Review Article

Mouth Dissolving Tablets – A Comprehensive Review

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ABSTRACT

From the last decade Mouth dissolving tablets are gaining more prominence as a novel drug delivery system & emerges as one of the popular & widely accepted dosage forms, especially for pediatric patients because of incomplete development of muscular & nervous system & in case of geriatric patients suffering from Parkinson's disorder or hand tremors, from both pharmaceutical industries as well as patients because they are convenient to be manufactured & administered, free of side effects, offering immediate release & enhance bioavailability , so as to achieve better patient compliance. MDT is a good choice of drug delivery for pediatric & geriatric patients because it troubleshoots the problem of dysphagia i.e. difficulty in swallowing which is seen in many elderly patients. Mouth dissolving tablets offers rapid disintegration so as it dissolves very fast in saliva & then easily swallowed without the need of water which is a major benefit over conventional dosage form. The popularity and usefulness of the formulation resulted in development of several mouth dissolving tablet technologies for preparation. The current article is focused on ideal characteristics, advantages and disadvantages, formulation aspects, formulation technologies, evaluation of products and future potential. Various marketed preparations along with numerous scientific advancements made so far in this avenue have also been discussed.

Keywords: Disintegration, freeze drying, mouth dissolving tablet, sublimation, superdisintegrant.

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1. INTRODUCTION [1-9]

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. Tablets and capsules are currently accounted for the highest proportion of all drug presentations. This is because of several reasons like

- ✓ Ease of administration.
- ✓ Accurate dosage.
- ✓ Self- medication.
- ✓ Pain avoidance.
- ✓ Patient compliance.

The most common solid dosage forms in contemporary use are tablets, which may be defined as unit forms of solid medicaments prepared by compaction. Now there are many types of tablet formulations that provide for the release of drug to be delayed or control the rate of the drug's availability but one important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing for many patients almost 50% of the population is affected by such problem.

This problem of dysphagia/swallowing conventional dosage forms is seen mainly in case of pediatric patients because of incomplete development of muscular & nervous system & in case of geriatric patients suffering from Parkinson's disorder or hand tremors also it can be seen in case of mentally ill & bedridden patients, patients who are uncooperative or nauseated, patients having persistent cough or gag reflex also in case of certain medical conditions like stroke, motion sickness, sudden episode of allergic attack, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy.

To overcome all these problems scientist have developed an innovative new drug delivery system known as mouth dissolving drug delivery or fast dissolving drug delivery system. Mouth dissolving tablets are those when placed on tongue, disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. As drug goes faster into solution, quicker is the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The dispersible tablets allows dissolution or dispersion in water prior to administration but the mouth dissolving tablets instead of disintegrating or disintegrating in water is expected to dissolve or disintegrate in oral cavity without drinking water. The disintegrated mass then slides down smoothly along the esophagus with saliva. Mouth dissolving tablet is also known as Orally disintegrating tablet, Orodispersible tablet, Fast dissolving tablet, Fast disintegrating tablet, Quick disintegrating tablets, Porous tablet, Rapimelt tablets, Rapid dissolving tablets, Melt in mouth tablet.

The centre for drug evaluation and Research defines orally disintegrating tablets as a dosage form "A solid dosage form which disintegrates rapidly within a matter of seconds when placed under the tongue". The disintegrating time for orally disintegrating tablet varies from seconds to minutes, depends upon the size of tablet and formulation. European pharmacopeia defined orally disintegrating tablets as "Uncovered tablet which disperse before ingestion in the buccal cavity".

1.1 Desired Criteria for MDDS

Mouth Dissolving Tablets should [10-11]

- ✓ Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- ✓ Be compatible with taste masking.
- ✓ Be portable without fragility concern.
- ✓ Have a pleasing mouth feel.
- ✓ Leave minimal or no residue in the mouth after oral administration.
- ✓ Exhibits low sensitivity to environmental conditions as humidity and temperature.
- ✓ Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

1.2 Salient Features of MDDS

- ✓ Ease of administration to pediatric, geriatric and psychiatric patients who refuse to swallow tablets.
- ✓ To swallow the dosage form, water not required which is highly convenient feature for patients who are depressed.
- ✓ Good mouth feel property helps to change the basic impression of bitter medication.
- ✓ Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- ✓ Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs.
- ✓ Ability to provide advantage of liquid medication in the form of solid preparation.

