MOUTH DISSOLVING TABLETS: A FUTURE COMPACTION

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ABSTRACT:
An orally disintegrating tablet or mouth dissolving tablet (MDT) is a drug dosage form available for a limited amount of over-the-counter (OTC) and prescription medications. MDTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. A variety of pharmaceutical research has been conducted to develop new dosage forms. Among the dosage forms developed to facilitate ease of medication, the mouth dissolving tablet (MDT) is one of the most widely employed commercial products. As our society is becoming increasingly aged, the development of mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and travelling and may not have access to water. Such formulations provide an opportunity for product line extension in the many elderly persons will have difficulties in taking conventional oral dosage forms (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Recent development in fast disintegrating technology mainly works to improve the disintegration quality of these delicate dosage forms without affecting their integrity. This article focuses on the patented technologies available and the advances made so far in the field of fabrication of mouth dissolving tablets. Apart from the conventional methods of fabrication, this review also provides the detailed concept of some unique technologies like freeze drying, direct compression, spray drying, tablet molding, sublimation, fast dissolving films cotton candy process, along with their advantages and limitations.

Keywords: Fast disintegrating tablets, Direct compression, Disintegration time, Super-Disintegrants, spray drying, sublimation, freeze drying etc.

INTRODUCTION
Difficulties with and resistance to tablet-taking are common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric, and psychiatric patients. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, rapid-dissolving oral drug formulations have been developed to overcome problems related to swallowing difficulties 1. Over a decade, the demand for development of mouth disintegrating tablets (MDTs) has enormously increased as it has significant impact on the patient compliance. It has been reported that dysphagia (difficulty in swallowing) common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications 2. For this reasons, tablets that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention. Also, possibilities of missing out the doses will be minimized because this dosage form will encourage the patient to adhere to dosage regimen and provide patient compliance. The use of orally disintegrating tablets would facilitate dose administration even during travelling or in cases where there is no access to water. MDTs are solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water. MDT can be prepared by various methods such as freeze drying, sublimation of volatile salts, addition of superdisintegrant, wet compression method and use of sugar based excipients. The problem of certain MDT is their low physical resistance and high friability. This work describes a new approach to prepare MDT with sufficient mechanical integrity, involving the use of sugars by melt granulation technique. Sugars not only have good compatibility but also have good solubility which will help in faster disintegration 3. Addition of super disintegrating agent in the formulation is one of the approaches to formulate orodispersible tablets. Orally disintegrating tablets contain wide variety of pharmaceutical active ingredients covering many therapeutic categories. The time for disintegration of orally disintegrating tablets are generally considered less than one minute. Orally disintegrating tablets are characterized by high porosity, low density and low hardness. When administered, an in-situ suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed 4.

Overview of oral mucosa
The anatomical and physiological properties of the oral mucosa have been extensively reviewed by several authors. The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Figure. 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss. Beneath the epithelium are the basement membranes, lamina propria and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingival (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The
masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propria tightly binds the mucosa to the underlying peristomeum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propria and a sub mucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces which are both keratinized and some non-keratinized.

**Salient feature of fast dissolving drug delivery system**:  
- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.  
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.  
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.  
- 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 increased.  
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.  
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.  
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.  
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.  
- Beneficial in cases such as motion sickness, sudden 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.  
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

**Ideal properties of MDTs**:  
- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.  
- Allow high drug loading.  
- Be compatible with taste masking and other excipients.  
- Have a pleasing mouth feel.  
- Leave minimal or no residue in the mouth after oral administration.  
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.  
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.  
- Be adaptable and amenable to existing processing and packaging machinery.  
- Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.  

**Advantages of MDTs**:  
- 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 the patients who can not swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.  
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.  
- Convenient for administration and patient compliant for disabled, bedridden patients and for travellers and busy people, who do not always have access to water.  
- The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.  
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.  
- No specific packaging required can be packaged in push through blisters.  
- Cost effective.  
- Good chemical stability as conventional oral solid dosage form.  
- Provide advantage of liquid medication in form of solid preparation.  
- Adaptable and amenable to existing processing and packaging machinery.  
- Rapid onset of action.

**Challenges in MDTs**:  
1. Rapid disintegration: MDT is required to disintegrate rapidly in matter of seconds.  
2. Taste and mouth feel characteristics: Approved sweeteners and flavours are typically included to achieve a palatable formulation, but additional taste masking strategies may also be required such as ion – exchange resin and active pharmaceutical ingredient encapsulation. Delivery systems dissolve or disintegrate in patient’s mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.  
3. Good package design: Packing requirements need to be considered early in the development processes to protect MDTs from moisture and other environmental hazards.  
4. Ease of administration: Fast Dissolving Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.  
5. Mechanical strength: In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets.  
6. Sensitivity to environmental conditions: MDTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature.
as most of the materials used in a Rapimelts are meant to dissolve in minimum quantity of water\textsuperscript{11}.

