

Fast Dissolving Tablet- A Review

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The convenience of administration and improved patient compliance are important in the design of oral drug delivery system which remains the preferred route of drug delivery inspite of various disadvantages. One such problem can be solved in the novel drug delivery system by formulating “mouth dissolving tablets” (MDTs) which disintegrates or dissolves rapidly without water within few seconds in the mouth due to the action of superdisintegrant or maximizing pore structure in the formulation. Mouth dissolving tablets are advantageous particularly for pediatric, geriatric and mentally ill patients who have difficulty in swallowing conventional tablets and capsules. The review describes the various formulation aspects, superdisintegrants employed and technologies developed for MDTs, along with various excipients, evaluation tests, marketed formulation and drugs used in this research area.

Keyword: Fast-disintegrating tablet, Urea, Sublimation, Mouth Dissolving Tablets

INTRODUCTION:

The tablet is the most widely used dosage form existing today because of its convenience in terms of self-administration, compactness and ease in manufacturing. However, geriatric, pediatric and mentally ill patients experiences difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome these problems, scientists have developed innovative drug delivery system known as mouth dissolving/disintegrating tablets (MDTs).

These are novel types of tablets that dissolve/disintegrate/ disperse in saliva within few

seconds without water. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem. The benefits of MDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market ^{1, 2, 3}. Mouth dissolving tablets are also called as orodispersible tablets, fast disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets. However, of all the above terms United States Pharmacopoeia (USP) approved these dosage forms as ODTs. United States Food and Drug Administration (FDA) defined ODTs as “A solid dosage form containing medicinal

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substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue”^{4, 5}. Mouth dissolving tablets are formulated mainly by two techniques first use of super disintegrants like crosscarmellose sodium, sodium starch glycolate and crosspovidone. Another method is maximizing pore structure of the tablets by freeze drying and vacuum-drying. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pre-gastric absorption of saliva containing dispersed drugs that pass down in to the stomach. Moreover the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets^{6, 7}.

Criteria for Fast dissolving Drug Delivery System:

The tablets should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.

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 traveling 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.
- Pre-gastric 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 extensions 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.

Benefits of fast dissolving tablets:

- Administered without water, anywhere, any time.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disabled and the patients who are uncooperative, or are on reduced liquid intake plans or are nauseated.

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Limitations of Mouth Dissolving Tablets

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Technologies used for manufacturing of MDTs:

In the recent past, several new advanced technologies have been introduced for the manufacturing of MDTs with ideal properties like less disintegration time, pleasant mouth feel, exceptional taste masking and sugar free tablets for diabetic patients. The technologies used for manufacturing of MDTs broadly classified in two category one is patented another one is non-patented technologies.

Lyophilization or Freeze-drying:

Formation of porous product in freeze-drying process is exploited in formulating MDTs. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has Rapid disintegration and dissolution when placed on the tongue and the

freeze-dried unit dissolves instantly to release the drug. However, the MDTs formed by lyophilization have low mechanical strength, poor stability at higher temperature, and humidity⁸.

Molding: In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that increase dissolution⁹.

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 process¹⁰ involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized 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 MDTs.

Spray drying: This technology produces highly porous and fine powders as the processing solvent is evaporated during the process¹¹. In this method to prepare MDTs hydrolyzed and non-hydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent and sodium starch glycolate or crosscarmellose sodium as superdisintegrant. Disintegration and dissolution were further increased by adding acidic substances like citric acid or alkali substance like sodium bicarbonate. This formulation technique gives porous powder and disintegration time < 20 sec^{12,13}.

Mass extrusion: This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a

cylinder of the product into even segments using heated blade to form tablets¹⁴.

Melt granulation: In this process, MDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate is a waxy material with an m. pt. of 33-37°C and a hydrophilic-lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of MDTs by melt granulation method where granules are formed by the molten form of this material¹⁵.

Phase transition process: Kuno et. al.,¹⁶ investigated processes for the disintegration of MDTs by phase transition of sugar alcohols using erythritol (m. pt. 122°C), xylitol (m. pt. 93-95°C), trehalose (97°C), and mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Sublimation: The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of MDTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet¹⁷. Developed MDTs utilizing camphor, a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

Direct compression methods: This technique is easy way to formulate MDTs since limited number of processing steps, low manufacturing cost and also accommodate high dose the final weight of tablet can easily exceed that of other production method¹⁸. The disintegration and dissolution of directly compressed tablets depends on single or combined effect of disintegrant, water soluble excipients and effervescing agents. Disintegrant efficacy is strongly affected by tablet size and hardness. Disintegration properties can be optimized by medium or low tablet size, low hardness and low physical resistance. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure fast disintegration and high dissolution rates^{18, 19}. The addition of water soluble excipients or effervescent agent can further increase dissolution or disintegration properties. Super disintegrants provide fast disintegration due to combine effect of swelling and water absorption.

