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Melt In Mouth Tablet-A Futuristic Drug Delivery System

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ABSTRACT:

Melt in mouth tablets are oral solid dosage form which when placed on tongue disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed with or without heat of saliva. Melt in Mouth tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. It is very important drug delivery system in case where drug absorbed from buccal cavity. Rapid disintegration of tablet cause quick dissolution and thus fast onset of action. It provides good stability, accurate dosing, easy manufacturing, reduced packaging size; self administration is possible during travelling as water is not required and easy to handle by patients. It is easy to administer for pediatric, geriatric, and institutionalized patients especially for uncooperative patients.

KEYWORDS: Melt in Mouth, Rapid Melt, Mouth Dissolving, Oro Dispersible, buccal cavity.

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INTRODUCTION

Melt-in-mouth tablets (MMT) can be defined as an oral solid dosage form which when placed on tongue disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down in to the stomach.^{1,2}

The drug having molecular size between 75-600 Daltons, molecular weight between 200-500 Daltons, stable at buccal pH and are either lipophilic or hydrophilic in nature will be easily absorbed from the buccal mucosa.³

The tablet is the most widely used dosage form because its convenience in terms of compactness, self administration and also in manufacturing. Patients are like Pediatric, geriatric experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness scientists have developed innovative drug delivery system which known as "Melt in Mouth

"Fast Dissolve", "Rapid Melt", "Quick Disintegrating", "Mouth Dissolving" "Orally disintegrating", "Oro Dispersible" are the terms that represents same Drug delivery system.^{4,5,6}

These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds. According to European Pharmacopoeia, the MMT should disperse or disintegrate in less than three minutes.

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The basic approach used in development of MMT is the use of superdisintegrants which provide instantaneous disintegration of tablet after putting on tongue, there by releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water.

A major claim of the some Melt in Mouth tablet is increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those cases where the drug dissolves quickly.

Poor compliance is a major concern in the treatment of depression. Between 30 and 68% of depressed patients discontinue treatment within one month significantly increasing their risk of relapse. Poor compliance is promoted by many factors including dislike to antidepressant therapy. This dislike is mainly caused by the shame associated with depression and drug-related effects, including the slow onset of action observed with conventional antidepressants.

The problem of patient compliance in the administration of oral antipsychotic drugs can be overcome by development of an appropriate dosage form. Melt in mouth tablets are best suited and have gained popularity in the recent years in oral antipsychotic drug therapy.

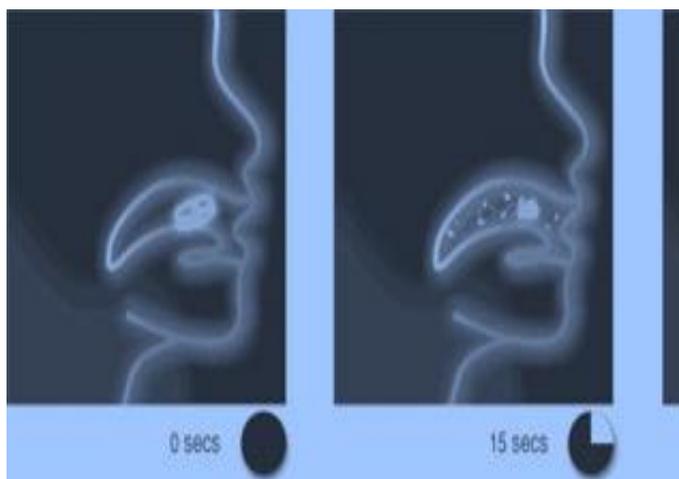


Figure-1.1: Disintegration of Tablet in Mouth

ADVANTAGES

Melt in Mouth tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

- As MMTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients⁷.
- Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in MMTs⁸.
- No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water⁹.
- Easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients)¹⁰
- Rapid disintegration of tablet cause quick dissolution and thus fast onset of action¹¹.
- Bioavailability of drugs that are absorbed from mouth, pharynx, and esophagus is increased.^{12, 13}
- Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.¹⁴