7. Cost:
The technology used for a Rapimelts should be acceptable in terms of cost of the final product. Methods like Zydus and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent\textsuperscript{11}.

8. Hygroscopicity
Several orally disintegrating 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\textsuperscript{12}.

9. Amount of drug
The application of technologies used for ODTs 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 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers\textsuperscript{12}.

10. 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\textsuperscript{12}.

11. Size of tablet
The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve\textsuperscript{12}.

Excipients commonly used for MDT preparation\textsuperscript{13}
Mainly seen excipients in MDT are as follows at least one disintegrant, a diluents, a lubricant, and, optionally, a swelling agent, a permeabilizing agent, sweeteners, and flavourings.

1. Role of superdisintegrants in MDT
The basic approach in development of MDTs is use of disintegrant. Disintegrant play a important role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Super disintegrant provide quick disintegration due to water soluble and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wet ability and dispersibility of the system, thus enhancing the disintegration and dissolution. Care should be taken when selecting concentration of the super disintegrant. Super disintegrates are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the super disintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Common disintegrants used in this formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmelllose (NS-300), carmellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have super-disintegrant property and are widely used in pharmaceutical industry. Swelling index of the superdisintegrants is commonly studied in simulated saliva. Volume occupied by the material at the end of 4 h should be noted and swelling index is calculated by the formula: (final volume-initial volume/initial volume) X 100\textsuperscript{8}.

2. Role of binders in MDT
Main role of Binders is to keep the composition of these fastmelting tablets together during the compression stage. Binders commonly used are cellulose polymers,povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulose polymers it will be advantageous to select ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures, and the most commonly acrylic polymers are used are the ammonio-methacrylate copolymer (Eudralt. RL and RS), polyacrylate (Eudralt. NE), and polymethacrylate (Eudralt. E). The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30-35\textdegree C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast-dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredient.

3. Role of antistatic agent and diluents in MDT
The most common antistatic agents used are colloidal silica (Aerosil), precipitated silica (Syloid.FP244), micronized or nonmicronized talc, maltodextrins, beta-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearylfumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant\textsuperscript{1}. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. Commonly used Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols and preferably mannitol.

Mechanism of super-disintegrants\textsuperscript{14}
There are four major mechanisms for tablet disintegration as follows

1. Swelling
Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

2. Porosity and Capillary Action (Wicking)
Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or “wicked” into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart.
3. Deformation

Starch grains are generally thought to be “elastic” in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be “energy rich” with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in “energy rich” starch grains than it is for starch grains that have not been deformed under pressure.

4. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with ‘non swellable’ disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

Techniques employed for MDTs

1. Melt-Granulation
2. Phase transition process
3. Sublimation
4. Tablet moulding
   a. Compression moulding
   b. Heat moulding
   c. No vacuum lyophilization
5. Freeze drying OR Lyophilization
6. Mass extrusion
7. Spray drying
8. Direct compression
   a. Superdisintegrant
   b. Sugar based excipients
9. Nanonization
10. Cotton candy process
    a. Floss blend
    b. Floss processing
    c. Floss chopping and conditioning
    d. Blend and compression

1. Melt-Granulation

In this technique powdered drugs are efficiently agglomerated by the use of a meltable binder which can be a molten liquid, a solid or a solid that melts during the process usually in high shear mixers, where the product temperature is raised higher than the melting point of the binder either by a heating jacket or, when the impeller speed is high enough, by the heat of friction generated by the impeller blades. In this technique no water or organic solvents are needed and there is no drying step therefore the process is environmentally safe, less time consuming and uses less energy than conventional wet granulation. Polyethylene glycol is widely used as a molten binder due to its complimentary solution properties, low melting point, rapid solidification rate, low toxicity and little cost. The increase in dissolution rate can be ascribed to the hydrophilic character of the system due to the presence of water-soluble carriers and the fact that the drug forms monocentric mixtures with PEG.

2. Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

3. Sublimation

The basic principle involved in preparing fast dissolving tablets by sublimation technique is addition of a volatile salt to the tableting components, mixing the components to obtain a substantially homogeneous mixture and volatizing a volatile salt. The removal of volatile salts creates pores in the tablet, which help in achieving rapid disintegration when the tablet comes in contact with saliva. (Figure 2) explains how the sublimation makes the surface of dosage form porous for enhancement of its dissolution properties. Camphor, Naphthalene, Urea, ammonium bicarbonate, etc, can be used to prepare porous tablets of good mechanical strength. Koizumi et al. used mannitol as diluent and camphor as a volatile material to prepare porous compressed tablets.