1.3 Advantages of Mouth Dissolving Tablets

- ✓ Leave minimal or no residue in mouth after administration.
- ✓ Rapid drug therapy intervention.
- ✓ Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- ✓ Administration to such as pediatric, geriatric & psychiatric patients.
- ✓ Achieve increased bioavailability/rapid absorption through pregastric absorption.
- ✓ Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- ✓ The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- ✓ Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.

- ✓ An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- ✓ It provides advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- ✓ High degree of vascularization, minimal enzymatic pool and passing of first pass metabolism increase bioavailability of drugs ideally suited for delivering drugs that are absorbed buccally.
- ✓ In condition of pain their rapid disintegration also impose a placebo effect before the medicine's effect actually begins and patient get relief quickly.

1.4 Limitations of Mouth Dissolving Tablets

- ✓ 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 properly.
- ✓ Drugs with relatively larger doses are difficult to formulate into MDT.
- ✓ Patients who concurrently take anticholinergic medications & patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

2. Drug candidates suitable for Mouth dissolving tablets [12]

Selection of drug candidate for MDT is a very crucial step while developing such dosage forms because of the following factors:

- ✓ Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
- ✓ Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- ✓ Patients with Sjogren‟ s syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
- ✓ Drugs with a short half-life and frequent dosing.
- ✓ Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- ✓ The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g. selegiline, apomorphine, buspirone etc.
- ✓ The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.
- ✓ Drugs having ability to diffuse and partition into the epithelium o f the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.

3. Challenges in Formulating MDT

The challenges in formulating MDT are given as [13, 14]

3.1 Faster disintegration

MDT's should disintegrate rapidly in matter of seconds.

3.2 Palatability

As most drugs are unpalatable, mouth dissolving drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

3.3 Mechanical Strength

In order to allow MDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost.

3.4 Hygroscopicity

Several mouth dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

3.5 Amount of Drug

The application of technologies used for MDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400mg for insoluble drugs and less than 60mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

3.6 Aqueous Solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

3.7 Size of Tablets

The degree of ease when taking tablets depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8mm while the easiest size to handle was one larger than 8mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

3.8 Amount of drug

According to USP generally, the ODT tablet weight should not exceed 500 mg. For lyophollized dosage form the drug dose should be lower than 400 mg for insoluble drug & less than 60 mg for soluble drug.

3.9 Good packaging design

For protection of MDT's from moisture & other environmental hazards the package design should be considered early in the development stages.

4. Excipients used for preparation of MDT [6, 15-19]

4.1 Superdisintegrants: The proper choice of disintegrant or superdisintegrant and its consistency of performance are of critical importance to the formulation development of mouth dissolving tablets. Disintegrants are substances or mixture of substances added the drug formulation that facilitates the breakup or disintegration of tablets or capsules content into smaller particles that dissolve more rapidly than in the absence of disintegrants & helps in fast release of drug. The development of fast dissolving or disintegrating tablets provides an opportunity to take an account of tablet disintegrants. Recently new materials termed as superdisintegrant have been developed to improve the disintegration processes. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablets. The stronger the binder, the more effective must be the disintegrating agents in order for the tablets to release its medication. Ideally, it should cause the tablets to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared.

4.2 Method of Addition of Disintegrants [15, 18]

The requirement placed on the tablet disintegrants should be clearly defined. The ideal disintegrant has:

- ✓ Poor solubility
- ✓ Poor gel formation
- ✓ Good hydration capacity
- ✓ Good molding and flow properties
- ✓ No tendency to form complexes with the drugs

There are three methods of incorporating disintegrating agents into the tablets:

1. Internal Addition (Intragranular)
2. External Addition (Extragranular)
3. Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression.

In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules.

