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REVIEW ARTICLE

MOUTH DISSOLVING TABLETS: GENERAL OVERVIEW AND FORMULATION ASPECTS

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Recent pharmaceutical preparations including Novel Drug Delivery Systems (NDDS) aim to enhance safety and efficacy of drug molecule to improve the treatment compliances and quality of life of patients. One such approach is "Mouth Dissolving Tablet" (MDT) which disintegrates instantly when placed on tongue, releasing the drug that dissolves or disperses in the saliva. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. The saliva containing dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach and it may produce rapid onset of action, with bioavailability of drug significantly greater than those observed from conventional tablet dosage form. Present article includes general overview and formulation aspects of MDTs making this a vital approach for enhanced patient compliance.

Key words: Mouth dissolving tablets (MDTs), Superdisintegrants, Taste masking, Patented technology.

INTRODUCTION

In recent decades, a wide variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, and enhance the patient compliance; mouth dissolving tablet (MDT) is the most widely preferred commercial products (Dahiya *et al* 2011; Bhatere *et al* 2012; Bhimavarapu *et al* 2012). The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like tablets, capsules, liquid preparations are administered by oral route. During the last decade, MDT technologies that make tablets disintegrate in the mouth without chewing and additional water intake has drawn a great deal of attention. The MDT is also known as fast melting, fast dissolving tablets (FDTs), rapid dissolve, rapid melt, and or quick disintegrating tablets. All MDTs approved by FDA are classified as orally disintegrating tablets. Recently, the European Pharmacopoeia adopted the term mouth dissolving tablet for a tablet that disperses or disintegrates in less than 3 min in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good MDTs varies from several seconds to about a minute. Moreover, drug candidates that undergo pre-gastric absorption when formulated as MDTs may show increased oral bioavailability. It provides good stability, accurate dosing, and easy manufacturing. The basic approach in development of MDTs is the use of superdisintegrants, which provide instantaneous

disintegration of tablet after putting on tongue, thereby release the drug in saliva. Mouth dissolving tablets are also called as Fast dissolving tablets, melt-in-mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablets etc. The fast dissolving tablets are rapidly dissolved or disintegrated by the use of superdisintegrants (FDTs) (Goel *et al* 2008; Ashish *et al* 2011; Yadav *et al* 2010; Jeong *et al* 2008; Sastry *et al* 2000). This review presents general overview and formulation aspects of MDTs including role of ingredients and techniques used, evaluation parameters and market status of MDTs making this a potential approach for enhanced patient compliance.

Advantages of MDTs

Main advantages of MDTs are in terms of ease of swallowing without risk of chocking. Other advantages are no need of water to swallow the tablet; can be easily administered to pediatric, elderly and mentally disabled patients; accurate dosing as compared to liquids; dissolution and absorption of drug is fast; offering rapid onset of action; bioavailability of drug is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down into the stomach; advantageous over liquid medication in terms of administration as well as transportation; first pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects; free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety; suitable for sustained/controlled release actives; allows high drug loading (Kaur *et al* 2011; Pawar *et al* 2011; Reddy and Ghosh, 2002; Habib *et al* 2002; Biradar *et al* 2005).

Limitations to MDTs

Drugs with relatively larger doses are difficult to formulate into FDT *e.g.* antibiotics like ciprofloxacin with adult dose tablet containing 500 mg of the drug. Patients who concurrently take anti-cholinergic medications may not be the best candidates for FDT. Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations (Udaykumar *et al* 2012; Chang *et al* 2000). Current method of taste masking in mouth dissolving/disintegrating tablet include sweeteners and flavors, however, these are not a sufficient means for masking the taste of many bitter drugs. Another bioequivalent process of taste masking is a physical process of effervescence. Frequently, the active drug powder is coated and coating doesn't dissolve completely until the drug has been swallowed. FDT requires special packaging for properly stabilization and safety of stable product (Saka and Singh, 2012; Dutta and De, 2011; Khan *et al* 2011).

Salient features of mouth dissolving tablets

These include ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric and psychiatric patients; convenience in administration and accurate dosing as compared to liquids; no need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water; good mouth feels properly of ODTs helps to change the basic view of medication as "bitter pill", particularly for pediatric patients; rapid dissolution of drug and absorption leading to rapid onset of action; some drugs are absorbed from the month, pharynx and esophagus, as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased; ability to provide advantages of liquid medication in the form of solid preparation; pregastric absorption can result in improved bioavailability, leading to reduction in dosage and improved clinical performance preventing unwanted side effects (Bhardwaj *et al* 2010); challenging molecules, likely to exhibit low bioavailability; option to increase permeability; modify APIs as 'prodrugs' *e.g.* hydrochlorothiazide, furosemide (Amidon *et al* 1995).