Tablet Molding:

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

Different moulding techniques can be used to prepare mouth-dissolving tablets:

a. Compression moulding:
   The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

b. Heat moulding:
   A molten matrix in which drug is dissolved or dispersed can be directly moulded into Mouth dissolving tablets.

c. No vacuum lyophilization:
   This process involves evaporation of solvent from a drug solution or suspension at a standard Pressure.

5. 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 bulk ing agent and sometimes to the drug, thereby enhancing the dissolution characteristic of
the formulation. The entire freeze drying process is done at
nolevated temperature to eliminate adverse thermal effects
that may affect drug stability. The major disadvantages of
lyophilisation 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.49

6. Mass extrusion
In this technique, a blend of active drug and other ingredients
is softened using solvent mixture of water soluble
polyethylene glycol, using methanol and then the softened
mass is extruded through the extruder or syringe to get a
cylinder of product, which is finally cut into even segments
with the help of heated blades to get tablets. The dried
cylinder can be used to coat the granules of bitter tasting
drugs and thereby masking their bitter taste.20

7. Spray drying
Spray drying is a process by which highly porous, fine
powders can be produced. Spray-dryers are invariably used in
the pharmaceutical industry to produce highly porous
powders. Allen et al. have reported applying this process to
the production of fast dissolving tablets. The formulations
that were produced contained hydrolyzed and unhydrolyzed
gelatine as a support agent for the matrix, mannitol as a
bulking agent, and sodium starch glycocide or crosscarmellose as a disintegrant. Disintegration and
dissolution was further enhanced by adding an acid (e.g.,
citric acid) or an alkali (e.g., sodium bicarbonate). The
formulation was spray dried to yield a porous powder.
Tablets manufactured from this powder disintegrated in less
than 20 second in an aqueous medium.21

8. Direct Compression
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Direct compression represents the simplest and most cost
effective tablet manufacturing technique. This technique can
now be applied to preparation of MDT because of the
availability of improved excipients especially
superdisintegrants and sugar based excipients.
(a) Superdisintegrants
In many orally disintegrating tablet technologies based on
direct compression, the addition of superdisintegrants
principally affects the rate of disintegration and hence the
dissolution. The presence of other formulation ingredients
such as water-soluble excipients and effervescent agents
further hastens the process of disintegration.
(b) Sugar Based Excipients
This is another approach to manufacture ODT by direct
compression. The use of sugar based excipients especially
bulking agents like dextrose, fructose, isomalt, lactitol,
maltitol, 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. Mizumito et al have
classified sugar-based excipients 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 maltitol) exhibit high
mouldability and low dissolution rate.

9. Nanonisation
In this process, the particles of the drug are reduced in size to
nanoparticles by milling the drug in the proprietary wet
milling process. The agglomeration can be prevented by
surface adsorption of the nanocrystals. These are then
compressed and changed into a tablet. This technique is
advantageous for less water soluble drugs. The bioavailability
of the drug is increased as the disintegration time is reduced
to a significant extent.22

10. Cotton Candy Process
The FLASHDOSE® is a MDDDS manufactured using
Shearform™ technology in association with Ceform TITM
technology to eliminate the bitter taste of the medicament. A
matrix known as ‘floss’, with a combination of excipients,
either alone or with drugs is prepared by using shear form
technology. Like cotton-candy fibers floss is fibrous material
made of saccharides such as sucrose, dextrose, lactose and
fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins
and poly-dextrose can be transformed into fibers at 30–40% lower temperature than sucrose. Due to this modification
thermo labile drugs can be safely incorporated into the
formulation. This process results in a highly porous product
and offer very pleasant mouth feel due to fast solubilization
of sugars in presence of saliva.23. The manufacturing process
can be divided into four steps as detailed below:
a. Floss blend:
The floss mix is prepared by blending the 80% sucrose in
combination with mannitol/dextrose and 1% surfactant. The
surfactant maintains the structural integrity of the floss fibers
by acting as crystallization enhancer. This process helps in
retaining the dispersed drug in the matrix, thereby minimizes
the migration out of the mixture.23
b. Floss processing
The floss formation machine uses flash heat and flash flow
processes to produce matrix from the carrier material. The
machine is similar to that used in ‘cotton-candy’ formation
which consists of a spinning head and heating elements. In
the flash heat process, the heat induces an internal flow
condition of the carrier material. This is followed by its exit
through the spinning head (2000–3600 rpm) that flings the
floss under centrifugal force and draws into long and thin
floss fibers, which are usually amorphous in nature.23
C. Floss chopping and conditioning
In this step fibers are converted into smaller particles in a
high shear mixer granulator. The partial crystallization is
done by spraying ethanol (1%) on to the floss and
subsequently evaporated it to impart improved flow and
cohesive properties to the floss. This is called “conditioning”.
d. Blending and compression
Finally, the chopped and conditioned floss fibers are blended
with drug and other excipients and compressed into tablets.
Exposure of the dosage forms to elevate temperature and
humidity conditions (40 °C and 85% RH for 15 minutes)
improve the mechanical strength of tablets due to expected
crystallization of floss material that results in binding and
bridging, to improve the structural strength of dosage forms.23
11. Three-dimensional Printing (3DP)
Three-dimensional printing (3DP) is a rapid prototyping (RP)
technology. Prototyping involves constructing specific layers
that uses powder processing and liquid binding materials. A
novel fast dissolving drug delivery device (DDD) with loose
powders in it was fabricated using the three dimensional
printing (3DP) process. Based on computer-aided design
models, the DDD containing the drug acetaminophen were
prepared automatically by 3DP system.10 It was found that
rapidly disintegrating oral tablets with proper hardness can be
prepared using TAG. The rapid disintegration of the TAG
tables seemed due to the rapid water penetration into the
tablet resulting from the large pore size and large overall pore
volume.31.
Patented Technologies For Orally Disintegrating Tablets