CHALLENGES TO DEVELOP MMT

- Rapid disintegration of tablet
- Have sufficient mechanical strength
- Avoid increase in tablet size
- Minimum or zero residue in mouth
- Protection from moisture
- Good package design
- Compatible with taste masking technology
- Not to affect drug properties

FORMULATION ASPECTS IN DEVELOPING MMTS

Melt in Mouth tablets are formulated by utilizing several processes, which differ in their methodologies and variation in their properties such as,

- Mechanical strength of tablets
- Taste and mouth feel
- Swallowability
- Bioavailability
- Stability, etc.

APPROACHES FOR PREPARATION OF MMTs^{15 to 20}

Various technologies used in the manufacture of MMT include:

- Freeze-drying,
- Sublimation,
- Molding,
- Spray drying,
- Mass extrusion,
- Disintegrant addition, and
- Effervescent tableting
- Cotton Candy Process

Freeze-drying

The tablets prepared by using freeze-drying or lyophilization technique are highly porous in nature and disintegrated or dissolved rapidly when come in contact with saliva. First of all, the material is frozen to bring it below its eutectic point. Then drying is carried out to reduce the bound moisture to the required volume. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. However the use of freeze-drying is limited due to high cost of equipment and processing, packaging, low mechanical strength, poor stability at higher temperature and humidity.

Sublimation

This process involves addition of some inert volatile substances like Urea, Urethane, Naphthalene, Camphor, Menthol, Ammonium bicarbonate, etc. to other Excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores (**Figure 1.2**) in tablet structure, due to which tablet disintegrates when comes in contact with saliva. Melt in Mouth Tablets with highly porous structure and good mechanical strength can be developed by this method.

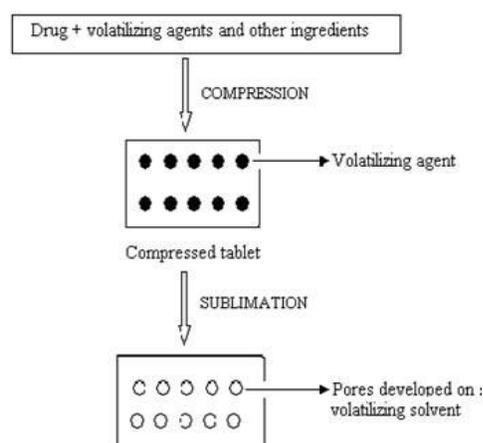


Figure -1.2: Schematic Diagram of Sublimation Technique for Preparation of MMT

Molding

Tablets prepared by molding method are solid dispersions. The drug can exist as discrete particles or micro particles in the matrix. Molded tablets are less compact than compressed tablets, with a porous structure that facilitates rapid disintegration and easy dissolution. Molded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But molded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding Sucrose, Acacia or Polyvinyl pyrrolidone can increase mechanical strength to some extent.

Spray Drying

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet. It provides immediate dissolution (<20 sec). However, this approach involves high cost and time of production, and also very poor mechanical strength of tablets.

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.

Addition of Disintegrants

Use of disintegrants is the basic approach in the development of MMTs. Disintegrants play a major role in the disintegration and dissolution of MMT. It is critically essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Sodium starch glycolate, Ac-di-sol (Croscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised starch, etc. are some examples of disintegrants. Additionally, sugar based excipients are used for taste masking and as bulking agents. Sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used for aqueous solubility and sweetness to impart a pleasant mouth feel and good taste masking.

Effervescent tableting

This approach is designed to produce a solution rapidly with the simultaneous release of carbon dioxide due to chemical reaction between the tablet ingredients that involve an organic acid (citric acid or tartaric acid) and an alkaline substance (carbonates or bicarbonates). When such a tablet is dropped into a glass of water, a rapid chemical reaction occurs producing a pleasantly flavored carbonated drink, which assists in masking the taste of certain drugs. However the disadvantage of the effervescent tablet is the difficulty of producing a chemically stable product. The effervescent tablets are specially packaged in hermetic-type foil pouches or are stack packed in cylindrical tubes with minimal air space.

Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to MMT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high-process temperature limits the use of this process

1.2.5 PATENTED TECHNOLOGIES^{13, 14, 15, 16, 17, 18}

A. Zydis technology

Zydis is a technique which is patented by R.P. Scherer. This technology includes physical trapping of the drug in a matrix composed of a saccharide and a polymer. Polymers generally employed are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, polyvinyl alcohol, polyvinyl pyrrolidone, acacia, and these mixtures. The methodology involves solution or dispersion of components is prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers. Peelable backing foil is used to pack Zydis units. Zydis formulation is sensitive to moisture and may degrade at humidity greater than 65%.

Desired characteristics of Zydis technology:

- Drug should be chemically stable
- Water insoluble
- Particle size should be smaller than 50 μm .
- Dose for water-soluble drugs is limited (60 mg)

B. Lyoc

Lyoc is a technique which is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Nonhomogeneity 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.

C. Quick solv

This technology is patented by Janssen Pharmaceuticals. It utilizes 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 an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

D. 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 in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.

E. FlashTab technology

This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types.

1. Disintegrating agents include reticulated polyvinylpyrrolidone or carboxy methylcellulose.
2. Swelling agents include carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

F. OraSolv technology

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the ODTs. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight.

As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv, a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet with in the depression. Paksolv offers moisture, light, and child resistance packing.

G. Durasolv technology

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants.

Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in bottles and blisters. Nondirect compressible fillers generally used in the range of 60-95%, lubricant in 1-2.5%.

H. WOW tab technology

Yamanouchi patented this technology. WOW means With Out Water. This technology utilizes conventional granulation and tableting methods to produce ODT employing low- and high-moldability saccharides:

Low moldability saccharides are lactose mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration.

I. Dispersible tablet technology

Lek, Yugoslavia patents this technology. It offers development of ODT 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 improved disintegration of tablets usually less than 1 min.

J. Pharmaburst technology

SPI Pharma, New Castle, patents this technology. It utilizes the

dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles³.

K. Frosta technology

Akina patents this technology. 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.

L. Oraquick

This technology is patented by K.V Pharmaceuticals. It utilizes taste masking microsphere technology called as Micromask[®], which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of microparticles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat-sensitive drugs. Oraquick product dissolves within few seconds.

M. Ziplets/advatab

This technology is patented by Pessano con Bornago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce MMT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles.

N. Flashdose

Fuisz has patented Flashdose technology. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using Flashdose technology is the first commercial product launched by Bioavail Corporation. Flashdose tablets consist of self-binding shearform matrix termed as "Floss." Shearform matrices are prepared by flash heat processing.

1.2.6 MECHANISM OF TABLET DISINTEGRATION¹⁵

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

A. By Capillary Action

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

B. By Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the 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.

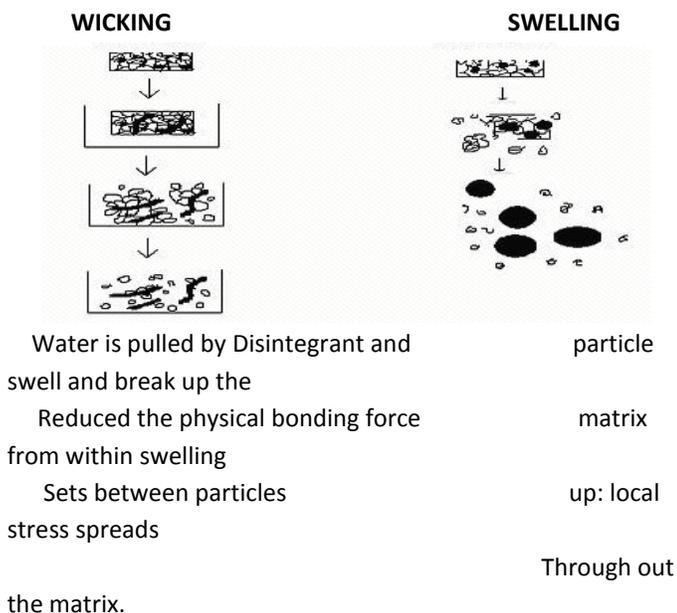


Figure-1.3: Disintegration by Wicking and Swelling¹⁵

C. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

D. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants.

