,34.]

Table 3.The permissible limits of weight variation according to I.P. and U.S.P.

specification as per I.P.	
Average weight of tablet	**% deviation**
80 mg or less	10
More than 80 mg or less	7.5
250 mg or less	5
specification as per U.S.P.	
Average weight of tablet	**% deviation**
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

Friability

The friability of tablets using 10 tablets as a sample is measured using a Roche Friabilator. Tablets are rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets are then taken out, dedusted and reweighted. The percentage friability is calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

%Friability = (initial weight- final weight) x 100 (initial weight)

Drug Content

Ten randomly selected tablets from each formulation are finely powdered and fixed amount of powder is accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer (pH 6.8) or 0.1 N HCl solution. The flasks are shaken to mix the contents thoroughly and filtered. One ml of the filtrate is suitably diluted and drug content is estimated at respective wavelength using a double beam UV -visible spectrophotometer. This procedure is repeated thrice and the average value is calculated.

Wetting Time

The tablets wetting time is measured by a procedure modified from that reported by Bi et al. The tablet is placed at the center of two layers of absorbent paper fitted into a dish. After paper is thoroughly wetted with distilled water, excess water is completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet is then recorded using a stopwatch.

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 tissue paper and allowed to completely wet. The wetted tablet is then weighted. Water absorption ratio, R is determined using following equation.

$$R = 100 \times Wa - Wb/Wa$$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of tablet before water absorption

In- vitro Disintegration Time

Disintegration times for sublingual tablets are determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 or 0.1N HCl as medium. The volume of medium is 900 ml and temp is 37± 2 °C. The time in seconds is taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus is measured.

In- vitro drug release study [35]

In-vitro release rate of sublingual tablets are carried out using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus (Paddle method, basket method). The dissolution test is carried

out using 900 ml of 6.8 pH phosphate buffer or 0.1 N HCl, at 37± 20C and 50 rpm. A sample (5 ml) of the solution is withdrawn from the dissolution apparatus at different time intervals (min). The samples are replaced with fresh dissolution medium of same quantity. The samples are filtered and analyzed for drug after appropriate dilution by UV spectrophotometer at respective wave length. The percentage drug release is calculated using an equation obtained from the calibration curve.[35]

CONCLUSION

MDTs have better patient acceptance and compliance and may offer improved Biopharmaceutical properties – improved efficacy and better safety as compare to conventional dosage forms. MDTs will continue to provide enhanced commercial and therapeutic benefits. With continued development of new pharmaceutical excipients can expect the emergence of more novel technologies for MDTs in the day to come. The successful MDTs have good taste and rapid release properties. Never the less, almost all types of drugs indicated for chronic use are either formulated as MDTs or in the process of getting formulated. It will also help the physician to prescribe the alternative dosage form to pediatric and geriatric patients where swallowing of tablet is a significant problem.

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