1. Zydis technology
2. OraSolv technology
3. Durasolv technology
4. Flash Dose technology
5. Shear form technology
6. Wowtab technology
7. Flashtab technology
8. Dispersible tablet technology
9. Frosta technology
10. Pharmaburst technology
11. Oraquick technology
12. Quick –Dis technology
13. Nanocystal technology
14. Zipllets/Advatab technology
15. Ceform technology
16. Quick solv technology
17. Lyo technology

1. Zydis technology

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

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevents the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in a blister packs to protect the formulation from moisture in the environment.

Limitations

a. The amount of the drug could be incorporated should generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs.
b. The particle size of the insoluble drug should not be less than 50 µm and not more than 200 µm to prevent sedimentation during processing.

Advantages

a. Buccal pharyngeal and gastric regions are all area of absorption from this formulations. Any Pregastric absorption avoids first pass metabolism and can be an advantage in drug that undergo a great deal of hepatic metabolism.
b. The zydis formulation self preserving because the final water concentration in the freeze dried product is too low to allow for microbial growth.

Disadvantages

a. The process of freeze drying is a relatively expensive manufacturing process.
b. The formulation is very light weight and fragile and therefore should not be stored in backpacks or the bottom of purses.
c. It has poor stability at higher temperature and humidities.
d. The freeze drying is time consuming process.
e. It has poor physical resistance.
f. Loading of high dose of water soluble drug is not possible.

2. OraSolv technology

OraSolv was Cima’s first mouth-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost impeccable effervescence. The OraSolv technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolv formulations are not very hygroscopic.

3. Durasolv technology

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

4. Flash Dose technology

This technology is based on the preparation of sugar based matrix known as floss, which is made from a combination of excipients either alone or in combination of drugs. Two platform fluoride technologies called Shearform and Ceform are currently being utilized in the preparation of a wide range of oral fast dissolving products. Fuisz has patented Flash dose technology. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovial Corporation. A flash dose tablet consists of self-binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

5. Shear form technology:

It is based on preparation of floss that is known as shear form matrix, which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, 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 mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystalised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystalised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystalisation. The shear form floss, when blended with the coated or uncoated microspheres, is compressed into flash dose or EZ chew tablets.

6. Wowtab technology

The wowtab technology has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi pharmaceutical co. The wow in wow tab
signifies the tablet is to be given “without water”. It has just recently been introduced into the US. The wowtab technology utilizes sugar and sugar – like (e.g mannitol) excipients. this process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharides (good binding property) the two types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. due to its significant hardness, the wowtab formulation is a bit more stable to the environment than the zydis and orosolv.30

7. Flashtab technology
This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method followed by compression into tablets. Excipients used in this technology are of two types. Disintegrating agents include reticulated polyvinylpyrrolidone or carboxy methylcellulose. Swelling agents include carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance.31

8. Dispersible tablet technology
Lek, Yugoslavia patents this technology. It offers development of MDTs with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration. Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improves disintegration of tablets usually less than 1 min.32

9. Frosta technology
This technology patents by Akina. It utilizes the concept of formulating plastic granules and compressing 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 usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet.32

10. Pharmaburst technology
SPI Pharma, New Castle, patents this technology. It utilizes the coprocessed excipients to develop MDTs, which dissolves within 30-40 s. This technology involves dry blending of drug, flavour, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.32

11. Oraquick technology:
The oraquick ODT formulation utilizes a patented taste masking technology by K V Pharmaceutical Company, who claims that its taste masking technology i.e., microsphere technology (Micromask) has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and superior efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression. Oraquick claims quick dissolution in matter of seconds with good taste masking. There are no products yet in the market using oraquick technology, but KV pharmaceutical has products, having different classes of drugs such as analgesics, cough and cold, psychotics and ant infective, in developmental stage.32

