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Dr. Sayeed Ahmad
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# TRUE MDTS: MOUTH DISINTEGRATING TABLETS OR MOUTH DISSOLVING TABLETS, A COMPARATIVE STUDY

Atul Kumar Gupta*[1], Manisha Dalal[1], Ashok Kumar[1], Dinanath Mishra[2], Shailendra Kumar Singh[2]

**Affiliation**

[1] M. M. College of Pharmacy, M. M. University, Mullana, Haryana (India)
[2] Department of Pharmaceutical Sciences, G. J. U. S & T., Hisar, Haryana (India)

**Abstract**

Recent advancements in technology provide feasible dosage alternative for patients having difficulty in swallow the tablets. Oral disintegrating and dissolving tablets are one of them and differ from traditional tablets in that they are designed to be dissolving on tongue rather than swallow whole. Various technology used in the manufacturing of mouth dissolving/disintegrating tablets are; freeze drying, direct compression, spray drying, sublimation etc. Many patented technologies like Durasolv®, Flash Dose®, Flashtab®, Oraquick®, Orasolv®, and Zydis® have also gained importance in the international market. Orodispersable tablets dissolve and/or disintegrate quickly in mouth with saliva without intake of water. Tablets which dissolve in mouth quickly without any residue, is true mouth dissolving tablets. The basic techniques for mouth dissolving tablets include use of highly water soluble ingredients with increases in porosity of tablet. Whereas tablet containing super-disintegrant for quick disintegration, are more appropriate termed as mouth disintegrating tablet. Commercially available mouth disintegrating products are; Nimulid-MD, Romilast, Torrox MT etc. Most of are based on rapidly disintegrating in saliva by using super disintegrates such as Microcrystalline Cellulose, Sodium Starch Glycolate etc and making slurry in mouth followed by swallowing giving rough texture in mouth. In conclusion, for mouth dissolving tablets, all the excipients should be highly water-soluble and research should be concentrated on complete dissolution of all ingredients rather than use of insoluble super disintegrates.

**Keywords:** Oro dispersible tablets (ODTs), Mouth dissolving/disintegrating tablets (MDTs), superdisintegrant, taste masking resins.

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## Introduction:

Formulation of feasible dosage alternative for older patients, children, bed ridden patients, mentally retarded, uncooperative, nauseated patients being desired as it become difficult to treat such patients for their cooperation to administer the conventional tablets1. Orodispersable tablets (ODTs), being best alternative of conventional tablets, defined as solid dosage form that disintegrates within seconds2. Two different types of dispersible tablets distinguished as one that disintegrates/dissolves quickly in mouth and swallowed without water intake3, while the other can be dispersed in water externally to form a dispersion4 which can be easily taken by the patient5. The ODTs

formulations have interesting features like exceptional taste masking ability6, extremely low disintegration time, and pleasant mouth feel7. The drugs which absorbed in mouth followed by oesophagus as drug slurry passes down to stomach, the bioavailability of the drug increased and this pre-gastric drug absorption results in bioavailability improvement8 thus reduction in drug dose, reduced side effects with improvement in clinical performance9. United States Food and Drug Administration (FDA)10 defined mouth dissolving and mouth disintegrating tablets as "A solid dosage form having medicinally active substances or ingredients which disintegrate quickly within seconds when placed in mouth with saliva contact11. Mouth dissolving and mouth disintegrating tablets are offering the combined advantages of both liquid and conventional dosage form but our aim of this review is to provide the basic difference between mouth dissolving and mouth disintegrating tablets.

**Essential requirement of mdts[12]:**

1. No need of water for administration as it should disintegrate, disperse and dissolves quickly in mouth.
2. Should have a pleasant mouth feel with pleasant taste and without residue in mouth after disintegration to avoid rough texture of tablet.
3. Patient compliance should be one of the most valuable requirements.

**Challenges in formulation of mdts:**

**1. Taste masking of drugs**

MDT technology is relatively new to the industry and had a significant impact on patients of all ages and masking of bitter taste become essential for MDTs for its commercial success. Taste masking of bitter drugs become necessity in case of oral administration and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents without affecting the bioavailability of drug. Bitter sensation of the drug is due to the signal produced from the taste receptor[13]. Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs. Two approaches are commonly used, first by reduced drug solubility in mouth or secondly by decreasing drug interaction with taste buds[14]. Approaches used in taste masking for liquid dosage form include use of flavor followed by viscosity modification and if failed, by ion exchange resin. In case of solid dosage form, chemical modification (Prodrug and salt formation), Host Guest locking, solid dispersion method effectively masked the unpleasant taste. Drug particle coating technique successfully masks the taste in all type of formulation.