As an effect of swelling of super disintegrant the wetted surface of the carrier increase, which promotes wettability and dispersibility of the system and thereby increase the disintegration and dissolution^{20, 21, 22}. The optimum concentration of superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration the tablet disintegration time is inversely proportional to the concentration of superdisintegrant, where as if concentration of superdisintegrants incorporated in tablet is above the critical concentration, the disintegration time remains approximately constant or even increases.

Patented Technologies for Fast Dissolving Tablets:

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 zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is

composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts 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 while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze-drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

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

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.

Flash Dose Technology: Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

Wow tab Technology: Wow tab technology is patented by Yamanouchi Pharmaceutical Co.

List of Marketed Fast Dissolving Tablets (Yourong F et. al. 2004).

Trade Name	Active Drug	Manufacturer
Felden fast melt	Piroxicam	Pfizer Inc., NY, USA
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexa	Olanzapine	Eli Lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Zomig-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegiline	Amarin Corp., London, UK
Tempra Quiclets	Acetaminophen	Bristol Myers Squibb, NY, USA
Febrectol	Paracetamol	Prographam, Chateaufneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi, India
Torrox MT	Rofecoxib	Torrent pharmaceuticals, India
Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA
Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceuticals
Risperdal MTab	Risperidone	Janssen pharmaceuticals
Spasfon Lyoc	Phloroglucinol Hydrate	Farmalyoc
Nurofen FlashTab	Ibuprofen	Ethypharm
Tempra Quicklets	Paracetamol	Cima Labs, Inc
Zomig Repimelt	Zolmitriptan	Cima Labs, Inc
NuLev	Hyoscyamine Sulfate	Cima Labs, Inc
Gaster D	Famotidine	Yamanouchi Pharma Tech. Inc.
Cibalgina DueFast	Ibuprofen	Eurand International
Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd
Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc
Abilify Discmelt	Aripiprazole	Otsuka America/Bristol-Myers Squibb
Allegra ODT	Fexofenadine	Sanofi Aventis
Aricept ODT	Donepezil	Esai Co.
Clarimex RediTabs	Desloratadine	Schering-Plough
Alavert Quick Dissolving Tablets	Loratadine	Wyeth
Clonazepam ODT	Clonazepam	Par Pharmaceutical
FazaClo	Clozapine	AzurPharma
Jr. Tylenol Meltaways	Acetaminophen	McNeil Consumer Healthcare
Loratadine Redidose	Loratadine	Ranbaxy
Mirtazapine ODT	Mirtazapine	Teva Pharmaceuticals
Niravam	Alprazolam	Schwarz Pharma
Ondansetron ODT	Ondansetron	Teva Pharmaceuticals
Orapred ODT	Prednisolone	Sielele Pharma
Parcopa	Carbidopa/levodopa	Schwarz Pharma
Prevacid SoluTab	Lansoprazole	Takeda Pharmaceuticals
Remeron SoliTab	Mirtazapine	Schering-Plough
Risperdal M-Tab	Risperidone	Janssen
UNISOM SleepMelts	Diphenhydramine	Chattam
Zomig-ZMT	Zolmitriptan	AstraZeneca
Zyprexa Zydis	Olanzapine	Eli Lilly and Company
Citalopram ODT	Citalopram	Biovail
Metoclopramide Zydis	Metoclopramide	Salix Pharmaceuticals
Reglan ODT	Metoclopramide	Schwarz Pharma
Tramadol/Acetaminophen ODT	Tramadol/Acetaminophen	Biovail
Zolpidem ODT	Zolpidem	Biovail

WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides) and compressed into table.

Flash tab Technology: Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.

EVALUATION OF MOUTH DISSOLVING TABLET:

MDTs formulations have to be evaluated for the following evaluation test 56, 57.

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

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight: I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Average weight of Tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Tablet hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of

the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre weighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as;

$$\% \text{Friability} = \text{loss in weight} / \text{Initial weight} \times 100$$

In-Vivo Disintegration test: The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting time: The method reported by Yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

In vitro dispersion time: In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

CONCLUSIONS:

The MDTs have potential advantages over conventional dosage forms, with their improved patient compliance, convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. MDTs formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. These MDTs can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently. They remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. As they have significant advantages as both solid and liquid dosage forms, MDTs may be developed for most of the available drugs in near future.

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