Partly Internal and External, When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the

granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

Table 1: Disintegrants used in MDT's [15]

Disintegrants	Mechanism	Conc. %w/w
Starch	It enables water to draw into the structure by capillary action, thus leading to disruption of tablet.	5-20
Pregelatinized starch	It increases dissolution rate by rapid disintegration due to superior swelling capacity.	5-15
Sodium Starch Glycolate (Explotab and Primogel)	It absorbs water readily leading to an increase in volume of granules result in rapid and uniform disintegration.	1-3
Cross-linked polyvinyl Pyrrolidone *(CrossPovidone, CrosspovidonM®,Kollidon®,Polyplasdone®)*	It acts by capillary action water is responsible for its tablet disintegration property.	0.5-5
Cellulose (Ac-Di-Sol, Nymce ZSX®, Primellose®, Solutab®)	They have ability to swell on contact with water results in rapid tablet disintegration.	1-3
Microcrystalline Cellulose (Avicel)	Allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals	10-20
Alginates (Alginic Acid, Satialgine®)	It has High affinity for water absorption and high sorption.	1-5
Soy polysaccharides (Emcosoy®)	Rapid swelling in aqueous medium orwicking action, it does not contain any starch or sugar.	5-15
Gums (Guar Gums, Gum Karaya, Agar, Gellan Gum)	Swells in water	3-8
Chitin and Chitosan	Moisture sorption and water uptake	1-5
Smecta	It has a large specific area and high affinity for water makes it good disintegrant	5-15
Isapghula Husk	It has high swellability and gives uniform and rapid disintegration	5-15
Polacrillin Potassium	It swells up at very fast rate upon contact with water or gastro intestinal fluid and act as an effective tablet disintegrant.	10-20
Ion Exchange Resins, Ambrelite IPR 88, Indion, Doshion	Resins have ability to swell in the presence of water, showed Disintegration of tablet.	0.5-5
Gas – Evolving disintegrants (Citic Acid , tatric Acid, Sodium Bi Carbonate)	These react in contact with water to liberate carbon dioxide that Disrupts the tablet.	>10%

4.3 Mechanism of Action of Disintegrants [16, 18, 19]

a) By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

b) By swelling

Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablets with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down

c) Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet.

d) Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets.

e) By enzymatic reaction

Enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

f) Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Particle repulsion theory proposes that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

g) Due to deformation

During tablets compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablets.

4.4 Sweeteners and sugar based excipients: Sugar based excipient act as bulking agents. They exhibit high aqueous solubility and sweetness and impart taste masking property e.g. Aspartame, Sugar derivative, Dextrose, Fructose, Mannitol, Sorbitol, Maltose etc.

4.5 Flavors: It increases patient compliance and acceptability. e.g. Vanilla, Citrus oil, Fruit essence, Eucalyptus oil, Clove oil, Peppermint oil etc.

4.6 Surface Active agents: It reduces interfacial tension and thus enhances solubilization of ODTs. e.g. Sodiumlaurlysulfate, Sodiumdoecylsulfate, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene stearte etc.

4.7 Binder: It maintains integrity of dosage form. Examples are-PVP, Polyvinylalchol, Hydroxy propyl methylcellulose.

4.8 Colour It enhances appearance and organoleptic properties of dosage form. Examples are-Sunset yellow, Red iron oxide, Amaranth.

4.9 Lubricants It helps reduces friction and wear by introducing a lubricating film. Examples are-Stearic acid, Magnesium stearte, Zinc stearte, Talc, Polyethylene

glycol, Liquid paraffin, Colloidal silicon-di-oxide etc.

4.10 Fillers It enhances bulk of dosage form. Examples are-Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate, Calcium sulfate, Magnesium trisilicate etc.

5. Excipients Updates for Orally Disintegrating Dosage Form [20, 21] Nowadays different varieties of co-processed excipients are available which fulfills special requirements, such as being soluble in water, pleasant taste, mouth feel, sweetness, and rapid dispersibility. Compared with existing excipients, the improved physical, mechanical, and/or chemical properties of such excipients have helped in solving formulation problems such as flowability, compres-sibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation. The composition & characteristics of these excipients are shown in (**Table 2**).