The need for development of MDTs

Patient factors

Mouth dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water.

This includes patients who have difficulty in swallowing or chewing solid dosage forms; very elderly patients of depression who may not be able to swallow the solid dosage forms; an eight-year old patient with allergies desires a more convenient dosage form than antihistamine syrup; a middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow H_2-blocker; a schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their

daily dose of an atypical antipsychotic; a patient with persistent nausea, who may be in journey, or has little or no access to water.

Mechanism of mouth dissolving tablets

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of a drug mainly depends on physiochemical properties of the drug. The rate of drug dissolution is greatly influenced by disintegration of the tablet. Disintegrants are important excipients of the tablet formulation, they are always added to formulate tablets to induce breakup of tablet when they come in contact with aqueous fluid and this process of disaggregation of constituent particles before the drug dissolution occurs, is known as disintegration.

Characteristics of mouth dissolving tablets

Fast disintegration

These tablets should disintegrate in the mouth without additional water or with a very small amount of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide smooth swallowing and good mouth feel.

Drug properties

Many drug properties could potentially affect the performance of MDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, bioavailability, flow property and bulk density of a drug can significantly affect the final tablets characteristics, such as disintegration and tablet strength.

Taste of active ingredients

MDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. An ideal taste-masking technology should provide drugs with good mouth feel without grittiness.

Moisture sensitivity

These tablets should have low sensitivity to humidity. This problem can be especially challenging because many highly water soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water soluble excipients are susceptible to moisture; some will even deliquesce at high humidity.

Tablet strength and porosity

The tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength.

Cost

The technology used for preparing MDTs should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

Hygroscopicity

Several fast 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 (Kumar *et al* 2012; Fu *et al* 2004; Jeong *et al* 2008).

Excipients used to prepare MDTS

Superdisintegrants

Superdisintegrants are the agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. There are three methods of incorporating disintegrating agents into the tablet: a) internal addition (intragranular); b) external Addition (extragranular); c) partly internal and external. In a direct compression process, drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet.

Characteristics of superdisintegrants include Poor water solubility with good hydration capacity, poor gel formation, good flow properties, good compressibility, inertness, non-toxic, effective in small concentration.

Mechanism of superdisintegrants for tablets disintegration

Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling (**Figure 1**). 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 tablet 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.

(a) (b)

Fig. 1. Swelling mechanism of super-disintegrants a) Granules with super-disintegrants in aqueous media; b) Swelling of granules due to superdisintegrants

Porosity and capillary action (Wicking)

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/excipients and on tableting conditions. For this type of disintegrants, maintenance of porous structure and low interfacial tension toward aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

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 no swelling particles also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

Due to deformation

During tablet 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 tablet.

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. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

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. The effervescent blend is either added immediately prior to compression or can be added in to two fraction of formulation.

By enzymatic reaction

Here, 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 (Deshmukh *et al* 2012; Shihora and Panda, 2011).

characteristics of some superdisintegrants are summarized in **Table 1**. Examples of excipients used in mouth dissolving tablets are depicted in **Table 2**.

Table 1. Characteristic of superdisintegrants (Ghenge *et al* 2011)

Synthetic superdisintegrant	Properties	Effective concentration for disintegrants
Crospovidone	♦ It is completely insoluble in water. Rapidly disperses and swells in water. Greatest rate of swelling compared to other disintegrants ♦ Available in grades if needed for improving state of dispersion in the powder blend ♦ Swelling index - 58±1.5% *v/v*	It is used in the range of 1-3% *w/w*.
Croscarmellose sodium	♦ It is insoluble in water, although it rapidly swells to 4-8 times its original volume on contact with water ♦ Specific surface area - 0.81-0.83 m^2/g ♦ Swelling index- 65±1.7% *v/v*	It may be used as a tablet disintegrant at concentration up to 5% *w/w*, although normally 2% *w/w* is used in tablets prepared by direct compression and 3% *w/w* in tablets prepared by wet-granulation process.
Sodium starch glycolate	♦ Absorbs water rapidly, resulting in swelling up to 6%. High concentration causes gelling and loss of disintegration ♦ Swelling index - 52±1.2% *v/v*	It is used in the range of 4-6%. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects
Polacrilin potassium	♦ No lump formation after disintegration ♦ High compatibility with excipients and common therapeutic	Used as a tablet disintegrant and as a taste masking agent for various drugs.