**2. Quick disintegration of tablets**

In the case of MDTs, the total stay time of tablet in mouth remains few seconds (less than 60sec.)[1] and has to disintegrate and dissolve within mouth in the salivary fluid. So quick disintegration of MDTs being an important step for success of MDTs and may be achieved by different mechanism[15, 16] as

**a. Swelling and Deformation**

Swelling and deformation believed to be a mechanism in which disintegrant (superdisintegrant) impart the disintegration when added to the tablet formulation and works on the mechanism that disintegrant swells upon water absorption, breaks the tablet matrix due to induced localized stress within the tablet (figure 1) and thus increases the available space for fast release of the drug.

**b. Porosity and Capillary Action (Wicking)**

This mechanism impart its action by makes the tablet porous and provides the structure for fluid penetration into the tablet (figure 2). The fluid tends

to drawn into these pores by capillary action and rupture the tablet in small particles.


*Figure 1: tablet disintegration by swelling and deformation of disintegrating agents*

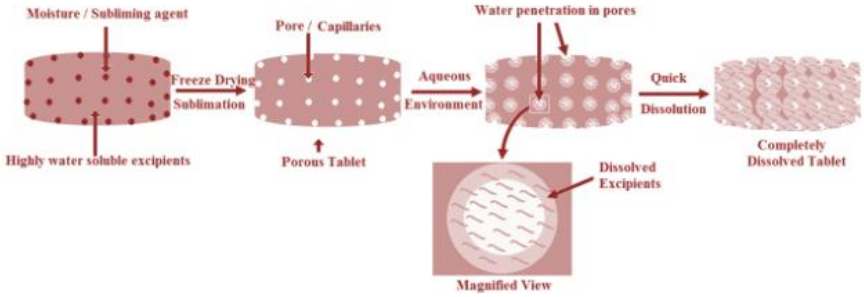


*Figure 2: Quick Dissolution*

### C. Enzymatic Reaction

Enzymes present in the body breaks the bond between particle and helps in disintegration by absorption of fluid, for examples in colon targeted drug delivery, tablets prepared using guar gum disintegrated in the colon by *E. coli*

### d. Release of Gases

Interaction between Sodium bicarbonate and citric acid produces carbon dioxide which generates pressure within the tablet and causes the disintegration of the tablet and must be added to the formulation before compression separately to avoid pre interaction.

### e. Industrial Adaptability

To make adaptable at industrial manufacturing, MDTSs should have adequate mechanical strength and durable to withstand the rigors of manufacturing[17], handling and environmental conditions (humidity) as well as cost effectiveness with adaptable and amenable to existing process and instruments[18].

### f. Patient compliance

MDTs overcome all the genuine swallowing problems in uncooperative patients in acute setting[19], compatibilty in term of taste[20], appearance, absence of grittiness (undissolved particles), no water requirement along with minimum stay in mouth[21] .

**Manufacturing Technology For Mdts**: - Manufacturing technologies used to prepare MDTs broadly divided into 3 generations on the basis of methods applied for preparation.

1st generation MDTs utilizes freeze-drying technique (Cardinal Health as Zydis®) which includes the drug suspension with specific additives and freeze dried followed by compression into tablets and shows fast dissolution in mouth, but offers some limitations such as the poor handling, friable and sensitive to moisture[22]. To overcome these limitations, Zydis® use supporting foil for packing.

In 2nd generation, MDTs prepared from wet mass of the drug and additives followed by drying/subliming of the tablets giving porous structure to the tablet and developed by Tushima[23]. In sublimation, volatile materials (such as camphor, menthol) compressed with highly soluble ingredients followed by sublimation to give highly porous table and disintegration time claimed as low as 25 seconds. In 3rd generation, tableting the dry mass of the drug and saccrides followed by moisture treatment gives Wowtab-Dry® a patented technology[24], which shows required hardness with quick disintegration and dissolution[25] Whereas OraSolv® prepared with foaming agents at low pressure compression and uses an effervescent technique for disintegration[26] and CO2 evolved due to effervescence gives "fizzing" sensation[27], which gives pleasant organoleptic sensation, so successfully utilized in OraSolv® patented technology[28].

PakSolv® uses a special packaging system which lowers the tablets friability during handling and storage[29].