Table 2: Composition & characteristics of excipients

Excipient	Composition and Characteristics
Ludiflash	Coprocessed blend of 90% Mannitol, 5% Kollidon® CL-SF(Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate)
F-MELT	Coprocessed blend of carbohydrates, disintegrant and inorganic in-gredients F-melt are commercially available Type C &Type M
Modified chitosan with silicon dioxide	Co precipitation of chitosan and silica, It acts as superdisintegrant and filler
Orocell 200 & OroCell 400	Spheronised mannitol with a binder, filler and carrier property Orocell 200 with 90% mannitol (<315µm) Orocell 400 with 90% mannitol (<500µm).
Mannogem EZ	Spray dried Mannitol Sweet taste (50%) as sweet as sucrose
Pearlitol SD	Spheronised granulated mannitol Pearlitol® 100SD, Mean diameter: 100 µm Pearlitol® 200SD Mean diameter 180 µm Sweetening power about 40% that of sucrose
Advantose	Spray dried disaccharide carbohydrate maltose powder
Glucidex IT	Agglomerated spray dried range of maltodextrins.
GalenIQ	Isomalt, a disaccharide alcohol act as fillers and binders
Polacrilin Potassium	Potassium salt of a cross linked polymer derived from methacrylic acid and divinyl benzene
Cellactose	MCC, lactose highly compressible, good mouth feel, low cost
Ludipress	Lactose, PVP, Crosspovidone , It has good flowability, low hygroscopicity, hardness independent of machine speed.
Starlac	Lactose, maize starch, It has Good flow.
Pharmatose DCL 40	Anhydrous lactose, lactitol, It has High compressibility, low lubricant sensitivity.
Avicel CE-15	MCC, Guar gum, It has good palatability, less grittiness, reduced tooth packing.
Prosol	MCC, colloidal silica, It has Better flow, hardness, reduced friability
Di-Pac	Sucrose, dextrin, It is Directly compressible.
Advantose FS-95	Fructose, starch
Finlac™ DC	Directly compressible lactitol
Plasdone S-630	Vinyl acetate, Vinyl pyrrolidone
Lycatab C	Filler disintegrate for hard gelatin capsules, Binder disintegrate for direct compression, flow aid in powder blends

6. Techniques for Preparing Mouth Dissolving Tablets

The different technique for formulating mouth dissolving tablets are given as [22-25]

6.1 Technologies Employing Heating Process

6.1.1 Cotton Candy Process or its Modifications: This process is also known as the "candy floss" process and forms the basis of Flash Dose technology. In this process formulation of matrix is carried out from saccharides or polysaccharides which are then processed into amorphous floss by simultaneous action of flash melting and centrifugal force. There are various preblend mixtures used in the manufacture of 'floss'. The matrix is then cured or partially recrystallised to provide a compound with active ingredients and other excipients and subsequently compressed to form an ODT. However, the high processing temperature limits the use of this technology to thermostable compounds only.

6.1.2 Tablet molding

6.1.2.1 Compression molding (solvent method): Tablet produced by molding are solid dispersion. Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is generally made from water soluble sugars. The manufacturing process of molding tablets involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mold plates to form a wetted mass. The solvent is then removed by air drying. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

6.1.2.2 Heat molding: It involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at 30^0C under vacuum. Another process used is called no-vacuum lyophilisation, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure.

6.1.3 Mass extrusion: It 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.

6.1.4 Sublimation: In this process substance directly gets converted to the gas phase without passing through an intermediate liquid phase. It involves formation of a porous matrix, by incorporating volatile ingredients in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, menthol, camphor, naphthalene, urea, urethane or phthalic anhydride could be compressed along with other excipients into a tablet. The volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique are reported to usually disintegrate in 10-20secs. Solvents like cyclohexane, benzene could be used for generation of porosity in the matrix.

6.1.3 Wet granulation: Wanare R S *et al* (2012) prepared fast dissolving tablets containing Azithromycin. A combination of superdisintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone were used as intragranularly in different concentrations. The prepared fast disintegrating tablets were evaluated for weight variation, content uniformity, hardness, disintegration time, wetting time and friability of tablets. Wetting time of formulations containing sodium starch glycolate was least and tablets showed fastest disintegration. The capecitabine tablet (approved for colon and breast cancer) prepared by using traditional disintegrants such as lactose and croscarmellose sodium is not easily swalloable due to its high dose and requires approximately 7-12 minutes for disintegration in water depending on the size of the tablet. This is because the tablet disintegrates by surface

erosion and is not amenable to rapid dispersion or disintegration in water prior to oral administration to swallowing- compromised patients.

6.2 Technologies not Employing Heating Process

6.2.1 Freeze Drying: Freeze drying is the process in which water is sublimed from the product after it is frozen. It creates an amorphous porous structure that can dissolve rapidly. In this process active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. 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.

6.2.2 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.

6.2.2.1 Addition of disintegrants

Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution.

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of fast dissolving tablets.