Table 2. Examples of excipients used in MDTs (Liang and Chen, 2011; Camarco *et al* 2006)

Flavours	Fillers	Surface active agents	Binder	Colour	Lubricants	Sweetners
Peppermint flavor	Directly compressible spray dried Mannitol	Sodium doecyl sulfate	Polyvinyl pyrrolidone (PVP)	Sunset yellow	Stearic acid	Aspartame
Cooling flavor	Sorbitol	Sodium lauryl sulfate	Hydroxy propylmethyl cellulose (HPMC)	Amaranth	Magnesium stearate	Sugars derivatives
Flavor oils and Flavoring aromatic oil,	Xylitol	Sorbitan fatty acid esters (spans)	Polyvinylalcohol (PVA)		Zinc state	
Peppermint oil	Magnesium carbonate	Polyoxy ethylene stearates			Calcium state	
Clove oil	Calcium phosphate	Polyoxy ethylene sorbitan fatty acid esters (tweens)			Polyethylene glycol	
Bay oil	Calcium sulfate				Liquid paraffin	
Anise oil	Pregelatinized starch				Colloidal silicon dioxide	
Oil of bitter almonds	Magnesium trisilicate				Magnesium lauryl sulfate	

Formulation techniques for MDTs

Formulation techniques used for preparing MDTs are summarized in **Table 3**.

Table 3. Formulation techniques used for MDTs

Conventional Techniques	Patented Techniques
Freeze drying/ Lyophilization	Zydis Technology
Spray drying	Orasolv Technology
Direct compression	OraQuick
Sublimation	Quick-Dis Technology
Cotton candy process	Durasolv Technology
Mass extrusion	Flash Dose Technology
Molding	Flashtab technology
Nanonization	Sheaform Technology
Fast dissolving films	Ceform Technology
Phase transition process	Wowtab Technology
Melt granulation	Lyoc tech
Three-dimensional printing	Pharmaburst technology
	Frosta technology
	Advatab

Conventional techniques

Freeze drying or lyophilization

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolve rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomycin (Jaccard and Leyder, 1985) in which drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouths. This technique creates an amorphous porous structure that can dissolve rapidly. Process of lyophilization is shown in **Figure 2**. The mixture is done by weight and 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. Advantages of this technique include that the tablets prepared by Lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs *i.e.* thermo-labile substances. Disadvantages of this method include that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions (Arya and Chandra, 2010; Jaccard and Leyder, 1985; Bhowmik *et al* 2009).

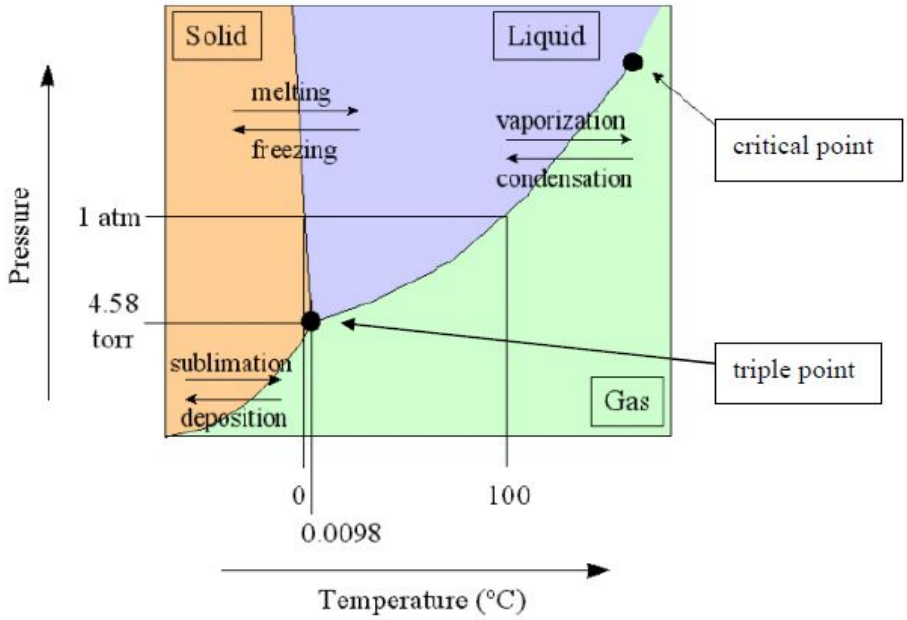

Fig. 2. Freeze drying or lyophilization method

Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. In this method, tablets are prepared directly by compression of the mixture of drug and excipients without any preliminary treatment. The mixture which is to be compressed must have good flow properties (**Figure 3**). Advantages of method includes high doses can be accommodated and final weight of the tablet can exceed that of other methods; easiest way to manufacture the tablets, conventional equipment and commonly available excipients are used, a limited number of processing steps are involved and cost-effectiveness.