**Comparative Study**

Tablet that contains insoluble taste masking resins and super disintegrant for quick disintegration in the mouth and does not dissolve in saliva but formulate dispersion which is easy to swallow without water, can be well termed as Mouth Disintegration tablet rather than Mouth Dissolving Tablets. In mouth disintegrating tablets, the basic challenges in formulating MDTs handled as

**1. Taste masking**

Taste masking in mouth disintegrating tablets normally done by ion exchange resins30 having salt forming groups in high molecular cross linked chain[31], chemically inert, free from local and systemic side effect, which have the ability to exchange counterions in aqueous solution surrounding them. As taste perception of bitter drugs is experienced in the mouth at taste buds, drug resinate complex does not release drug in mouth due of lack of exchangeable ions in the saliva and when comes in GIT fluids, complex brakes quickly and releases the drug[32]. Majority of MDTs containing bitter drugs are masked using cation exchange resins (table-1). Bitter cationic drugs get absorbed on to weak cationic exchange resins of carboxylic acid functionally to form the complex, which is not bitter. For complete taste masking of drug, higher concentration of resins (300-400 %) are exposed with drug for prolonged contact and drug binds with resin by weak ionic bond preventing dissociation in saliva.

***Table-1: Commonly used ion exchange resins for taste masking of MDTs***

| Type | Matrix Structure | Commercial Resins | Taste masked drugs |
|---|---|---|---|
| ***Weak cation*** | Methacrylic acid Divinylbenzene | Indion 204, Tulsion T-335, Amberlite IRC 50 | Gatifloxacin, Tramadol, Ondansterone, Norfloxacin, Ofloxacin, Roxithromycin, |
| | Methacrylic acid Divinylbenzene | Tulsion T-339 Indion 234, Amberlite IRP 88 | Diphenhydramine HCl, Ciprofloxacin, Chloroquinine |
| ***Strong cation*** | Polystyrene Divinylbenzene | Indion 244, Dowex 50, Amberlite IR 120 | Chlorpheneramine maleate, Ephedrine Hydrochloride |
| | Sodium polystyrene Divinylbenzene | Tulsion T-3 Amberlite IRP 69 Indion 254 | Dicyclomine, Dextromethorphen, Pseudoephedrine, Buflomedil, Rantidine |

### 2. Quick Disintegration

The basic principle in formulating mouth disintegrating tablets involved super disintegrant addition technique at optimum concentration to achieve rapid disintegration. Super disintegrants in comparison to classical disintegrant (starch) have very high swelling power with minimum viscosity effects[33], for example Isapghula seeds have high swellability, gives uniform and rapid disintegration at concentration of 5-15%[34]. Commonly used super disintegrants are modified starch, sodium carboxymethyl starch, sodium starch glycolate, modified cellulose includes crystalline cellulose and hydroxy propyl cellulose, crosslinked polyvinylpyrolidone[35].

### 3. Industrial Strength

Industries generally follows adaptable, easy techniques to produce a product so manufacturing of mouth disintegrating tablets widely produced at commercial level due to their higher mechanical strength, ease of production and all of this done at low cost. The mechanical strength of these tablets gives better results in respect to its hardness, better handling, and ordinary packing[18].

### 4. Patient compliance

In Patient compliance, absence of rough texture, grittiness being an important considerations and Mouth disintegrating tablets not upto the mark, that to be disintegrate using the salivary fluid within mouth. These MDTs consist of more than 70% insoluble ingredients including insoluble resins, Superdisintegrants which on disintegration makes suspension of the whole slurry rather than solution and giving rough texture to mouth and patient incompliance[19].

### Mouth Dissolving Tablets

Mouth dissolving tablets comprises highly water-soluble excipients rather than insoluble taste masking and disintegrating excipients and concentrated on complete dissolution of all ingredients in saliva within few seconds giving good patient compliance. The basic principle for mouth dissolving tablets involves absence of any insoluble ingredients and major focus on increasing the porosity of the tablet and incorporation of highly water soluble excipients[42]. Mouth dissolving tablets are easily administered by the patients who cannot swallow, such as bed ridden patients, elderly and stroke victims; patients who could not/refuse to swallow, such as psychiatric, pediatrics and geriatric patients. Good mouth feel property of true mouth dissolving tablets may change the sensing of medication as bitter pill[43].