12. Quick –Dis technology
Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked Quick-Dis™, is Lavipharm’s proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time is around 30 seconds for Quick Dis™ film with a thickness of 2 mm.26

13. Nanocrystal technology
This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water soluble ingredients filled into blister pockets. This method avoids manufacturing process such as granulation, blending and tabletting which is more advantages for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.33

14. Ziplets/Advatab technology
It utilizes waterinsoluble ingredient combined with one or more effective disintegrants to produce MDT with improved mechanical strength and optimal disintegration time at low compression force.29

15. Ceform technology
This technology involves preparation of microspheres of active drugs. Drug material alone or in combination with other pharmaceutical substance, and excipients is placed into a precision engineered rapid spinning machine. The centrifugal force come into action, which throw 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 are thus formed are compressed into tablets. As the drugs and excipients both can be processed simultaneously, it create a unique microenvironment in which the material can be incorporated into the microspheres that can alter the the characteristic of the drug, such as enhancing solubility and stability.34

16. Quicksolv technology
This technology uses two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.29

17. Lyo
Lyoc technology is patented by Pharmalyoc. Oil in watr emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.35

Evaluation of MDTs
1. Hardness
The limit of hardness of the MDTs is usually kept in lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness tester (Monsanto hardness tester). It is expressed in
Kg or pound\textsuperscript{35}.

2. Friability of tablet
To achieve $\%$ friability within limits for a MDT is a challenge to the formulator since all methods of MDT are are responsible for increasing the $\%$ friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1 to 0.9)\textsuperscript{17}. Friability of each batch was measured in “Electro lab friabilator”. Ten preweighed tablets were rotated at 25 rpm for 4 min or total 100 revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation\textsuperscript{38}

$$\text{Friability} = \left(\frac{\text{Weight loss}}{\text{Initial weight}}\right) \times 100$$

3. Wetting time
Wetting time of dosage form is related with the contact angle. Wetting time of MDT is another important parameter, which need to be assessed to give an insight into the disintegration properties of the tablets, a lower wetting time implies a quicker disintegration of the tablet.

The wetting time of the tablet can be measured using a simple procedure. Five circular tissue parers of 10 cm diameter are placed into a petridish with a 10cm diameter. Ten mm of water containing Eosin, a water soluble dye, is added to petridish. A tablet is carefully placed on the surface of tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time\textsuperscript{36}.

4. Moisture Uptake Study
MDTs usually contain high concentration of hydrophilic excipients with the minimum possible hardness which together contribute to their increased susceptibility to moisture uptake. In order to maintain their physical integrity and surface texture, special attention is required during the storage and packaging of these dosage forms. Therefore, moisture uptake studies are strongly recommended for MDTs. The test can be carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37 °C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing. The materials with high moisture resistant properties should be used for packaging for e.g. alu strip pack, alu-alu blister or polyethylene sealing on blister. The use of appropriate quantity of desiccant in HDPE bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life\textsuperscript{37}.

5. Measurement of Tablet Porosity\textsuperscript{37}
The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation II, where the pressure drop is inversely related to the pore size (perpendicular radius).

$$\Delta P = \frac{2\gamma}{r} \cos \theta$$

where $\gamma$ is the surface tension of the liquid, $r$ is the perpendicular radius and $\theta$ is the angle of contact between the liquid and the capillary walls. Pore radius is calculated from eq II using experimental data obtained in the form of P. In this test, the contact angle between mercury and the tablet is kept at 140° and the surface tension at the interface of mercury and the tablet is 0.486 N/m. Pore sizes in the range of 0.06–360 μm, can be efficiently measured by this technique.

Otherwise, the tablet porosity ($\varepsilon$) can also be calculated using equation III:

$$\varepsilon = \left(1 - \frac{m}{\rho V}\right)$$

Where $\rho$ is the true density, and $m$ and $V$ are the weight and volume of the tablet, respectively. Tablets prepared by spray drying, lyophilization and cotton candy process generally possess high porosity and therefore, have extremely low disintegration time.

6. Mechanical Strength\textsuperscript{38}
Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters for the determination of mechanical strength. Crushing Strength or Tablet Tensile strength: It is the force required to break a tablet by compression in the radial direction, it is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet was measured by using Pfizer hardness testers. It is calculated by an average of three observations. Tensile strength for crushing (T) is calculated using equation

$$T = \frac{2F}{\pi d^2 t}$$

Where $F$ is the crushing load, and $d$ and $t$ denote the diameter and thickness of the tablet respectively.

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\textsuperscript{38}.

8. Disintegration time
Conventional disintegration tests for ordinary tablets may not allow precise measurement of the disintegration time of MDTs because of their fast disintegration. It is also hard to distinguish among MDTs, which release their ingredients very quickly. In vitro testing may not always reflect the real in vivo disintegration of tablets. In general, the method described in the US Pharmacopoeia can produce data for evaluation of the disintegration time. When developing MDT formulations, it is important to evaluate the effect of different excipients on the disintegration time. In order to predict the disintegration time of MDTs and the effects of different formulation parameters, a few methods have been proposed\textsuperscript{39}.