6.2.2.2 Sugar based excipients

This is another approach to manufacture FDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel. Sugar-based excipient is classified into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

Mouldability is defined as the capacity of the compound to be compressed/molded. The mouldability of type 1 saccharides can be improved by granulating it with type 2 saccharides. Most commercial FDTs have been developed using mannitol as the bulk excipient of choice. Mannitol is overwhelmingly preferred over lactose because of its extremely low hygroscopicity, excellent chemical and physical compatibility, good compressibility and better sweetness. FDT formulators prefer to use a directly compressible mannitol, which enables the preparation of robust tablets that can withstand processing and transportation. Specially textured directly compressible, spray-dried, or granulated mannitol excipients have been designed to meet these needs. These excipients under defined manufacturing conditions gives a highly porous structure and friable exterior structure which helps in faster disintegration of FDT, they also provide a satisfactory mouth feel and so suitable for use in preparation of harder FDT by direct compression at low pressure.

6.2.3 Effervescent Disintegration System:

In this process, effervescent excipient (known as effervescent couple) is prepared by coating the organic acid crystals with alkaline material. The particle size of the organic acid crystals is chosen to be larger than the alkaline material to ensure uniform coating. The coating process is initiated by the addition of a reaction initiator (water)

and the reaction is allowed to proceed to the extent of completing the coating of alkaline material on organic acid crystals. The required end point of coating is determined by measuring carbon dioxide evolution. Then, the excipient is mixed with the active ingredient & standard tableting excipients and finally compressed into tablets. Saliva activates the effervescent agent, causing the tablet to disintegrate.

6.2.4 Spray drying: In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose sodium or crosspovidone as a superdisintegrant , acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). Tablets manufactured from spray dried powder have been reported to disintegrate in less than 20 secs in aqueous medium.

6.2.5 Nanonization: It involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

7. Patented Technologies for Fast Dissolving Tablets:

Each technology has a different mechanism, and each Mouth dissolving / disintegrating dosage form varies regarding to mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of drug formulation in saliva, swallowability, rate of absorption from the saliva solution.

The patented technologies for fast dissolving tablets are given as [26-28]

7.1 Zydis Technology: This technology uses freeze drying process for manufacturing of the tablets, in which the active drug is incorporated in a water-soluble matrix, which is then transformed into blister pockets and freeze dried to remove water by sublimation. Matrix is made up of a number of ingredients like gelatin, dextran or alginates to impart strength during handling these form a glossy and amorphous structure, mannitol or sorbitol is added to impart crystallinity, elegance and hardness, various gums may be added to prevent sedimentation of dispersed drug particles. Collapse protectants like glycine may be used to prevent shrinkage of dosage form during freeze drying and long term storage. The main advantage of this technology is convenience and disadvantage is that the freeze drying process is quite expensive process. These products are packed in blister packs to protect the formulation from environmental moisture. When put into the mouth, Zydis unit quickly disintegrates and dissolves in saliva.

7.2 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 is used to prepare the tablets.

7.3 Durasolv Technology: Durasolv has much higher mechanical strength due to the use of higher compaction pressures during tableting. 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. Durasolv is so durable that it can be packaged in either traditional blister packaging or vials.

7.4 Wowtab Technology: 'wow' means 'without water'. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldability saccharides and then compressed into tablets.

7.5 Shearform Technology: In this procedure, 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 fling the floss. The floss so produced is amorphous in nature so it is further chopped and recrystallized. The recrystallized matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablets. The active ingredients and other excipients can be blended with floss before carrying out recrystallisation.

7.6 Ceform Technology: This technology involves preparation of microspheres of the active drug. Drug material alone or in combination with other pharmaceutical substances, and excipients is placed into a precision engineered rapidly spinning machine. The centrifugal force comes into action, which throws the dry drug blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form a sphere, without affecting the drug stability. The microspheres thus formed are compressed into tablets. As the drug and excipients both can be processed simultaneously, it creates a unique microenvironment in which the materials can be incorporated into the microspheres that can alter the characteristics of the drug, such as enhancing solubility and stability.

7.7 Flashdose Technology: The FlashDose technology uses a unique spinning mechanism so as to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the drug and be compressed into a tablet. The final product which is being produced has a very high surface area for dissolution. It disperses and dissolves quickly once placed on the tongue. The Flash dose tablets consist of self–binding shear form matrix termed as “floss”.