***Table-2: -Few commercially available mouth disintegrating tablet***

| Trade Name | Active Drug | Manufacturer |
|---|---|---|
| Alavert | Loratadine | Wyeth |
| Allegra ODT | Fexofenadine | Sanofi Aventis |
| Aricept ODT | Donepezil | Eisai Co. |
| Clarinex RediTabs | Desloratadine | Schering-Plough |
| Claritin RediTabs | Loratadine | Schering-Plough |
| Clonazepam ODT[36] | Clonazepam | Par Pharmaceutical |
| FazaClo | Clozapine | AzurPharma |
| Klonopin Wafers | clonazepam | Roche |
| Lamictal ODT | lamotrigine | Eurand / GlaxoSmithKline |
| Loratadine Redidose[37] | loratadine | Ranbaxy |
| Maxalt-MLT | Rizatriptan | Merck & Co. |
| Mirtazapine ODT | Mirtazapine | Teva Pharmaceuticals |
| Mosid-MT | Mosapride Citrate | Torrent pharmaceuticals |
| Nimulide-MD | Nimuslide | Panacea Biotech |
| Niravam[38] | Alprazolam | Schwarz Pharma |
| Nurofen Meltlets | Ibuprofen | Reckitt Benckiser |
| Olanex Instab | Olanzapine | Ranbaxy Labs Ltd |

| | | |
|---|---|---|
| Ondansetron ODT | Ondansetron | Teva Pharmaceuticals |
| Orapred ODT | Prednisolone | Sciele Pharma |
| Parcopa | Carbidopa/levodopa | Schwarz Pharma |
| Prevacid SoluTab[39] | Lansoprazole | Takeda Pharmaceuticals |
| Remeron SolTab | Mirtazapine | Schering-Plough |
| Risperdal M-Tab[40] | Risperidone | Janssen |
| Romilast | Montelukcast | Ranbaxy Labs Ltd |
| Torrox MT | Rofecoxib | Torrent pharmaceuticals |
| UNISOM SleepMelts[41] | Diphenhydramine | Eurand / Chattem |
| Zelapar | Selegiline | Valeant Pharmaceuticals Int'l |
| Zofran ODT | Ondansterone | Glaxowellcome Middlesex, UK |
| Zomig-ZMT | Zolmitriptan | AstraZeneca |
| Zyprexa Zydis | Olanzapine | Eli Lilly and Company |

**Taste masking**

1. In mouth dissolving tablets, slight unpalatable taste can be masked successfully using flavors and sweetners (table-3) for examples, Wowtab® used sugar like excipients (mannitol) 44 and the Zydis® also uses these sweeteners[22] and flavors for taste masking[17]. In the DuraSolv® tablet, taste of hyoscyamine sulfate45 was successfully masked by incorporation of sweetener and a flavor46.

***Table-3: Commonly used natural flavoring agents for taste masking***

| *Taste* | *Masking agents* |
|---|---|
| ***Bitter*** | Lemon, Orange, Cheery, Grapefruit, Raspberry, Lime, Coffee, Chocolate |
| ***Sour*** | Lemon, Lime, Orange, Cherry, Grapefruit |
| ***Salty*** | Berries, Mints, Fennel, Anise, Grape |

In case of highly bitter drug, taste masking being an obstacle in formulation of mouth dissolving tablets[47]. In selective cases, Herbal excipients like Licorice, Coco powder effectively masked the taste, for example, taste masking of artemether by monoaminoglycyrrhzinate pentahydrate (extract of glycyrrhiza) [48]. Another rarely used but effective technique for soluble taste masking is solid dispersion technique which refers to solid products derived from at least two different components, generally a hydrophilic matrix49 and a drug, done by dissolving the both in common solvent and evaporating the solvent to give solid mass[50]. For example, solid dispersion of bitter drugs with Cyclodextrins in ethanol produces a water soluble matrix which effectively masked the bitter taste.

2. **Quick Disintegration/dissolution**

For tablets to disintegrate and dissolve quickly in saliva, mouth dissolving tablets utilizes highly water soluble porous excipients along with capillaries or pore creation in tablets[51]. Spray dried excipients posses highly porous structure which when compressed into tablets provide quick disintegration and reported to disintegrate within 30 second in aqueous media[52]. Freeze drying/sublimation technique, mainly used to formulate mouth dissolving tablets, creates pores on the surface of the tablet and also imparts a glassy amorphous structure to the excipients thus improving the dissolution of the formulation[53]. Release of gases (effervescence) also utilizes in formulating MDTs like Triaminic Softchews using OraSolv® patented technology commercialized by Novartis Consumer Health (Table-4)[54,55]