9. Modified method for determination of disintegration time
Instead of using the disintegration apparatus described in the US Pharmacopoeia, a modified method has been proposed. The disintegration apparatus was the same as the USP dissolution test Apparatus 2, which uses a paddle stirring element and 1000-mL cylindrical vessel at 37 °C. Distilled water was chosen for the disintegration medium instead of a buffer solution. A tablet to be tested was put on the bottom of a sinker, which was placed in the middle of the vessel and hung by a hook to the lid of the vessel with a distance of 6–8.5 cm. Disintegration time was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely. The opening of mesh of the sinker was 3–3.5 mm in height and 3.5–4 mm in width\textsuperscript{39}.

10. Disintegration in oral cavity
The time required for complete disintegration of tablets in mouth was obtained from six healthy volunteers, who were given tablets from the optimum formulation.
11. Dissolution test

The dissolution methods for FDT are practically identical to conventional tablet when MDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of MDT in the same way as their ordinary tablet counterparts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of MDT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 25-75 rpm is commonly used. Since the dissolution of MDT is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets (≥1gram) may produce a mound in the dissolution vessel which can be prevented by using higher paddle speeds.

12. Thickness

The thickness of the tablets can be measured by using digital vernier calipers.

13. Uniformity of weight

20 tablets are weighed collectively and individually. From the collective weight, average weight is calculated. Each tablet weight is then compared with average weight to ascertain whether it was within permissible limits or not.

14. Drug content

20 tablets of each formulation are weighed and powdered. The quantity of powder equivalent to 5 mg of drug is transferred into a 100 ml standard flask and volume should be made up with methanol up to 50 ml. Further 5ml of the above solution is diluted to 50 ml with methanol and absorbance of the resulting solution is observed at respective wavelength.

15. In-vitro dissolution studies

The dissolution test has been carried out for all the formulations. The in vitro drug release is performed using USP dissolution apparatus- II, 24 type paddle apparatus using 900 ml of 0.1 N HCL at paddle rotation of 50 rpm at 37±0.5ºC. 5 ml of the samples are withdrawn at predetermined time intervals of 5, 10, 15, 20, 30, 45, 60 mins for a period of 60 mins and replaced with the fresh medium of 0.1 N HCL. The samples are filtered through 0.45 mm membrane filter, suitably diluted and analyzed at respective wavelength using double beam UV/Visible spectrophotometer. The content of drug is calculated.

Figure 1: Schematic representation of the different linings of mucosa in mouth

Figure 2: Steps involved in sublimation

Table 1: Name and weight percentage of various excipients

<table>
<thead>
<tr>
<th>Name of the excipients</th>
<th>Percentage used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disintegrant</td>
<td>1 to 15%</td>
</tr>
<tr>
<td>Binder</td>
<td>5 to 10%</td>
</tr>
<tr>
<td>Antistatic Agent</td>
<td>0 to 10%</td>
</tr>
<tr>
<td>Diluents</td>
<td>0 to 85%</td>
</tr>
</tbody>
</table>

Table 2 : Disintegrants used in MDTs

<table>
<thead>
<tr>
<th>Disintegrants</th>
<th>Mechanism</th>
<th>Conc. %w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>Disintegrate forms pathways throughout the tablet matrix that enable water to draw into the structure by capillary action, thus leading to disruption of tablet.</td>
<td>5-20</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>Responsible for increased dissolution rate from this tablet is rapid disintegration due to superior swelling capacity.</td>
<td>5-15</td>
</tr>
<tr>
<td>Sodium Starch Glycolate (Explotab and Primogel)</td>
<td>Involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration.</td>
<td>1-3</td>
</tr>
<tr>
<td>Cross-linked polyvinyl Pyrrolidone (Cross Povidone, CrosspovidonM®, Kollidon®, Polyplasdone®)</td>
<td>The capillary activity of cross povidone for water is responsible for its tablet disintegration property.</td>
<td>0.5-5</td>
</tr>
<tr>
<td>Cellulose (Ac-Di-Sol, Nymce ZSX® Primellose® Solutab®)</td>
<td>They show their ability to swell on contact with water results in rapid tablet disintegration.</td>
<td>1-3</td>
</tr>
<tr>
<td>Microcrystalline Cellulose (Avicel)</td>
<td>Allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals and exhibit very good disintegrant property</td>
<td>10-20</td>
</tr>
<tr>
<td>Alginates (Algmic Acid, Satalgence®)</td>
<td>High affinity for water absorption and high sorption capacity make it an excellent disintegrant.</td>
<td>1-5</td>
</tr>
<tr>
<td>Soy polysaccharides (Emcosoy®)</td>
<td>Natural super disintegrant, Rapid swelling in aqueous medium or wicking action, Does not contain any starch or sugar. Used in nutritional products.</td>
<td>5-15</td>
</tr>
</tbody>
</table>
Gums (Guar Gums, Gum Karaya, Agar, Gelam Gum) As disintegrants because of their tendency to swell in water 3-8