This method complete within 3 steps: milling of drug and excipients, mixing of drug and excipients, tablet compression (Yadav *et al* 2010; Jeong *et al* 2008).

Fig. 3. Direct compression method

Spray drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This fine powder is then mixed with active ingredients and compressed into tablets. Schematic of tablets manufactured from the spray-dried technique is shown in **Figure 4** and have been reported to disintegrate in less than 20 seconds in aqueous medium.

The formulation contained supporting matrix such as gelatin, bulking agent like mannitol and lactose, a superdisintegrants like sodium starch glycolate, croscarmellose sodium and acidic ingredient such as citric acid and/or alkaline ingredients such as sodium bicarbonate (Jeong *et al* 2008).

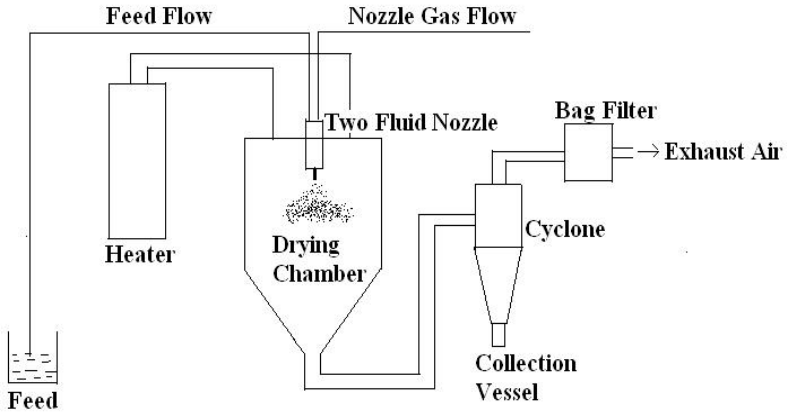

Fig. 4. Spray drying technique

Sublimation technique

This technique is based on the use of volatile ingredients such as camphor, ammonium bicarbonate, naphthalene, urea, urethane etc. to other tablet excipients and the mixture is then compressed into tablets and steps involved in sublimation techniques are shown in **Figure 5**. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported disintegrate usually in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents (Makino *et al* 1998).

Mass extrusion

It involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. Characteristic of this method is that the dried

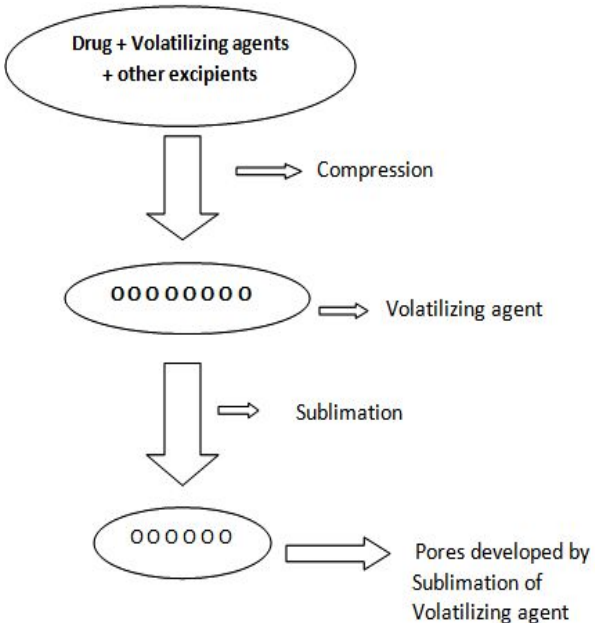

Fig. 5. Sublimation technique

product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste (Nayak and Kaushik, 2011).

Molding

Water soluble ingredients with a hydroalcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. Characteristic of this method is that molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased. Following are the different tablet moulding techniques:

Compression moulding

The powder blend is moistened with a hydro alcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets are less compact than compressed tablets and have a porous structure that enhances dissolution.

Heat moulding

A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C.