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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 particles 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.

E. 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. The increase in size of the deformed particles produces a break up of the tablet. This mechanism is not yet confirmed and studies are going on.

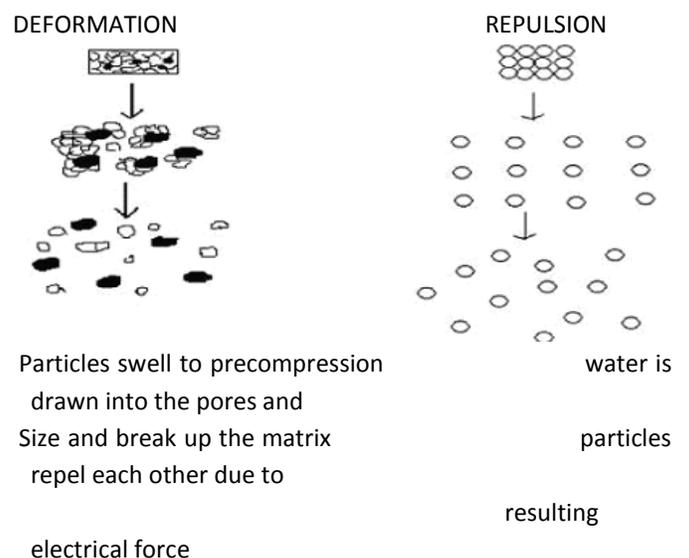


Figure-1.4: Disintegration by Deformation and Repulsion¹⁵

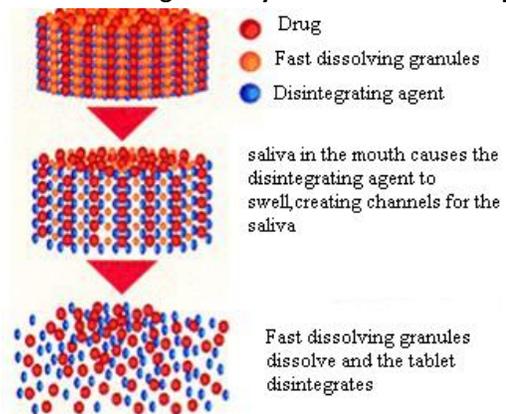


Figure-1.5: Mechanism for Disintegration¹⁵

MARKETED PRODUCTS¹⁵**Table 1.1: Marketed Products**

Trade Name	Active Drug	Manufacturer
Nimulid-MD [®]	Nimesulide	Panacea Biotech, New Delhi, India
Feldene Fast Melt [®]	Piroxicam	Pfizer Inc., NY, U.S.A
Zyrof Meltab [®]	Rofecoxib	Zydus Cadila, India
Pepcid RPD [®]	Famotidine	Merck and Co., NJ, U.S.A
Romilast [®]	Montelukast	Ranbaxy Labs Ltd., New Delhi, India
Torrox MT [®]	Rofecoxib	Torrent Pharmaceuticals, Ahmedabad, India
Zofran ODT [®]	Ondansetron	Glaxo Wellcome, Middlesex, UK
Mosid-MT [®]	Mosapride citrate	Torrent Pharmaceuticals, Ahmedabad, India
Febrectol [®]	Paracetamol	Prographarm, Chateaufeuf, France
Maxalt MLT [®]	Rizatriptan	Merck and Co., NJ, U.S.A
Zelapar TM [®]	Selegiline	Amarin Corp., London, UK

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