7.8 Flashtab Technology: In this technology, microgranules of the taste-masked active drug are used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion spheronisation. All these processes utilize conventional tableting technology. These taste-masked microcrystals of active drug, disintegrating agent, a swelling agent and other excipients like soluble diluents etc are compressed to form a multiparticulate tablet that disintegrates rapidly.

7.9 Nanocrystal technology: NanoCrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust. The freeze-drying approach also enables small quantities of drug to be converted into FDT dosage forms because manufacturing losses are negligible.

7.10 Advantol 200: Advantol 200 is a directly compressible excipient system offering "Soft-Melt" functionality and specially formulated for nutraceutical applications.It requires no special manufacturing equipment or tooling. It utilize a standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions to make robust “soft-melt” tablets.

7.11 Advatab: AdvaTab is distinct from other technologies as it can be combined with Eurand’s complimentary particle technologies like Microcaps taste-masking technology and its Diffucaps, controlled release technology. The pairing of AdvaTab with Microcaps creates products that offer the dual advantage of a patient preferred dosage form, together with a superior taste and smooth mouth feel.

7.12 Frosta Technology: It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder.

7.13 Oraqick Technology: The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disinte-grating technologies makes OraQuick appropriate for heat sensitive drugs.

7.14 Pharmaburst Technology: The tablet manufactured by this process involves a dry blend of a drug, flavors, and lubricant then followed by compression into tablets which then dissolve within 30-40 seconds. Tablets manufactured by this methodology have sufficient strength can be packed in blister packs and bottles.

7.15 Lyoc: Lyoc utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. It produces tablet by direct compression of powdered mixture with external lubrication.

8. Evaluation of MDTs

8.1 Precompression parameters [29, 30]

Evaluation of blend for the following parameters to be carried out before compression of MDT's

i) **Untapped Bulk Density:** Powder weighing 10 g is placed into 100 ml measuring cylinder. Volume occupied by the powder wis noted without disturbing the cylinder and bulk density is calculated by the following equation:

$$\text{Untapped Bulk Density} = \frac{\text{Mass of bulk drug}}{\text{Volume of bulk drug}}$$

ii) **Tapped Bulk Density:** Powder weighing 10 g is placed into 100 ml measuring cylinder. The cylinder is then subjected to a fixed number of taps (~100 times) until the powder bed volume had reached the minimum level. The final volume is recorded and the tap density is calculated by the following equation:

$$\text{Tapped Bulk Density} = \frac{\text{Mass of bulk drug}}{\text{Volume of bulk drug on tapping}}$$

iii) Compressibility: Compressibility of the drug is found out using the following formula:

$$\% \text{ Compressibility} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

iv) Hausner Ratio: Hausner of the drug is found out using the following formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

v) Angle of repose: The angle of repose gives an indication of the flow ability of the substance. Funnel is adjusted such that the stem of the funnel lies 2 cm above the horizontal surface. The drug powder is allowed to flow from the funnel under the gravitational force till the apex of the pile just touched the stem of the funnel, so the height of the pile is taken as 2 cm. drawing a boundary along the circumference of the pile and taking the average of six diameters determined the diameter of the pile. These values of height and diameter are then substituted in the following equation:

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left(\frac{2h}{d}\right)$$

Where, h - Height of the pile and d - Diameter of the pile.

8.2 Evaluation of tablets

All formulated MDT's are subjected to following quality control tests [31, 32]

8.2.1 Weight variation: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

Table 3: Weight variation

S.No.	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	More than 324	5

8.2.2 Hardness*:* The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester, Dr. Schleuniger Pharmatron-5Y etc.

8.2.3 Friability: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to

Withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the tablets which have average weight more than 6.5gm from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. The percentage of friability can be calculated using the formula

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test,

W2 = Weight of tablet after test

8.2.4 Disintegration test: The test was carried out on six tablets using distilled water at 37^{0}c ± 2^{0}c was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

8.2.5 Wetting time: Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablet is another important parameter, which needs to be assessed to give an insight into capillarity and subsequently the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. Wetting time was determined by method described. A piece of tissue paper folded twice was placed in a small Petri dish (I.D = 6.5 cm) containing 6 ml of water at room temperature. A tablet was put on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded in second.

8.2.6 Water absorption ratio*:* A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determine by using following formula

R= 100 x Wa-Wb / Wb

Where, Wb is the weight of tablet before water absorption

Wa is the weight of tablet after water absorption

8.2.7 In-vitro dispersion time: Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C. Time required for complete dispersion of a tablet was measured.