Chitin and Chitosan Moisture sorption and water uptake was found to be a major mechanism of disintegration when dissolution related to swelling capacity 1-5

Smecta Their layered leaves like structure consist of aluminium and octahedral layers sandwiched between two tetrahedral silica layers. It has a large specific area and high affinity for water makes it a good disintegrant. 5-15

Isapghula Husk Plantago ovata seeds husk 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, Ambreline 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, Tartic Acid, Sodium Bi Carbonate) These react in contact with water to liberate carbon dioxide that disrupts the tablet. >10%

Table 3: USP Specification for uniformity of weight

<table>
<thead>
<tr>
<th>S No.</th>
<th>Average weight of Tablets(mg)</th>
<th>Maximum % difference allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130 or less</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>130 to 324</td>
<td>7.5</td>
</tr>
<tr>
<td>3</td>
<td>More than 324</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4: Drugs promising to be incorporated in MDTs 11

Analgesics and Anti-inflammatory Agents

Anthemintics
- Albendazole, buphenium hydroxynaphthoate, cambendazole, ivermectin, mebendazole

Anti-arrhythmic Agents
- Amiodarone HCl, Disopyramide, flecainide acetate, quinidine sulphate

Anti-bacterial Agents
- Benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, doxycycline, erythromycin, ethionamide, imipemem

Anti-coaguulants
- Dicumarol, dipryidamole, nicoumalone, phenindione

Anti-depressants
- Amoxapine, cloxazolidine, maprotiline HCl, nortriptiline HCl, trazodone HCl, trimipramine maleate.

Anti-diabetics
- Acetohexamide, chlorpropamide, glimepiride, glibizide, glipizide, tolazamide, tolbutamide.

Anti-epileptics
- Beclamide, carbamazepine, clonazepam, ethosuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone.

Anti-fungal Agents
- Amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, fusicoccin, griseofulvin, itraconazole, ketoconazole, miconazole.

Anti-gout Agents
- Allylbutolin, probenecid, sulfinpyrazone.

Anti-hypertensives Agents
- Alnidipine, carvedilol, bendidine, darodipine, diltiazem HCl, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, nifedipine, nisoldipine, nicardipine HCl.

Anti-malarials
- Amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, meproguanil HCl, pyrimethamine, quinine sulphate.

Anti-migraine Agents
- Dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, sumatriptan succinate.

Anti-muscarinic Agents
- Atropine, benzhouxol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, mebeverine, mebeverine hydrochloride, neostigmine, omeprazole, ondansetron HCL, promethazine, propranolol.

Anti-neoplastic agents and Immunosuppressants
- Aminoglutethimide, amscaine, azathioprine, busulphan, chlorambucil, cyclosporin, daclizumab, erlotinib, etoposide, loratadine, melphalan, mercaptopurine, methotrexate, mitomycin, metotrexate.

Anti-parkinsonian Agents
- Bromocriptine mesylate, lysuride maleate

Anti-protozoals Agents
- Benznidazol, cloquindol, decoquinate, dihydroxysquisqualeine, diloxanide furoate, ditolmidol, furzolidone, metronidazol, nifuridazole, nitrofurazone, omedazole, tinidazole.

Anxiolytic, Sedatives, Hypnotics & Neuroleptics
- Alprazolam, amobarbital, barbitone, benzylaetham, bromazepam, bromperidol, brotizolam, chlorpromazine, clozapine, diazepam, depotidol, etizolam.

Cardiac Inotropic Agents
- Amrinone, digoxin, digoxin, enoximone, lanatoside C, medigoxin.

Corticosteroids
- Beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethylasone, dexamethasone, fludrocortisone acetate, flunisolide, flutocortolone, fluscinonate proponate.

Diuretics
- Acetazolamide, amiloride, bendroflumethiazide, bumetanide, chlorothiazide, chlorothalidone.

Gastro-intestinal Agents
- Bisisodiol, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mephenesin, metoclopramide, metronidazole, neramexane, omeprazole, ondansetron HCL, ranitidine HCl, sucralfate.

Histamine H1-Receptor Antagonists
- Acrivastine, azimexine, citazoline, cyclosine, cyproheptadine HCl, dimethylxylamine, flunoxazine HCl, loradamine, meclozine HCl, oxatidine, tepiridoline.

Lipid regulating Agents
- Bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.

Local Anaesthetics
- Lidocaine

Neuro-muscular Agents
- Pyridostigmine.