Molding by vacuum evaporation without lyophilization

This process involves pouring the drug excipients mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. Unlike lyophilization, vacuum drying helps to densify the matrix and thereby improves the mechanical strength of the product. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet. Advantages includes As the dispersion matrix is made from water-soluble sugars, moulded ODTs disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the molding process are used. In comparison to lyophilization process, tablets produced by moulding technique are easier to adapt to the industrial scale. Disadvantage include poor mechanical strength, they may undergo erosion and breaking during handling. Though hardening can enhance the tablet strength; but, it would be at the cost of their disintegration time (Nayak and Kaushik, 2011).

Nanonization

A recently developed Nanomelt technology involves size reduction of drug to nano size 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. Characteristics of this method is that it is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses that is up to 200 mg of drug per unit (Jeong *et al* 2008).

Fast dissolving films

In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer such as pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxy ethylcellulose, hydroxy propylcellulose, polyvinylpyrrolidone, polyvinyl alcohol or

sodium alginate, drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent.

In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2 × 2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste (Yadav *et al* 2010).

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 (Gupta *et al* 2010).

Cotton candy process

The FLASHDOSE® is a mouth dissolving drug delivery system (MDDDS) manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of medicament.

The Shearform technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180-266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30-40% lower temperature than sucrose.

This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

Floss blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

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.

Floss chopping and conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.

Blending and compression

Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form (Gupta *et al* 2010).

Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently

agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder. Superpolystate© is a waxy material with a melting point of 33-37 °C and HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilizes rapidly leaving no residues (Ashish *et al* 2011).

Three-dimensional printing

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 [25]. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume (Ashish *et al* 2011).

Patented Technology

Zydis technology

Zydis® was introduced By R. P. Scherer Corporation in 1986. The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure forming additives then the mixture is poured into the preformed blister pockets of a laminate film and freeze-dried. This results in a tablet shaped dosage form that spontaneously disintegrates in mouth in seconds. The two most commonly used structural additives are gelatin and mannitol although some other (*e.g.* starches, gums etc.) may be used depending on the properties of the active ingredient. The polymer gives the strength and resilience while the crystalline component gives the hardness and texture.

Orasolv technology

CIMA labs have developed 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 produce the tablets. The tablets produced are soft and friable.

OraQuick technology

KV Pharmaceutical claims its microsphere technology, known as 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 more efficient production. Also, lower heat of production than alternative fast-dissolving/ disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics and antiinfectives.

Quick-Dis Technology

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral 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. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 sec for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within

30 sec and 95% within 1 min.

Durasolv technology

DuraSolv is Cima's second-generation fast-dissolving/ disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabletting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more costeffective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction; the DuraSolv technology is best suited for formulations including relatively small doses of active compound.

Flash dose technology

By this technology, sugar based matrix known as floss which made from combination of excipients either alone or in combination of drugs. Nurofen meltelt, a new form of ibuprofen is based on same technology.

Flashtab technology

Prographarm patented this technology in which tablet consists of active ingredients in form of microcrystals. Rest of all procedure is followed in conventional technology.

Sheaform Technology

This technology makes Sheaform matrix consisting of floss preparation. Floss is produced by subjecting to a feed shock containing a sugar to flash heat processing.

Ceform technology

In this technology microspheres containing active ingredient are prepared. Basic requirement of this technology is placing dry powder containing either pure drug or special blend of drug and excipients. The microspheres then mixed and compressed into previously selected oral dosage form.

Wowtab technology

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

Lyoc tech

This is patented technology of Laboratories L. Lafon, Maisons Alfort, France . It utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent non-homogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the in process suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations.

Pharmaburst technology

Pharmaburst™ is a "Quick Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipients system with specific excipients, which allows rapid disintegration and low adhesion to punch faces. Mouldablilty saccharides are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldablilty saccharides.

Frosta technology

Akina patents this 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. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

Advatab

AdvaTab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is distinct from other ODT technologies as it can be

combined with Eurand's complimentary particle technologies like its world leading Microcaps® taste-masking technology and its Diffucaps®, controlled release technology. (Seager, 1998; Cilurzo *et at* 2005; Rasetti-Escarqueil and Grange, 2005; Abdelbary *et al* 2005; Ahmed *et al* 2006; Modi and Tayade, 2006). List of marketed MDTs are summarized in **Table 4**.