*Table-4: -Commercially available mouth dissolving tablets*

| MDTs Techniques | Marketed Products | Brand Name | Active Constituent | Company |
|---|---|---|---|---|
| Freeze Drying/ Sublimation | Zydis [53] | Zubrin | Tepoxalin | Schering Corporation |
| | Quicksolv | Propulsid quicksolv | Cisapride monohydrate | Janseen Pharmaceutica |
| | Lyoc [18] | Paralyoc | Acetaminophen | Cephlon |
| | Nanocrystal | Abbott's Tricor | Fenofibrate | Elan |
| Efferves cent | Orasolv | Tempra Quickl ets | Acetaminophen | Bristol-Myers Squibb |
| Spray Drying | Advatab [55] | Uniso n | Diphenhydramine Hydroclorid e | Eurand |
| Solid Dispersion | Flash Dose[56] | Zolpidem MDT | Zolpidem Tartrate | Biovail |
| | Shear Form | Tiazac | Diltizen Hydrochloride | Bioavail |
| Highly Water Soluble Excipients | Durasolv | Alavert | Loratidine | Astra Zeneca |
| | Wowtab [22] | Benadryl Fast Melt | Diphenhydramine Citrate | Pfizer |

## Industrial approach

The strength of the tablet is inversely proportional to the porosity, so mechanical strength being an important parameter with porosity. So there is a need of special packing to give sufficient mechanical strength thus producing a costly product.

## Patient compliance

Patient like formulations which have easy administration (small size, pleasant mouth feel, minimum saliva requirement for dissolution[56], disappear as soon as taken) and most of the mouth dissolving tablets comply with these requirements (table-5). Zyprexa Zydis® facilitated antipsychotic medication compliance in ill uncooperative patients.

*Table-5: Commonly used techniques in MDTs and comparative evaluation*

| MDTs Techniques | Taste masking | | Disintegrant | | | | Industrial Approaches | | | | Patient Compliance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Water insoluble agents | Water soluble agents | Swelling & deformation | Porosity | Release of gas | Highly Soluble Excipients | Mechanical strength | Industrial handling | Environmental sensitivity | Cost effective | |
| *Type* | Mouth Disintegrating Tablets | Mouth Dissolving Tablets | Mouth Disintegrating Tablets | Mouth Dissolving Tablets | | | | | | | |
| *Freeze Drying* | X | √ | X | √ | X | √ | X | X | X | X | √ |
| *Sublimation* | X | √ | X | √ | X | √ | X | X | X | X | √ |
| *Effervescent* | X | √ | X | X | √ | √ | √ | √ | X | √ | √ |
| *Spray Drying* | X | √ | X | √ | X | X | √ | X | X | X | √ |
| *Solid Dispersion* | X | √ | X | X | X | √ | √ | √ | √ | X | √ |
| *Direct Compression* | √ | X | √ | X | X | X | √ | √ | √ | √ | X |
| *Moisture Treated Tablets* | X | √ | X | √ | X | √ | √ | X | X | √ | √ |

**Current Scenario in Marketed Mdts**

Commercially available MDTs like Nimulid-MD, Romilast, Torrox MT (table-2) nowadays marketed under mouth dissolving tablets are actually mouth disintegrating tablets, which are perfect modified formulation of orodispersible tablets (ODTs) based on rapid disintegration in saliva by using super disintegrates such as Microcrystalline Cellulose, Sodium Starch Glycolate and making slurry in mouth followed by swallowing giving rough texture in mouth rather than complete dissolution and prepared by conventional tableting method using taste masking resins for taste masking of bitter drug, Superdisintegrants for quicker disintegration, flavors, and sweetners for patient compliance.

**Need of Research on Mouth Dissolving Tablets**

All the researchers working on MDTs concentrates their research on the disintegration behavior of the tablets using super disintegrants which does not full fill the basic requirements of the mouth dissolving tablets i.e. patient compliance. Industries who want to make a MDTs blindly incorporating insoluble taste masking resins, Superdisintegrants for disintegration and trading as mouth dissolving tablet and does not concentrate on formulating mouth dissolving tablets giving complete dissolution with minimum residue. Initially, mouth dissolving tablets comes into market was based upon freeze drying which still have best patient compliance. Due to lots of limitations like hardness, mechanical strength, no ease of manufacturing and most important cost of manufacturing, that's why, industries concentrate whole emphasis on the use of Superdisintegrants and make researchers not to work on mouth dissolving tablets instead moves on to mouth disintegrating tablets.

**Future Prospective**

Although the MDTs crossed the stage of its infancy indicated by arrival of a large number of commercial products in the market but holds a lot of potential for future oral dosage forms. A lot of improvement in formulation of true mouth dissolving tablets by inventing highly aqueous soluble taste masking agents and soluble disintegrants are required for better patient compliance.

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