Nitrates and other Anti-anginal Agents
- Amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetrinitrate.

Nutritional Agents
- Betacarotene, vitamin A, vitamin B 2 , vitamin D, vitamin E, vitamin K.

Opioid Analgesics
- Codeine, dextropropoxyphene, diamorphine, dicyclohexylamine, meptazinol, methadone, morphine, nalbuphine, pentazocine.

Oral Vaccines
- Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, AIDS, Measles.

Proteins, Peptides and recombinant drugs
- Insulin, glucagon, growth hormone, calcitonins, enkephalins, interferons (especially Alpha-2 interferon for treatment of common colds), LHRH and analogues (raflutrel, busrelin, sildales), GHRH (growth hormone releasing hormone)

Sex Hormones
- Clomiphene citrate, danazol, ethinylestradiol, medroxyprogesterone acetate, mestranol, methyltestosterone, norethisterone, norgestrel, oestradiol, conjugated oestrogens, progesterone, stanozolol, stibobestrol, testosterone, tibolone.

β-Blockers
- Acebutolol, alpenrolol, atenolol, labetalol, metoprolol, nadolol, oxpenrolol, pindolol, propranolol.
CONCLUSION

In today’s market world consumers satisfaction is the most important consideration and industries are trying continuously to achieve this objective. About one third of world’s population mainly contributed by pediatric and geriatric patients faces the problem of swallowing of tablets. Besides delivering drug to the body, a drug delivery system aim to improve patient compliance and convenience, and mouth dissolving tablets are no exception. The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world’s population. The MDTs have potential advantages over conventional oral dosage forms as they improved rapid onset of action and bioavailability which drawn the attention of many manufactures. MDTs are to incorporate super disintegrating agents in optimum concentration so as to achieve rapid disintegration and instantaneous dissolution of the tablet along with good taste masking properties and excellent mechanical strength. Many drugs can be incorporated in MDT especially unpalatable

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Trade Name</th>
<th>Active Drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Felden fast melt</td>
<td>Piroxicam</td>
<td>Pfizer Inc., NY, USA</td>
</tr>
<tr>
<td>2.</td>
<td>Claritin redi Tab</td>
<td>Loratadine</td>
<td>Schering plough Corp., USA</td>
</tr>
<tr>
<td>3.</td>
<td>Maxalt MLT</td>
<td>Rizatriptan</td>
<td>Merck and Co., NJ, USA</td>
</tr>
<tr>
<td>4.</td>
<td>Zyrtecia</td>
<td>Olanzapine</td>
<td>Eli Lilly, Indianapolis, USA</td>
</tr>
<tr>
<td>5.</td>
<td>Peppcid RPID</td>
<td>Famotidine</td>
<td>Merck and Co., NJ, USA</td>
</tr>
<tr>
<td>6.</td>
<td>Zofran ODT</td>
<td>Ondansetron</td>
<td>Glaxo Wellcome, Middleses, UK</td>
</tr>
<tr>
<td>7.</td>
<td>Zoming-ZMT</td>
<td>Zolmitriptan</td>
<td>AstraZeneca, Wilmington, USA</td>
</tr>
<tr>
<td>9.</td>
<td>Tempra Quiklets</td>
<td>Acetaminophen</td>
<td>Bristol myers Squibb, NY, USA</td>
</tr>
<tr>
<td>10.</td>
<td>Febrecol</td>
<td>Paracetamol</td>
<td>Paprograph, Chateauneuf, France</td>
</tr>
<tr>
<td>11.</td>
<td>Nimulid MDT</td>
<td>Nimesulide</td>
<td>Panacea Biotech, New delhi, India</td>
</tr>
<tr>
<td>12.</td>
<td>Torrox MT</td>
<td>Rofecoxib</td>
<td>Torrent pharmaceuticals, India</td>
</tr>
<tr>
<td>13.</td>
<td>Olanex instab</td>
<td>Olanzapine</td>
<td>Ranbaxy lab. Ltd. New-delhi, India</td>
</tr>
<tr>
<td>14.</td>
<td>Romilast</td>
<td>Montelukast</td>
<td>Ranbaxy lab. Ltd. New-delhi, India</td>
</tr>
<tr>
<td>15.</td>
<td>Benadryl Fastmelt</td>
<td>Diphenhydramine and pseudoephedrine</td>
<td>Warner Lambert, NY, USA</td>
</tr>
<tr>
<td>16.</td>
<td>Propulsid Quicksovl</td>
<td>Citrnapide monohydrate</td>
<td>Janssen pharmaceutics</td>
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Table 5 : Table List Of Marketed Fast Dissolving Tablets^1

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drugs. The research is still going on. More products need to be commercialized to use this technology properly. Thus MDT may be developed for most of the available drugs in near future.

REFERENCES