Table 4. List of marketed mouth dissolving tablets

Drug	Category	Company	Brand name
Piroxicam	Anti arthritis	Pfizer Inc., NY, USA	Feldene Melt
Loratidine	Anti-histaminic	Ranbaxy	Loratadine, Redidose
Famotidine	H_2 receptor blocker	Merck and Co., NJ, USA	Pepcid
Paracetamol	NSAIDs	Prographarm, Chateauneuf, France	Panadol,Tylenol
Nimesulide	NSAIDs	Panacea Biotech, New delhi , India	NisureMD
Olanzapine	Antipsychotic	Eli Lilly	Zyprexa Zydis
Montelukast	Anti asthmatic	Ranbaxy Lab. Ltd. Newdelhi,India	Romilast
Cisapride monohydrate	Anti-emetic	Jannsen	Propulsid
Ibuprofen	NSAIDs	Eurand International	Zyprexa
Promethazine	Antihistamine	Aventis	Phenergan
Cefixime	Antibiotic	Lupin	Suprax
Glipizide	Anti-diabetic	Pfizer	Glucotrol
Valsartan	Anti-hypertensive	Abbott	Humira

Evaluation tests for MDTs

General appearance

MDTs are evaluated for it includes the visual identity, elegance, consumer acceptance and the size and shape of the tablet.

Size and shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation is determined and then averaged. The individual weights of the tablets were also determined accurately and the weight variation is calculated by the under given formula. The specification as per I.P. are shown in **Table 5**.

% wt. variation = (Individual wt. - Average wt.) / Individual wt. × 100

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.

Table 5. Wt. variation specification as per IP 2007

Average weight of tablet (mg)	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (W_{initial} - W_{final}) / W_{initial} \times 100$$

In vitro dispersion time

Tablet was placed in 10 ml phosphate buffer solution, pH 6.8±0.5°C. Time required for complete dispersion of a tablet was measured.

In vitro disintegration time

The *in vitro* disintegration time of a tablet can be determined using disintegration test apparatus as per pharmacopoeial specifications. One tablet is placed in each of the six tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured and recorded.

Thickness

Tablet thickness can be measured using a simple procedure. Ten tablets are taken and their thicknesses are measured using vernier calipers, mean value is calculated.

Accelerated stability study

The orally disintegrating tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies at (i) 40 ± 1 °C (ii) 50 ± 1°C (iii) 37±1 °C and Relative Humidity 75% ± 5%.

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization including visual defects, hardness, friability, disintegrations, dissolution and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotted according to Arrhenius equation to determine the shelf life at 25 °C.

Wetting time

Five circular tissue papers of 10 cm diameter will place in a petridish with a 10 cm diameter. Ten millimeters of water containing Eosin, a water soluble dye, will add to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet will note as a wetting time.

Water absorption ratio

A piece of tissue paper folded twice will place in a small Petri dish containing water. A tablet will put on the paper and the time required for complete wetting will measured. The wetted tablets are then weighed. Water absorption ratio (R), will be determined using following equation.

In vitro dissolution test

The development of dissolution methods for MDTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent FDT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for MDTs in the same way as their ordinary tablet counterparts. It has been suggested that USP type 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used (Chaturvedi *et al* 2012; Kulkarni *et al* 2011; Bharawaj *et al* 2010; Lokesh *et al* 2011).

Patient counseling points for MDTs

As pharmacists are ideal persons to become familiar with recent technological advancement in novel dosage form, thus have opportunity to counsel the patient for effective treatment. Educating the patients about MDTs can avoid any confusion and misunderstanding about usage of this dosage form. Counseling points to the patients include:

1. Patients may mistake MDT for effervescent tablets, pharmacist need to be clearly told about the different between them. The cima technologies, orosolv and durasolv use slight effervescence, patients may experience a pleasant tingling effect on the tongue.
2. MDT need to be handled carefully because some of MDTs developed may not have sufficient mechanical strength.
3. Patients with dryness of mouth or with siogrens syndrome or those who taking anticholengic drugs may not be suitable population for administering MDT. Although no water is needed to allow the drug to dispense quickly and efficiently but most technologies of MDT utilizes the body own salivation but decreased volume of saliva may slow down dissolution/disintegration/ bioavailability of the product.
4. Although chewable tablets have been in the market for long time, patients need to be counseled properly the difference between chewable and MDT tablets. MDTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth and also for geriatric patients who have lost their teeth permanently.
5. With the pharmacist counseling, intervention

and assistance all of these patients who taking MDT could be more properly treated with greater convenience.

CONCLUSION

Mouth dissolving tablets (MDTs) offer many advantages over the conventional oral tablets. With rapid acceptance by patients, the number of drug candidates available as mouth dissolving tablets have been considerably increased and the future of this dosage form in the pharmaceutical market seems to be promising with continuous growth in product pipe line.

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