8.2.8 In-Vitro dissolution test: *In-vitro* dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. The amount of drug dissolved is determined by suitable analytical technique.

8.2.9 Stability Studies: The optimized formulation of MDTs is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics.

Table 4: Category of drugs promising to be incorporated in MDTs [33]

Analgesics and Anti inflammatory Agents	Aloxiprin, Auranofin, Azapropazone, Etodolac, Fenbufen, Flurbiprofen, Indomethacin, Ketoprofen, Mefenamic acid, Nabumetone, Naproxen, oxaprozin, Phenylbutazone, Piroxicam, Sulindac.
Anti-coagulants	Dicoumarol, dipyridamole, nicoumalone, phenindione
Anti-arrhythmic Agents	Amiodarone HCl, Disopyramide, flecainide acetate, quinidine sulphate
Anti-bacterial Agents	Benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem
Anthelmintics	Albendazole, bephenium hydroxynaphthoate, cambendazole, ivermectin, mebendazole
Anti-depressants	Amoxapine, ciclazindol, maprotiline HCl, mianserin HCl, nortriptyline HCl, trazodone HCl, trimipramine maleate.
Anti-hypertensive Agents	Amlodipine, carvedilol, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, minoxidil, nicardipine HCl.
Anti-diabetics	Acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide.
Local Anaesthetics	Lidocaine
Anti-fungal Agents	Amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole
Anti-epileptics	Beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, parame thadione, phenacemide, phenobarbitone
Anti-gout Agents	Allopurinol, probenecid, sulphinpyrazone.
Anti-parkinsonian Agents	Bromocriptine mesylate, lysuride maleate
Anti-malarials	Amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl,mefloquine HCl, proguanil HCl, pyrimethamine, quinine sulphate.
Anti-muscarinic Agents	Atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, mepenzolate bromide, orphenadrine, oxyphencylcimine HCl, tropicamide
Anti-neoplastic agent and Immunosuppressants	Aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane.
Cardiac Inotropic Agents	Amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin.
Anxiolytic,Sedatives, Hypnotics & Neuroleptics	Alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clotiazepam, clozapine, diazepam, droperidol, ethinamate.
ß-Blockers	Acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol,propranolol.
Nitrates and other Anti anginal Agents	Amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbidemononitrate, pentaerythritol tetranitrate.

Table 5: List of Marketed Mouth Dissolving Tablets [34]

S. No.	Trade Name	Active Drug	Manufacturer
1.	Felden fast melt	Piroxicam	Pfizer Inc., NY, USA
2.	Claritin redi Tab	Loratidine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
4.	Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merck and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7.	.Zyprexa Zydis	Olanzapine	Eli Lilly and Company
8.	Citalopram ODT	Citalopram	Biovail
9.	Metoclopramide Zydis	Metoclopramide	Salix Pharmaceuticals
10.	Reglan ODT	Metoclopramide	Schwarz Pharma
11.	Parcopa	Carbidopa/levodopa	Schwarz Pharma
12.	Prevacid SoluTab	Lansoprazole	Takeda Pharmaceuticals
13.	Remeron SolTab	Mirtazapine	Schering-Plough
14.	Risperdal M-Tab	Risperidone	Janssen
15.	UNISOM SleepMelts	Diphenhydramine	Chattem
16.	Zomig-ZMT	Zolmitriptan	AstraZeneca
17.	Zeplar TM	Selegilline	Amarin Corp., London, UK
18.	Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
19.	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
20.	Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
21.	Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
22.	Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
23.	Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi,
24.	Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA
25.	Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceutics
26.	Spasfon Lyoc	Phloroglucinol Hydrate	Farmalyoc
27.	Nurofen FlashTab	Ibuprofen	Ethypharm
28.	Allegra ODT	Fexofenadine	Sanofi Aventis
29.	Orapred ODT	Prednisolone	Sciele Pharma
30.	Abilify Discmelt	Aripiprazole	Otsuka America/Bristol -Myers Squibb

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. MDTs prepared by direct compression usually have good mechanical properties, and the strength can

be enhanced further by subsequent treatment, such as moisture treatment.. Considering the many benefits of MDTs, it is only a matter of time until a majority of oral formulations are prepared in MDT forms.

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