



[Review article]

Oral Dispersible Tablets - A Review

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ABSTRACT

The convenience of administration and improved patients compliance are important in the design of oral drug delivery system which remains the preferred route of drug delivery inspite of various disadvantage.one such problem can be solved in the novel drug delivery system by formulating oral disintegrating tablets which disintegrates rapidly without water within few seconds in the mouth due to action of super disintegrants in the formulation. Oral disintegrating tablets are advantageous for pediatric, geriatric mentally ill, nausea patients who have difficulty in swallowing conventional tablets and capsules. Using various excipients, evaluation tests marketed formulation and drugs used in the research area.

Keywords: Oral dispersible tablets, super disintegrants, Fast dissolving tablets.

INTRODUCTION TO ORAL DISPERSIBLE TABLETS

An Oral route of drug administration have wide acceptance up 50-60% of total dosage form. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importance patience compliance¹.

The U.S food and drug administration center for drug evaluation and research (CDER) defines, an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue.

The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient,

regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules³. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmacokinetic and pharmacodynamics characteristics of drugs.

These dosage forms disintegrate within 30 sec with very less quantity of water. This can be achieved by addition of various super disintegrants like Croscarmellose sodium, Cross povidone, sodium starch glycolate².

These tablets are also called as Orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts³. However, of all the above

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terms, United States of pharmacopoeia (USP) approved these dosage forms as ODTs (orally disintegrating tablets). Recently, European Pharmacopoeia has used the term Orodispersible tablet for tablets that disperses readily within 3 min in mouth before swallowing¹. United States of Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.” The disintegration time for ODTs generally ranges from several seconds to about a minute.²

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^{1, 2,3,6,7}

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.
- 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.

Limitations of Mouth Dissolving Tablets⁸

- 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 FDTs⁴

In the recent past, several new advanced technologies have been introduced for the manufacturing of FDTs 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 FDTs broadly classified in two category one is patented another one is no patented technologies.

Lyophilization / Freeze-drying

Formation of porous product in freeze-drying process is exploited in formulating FDTs. 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 humidity.

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 dissolution.

Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimics cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharine 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 FDTs.

Spray drying

Spray drying can be used to prepare rapidly dissolving tablets. This technique is based upon a particulate support matrix that is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredient and compressed into tablet. Allen and Wang have employed spray drying technique to prepare Orodispersible tablets.

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 tablets.

(f) Melt granulation

In this process, FDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Superpolystate 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 material 15.

Phase transition process

Investigated processes for the disintegration of FDTs 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 FDTs. 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 tablet. Developed FDTs 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.

(i) Direct compression methods

This technique is easy way to formulate FDTs 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 effervescent agents. Disintegrant efficacy is

strongly affected by tablet size and hardness. 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 disintegrant 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

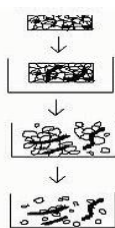
(j) Superdisintegrants addition

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of Superdisintegrants are Crosscarmellose, Crospovidone and sodium starch Glycolate, which are a cross linked cellulose, cross-linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets.

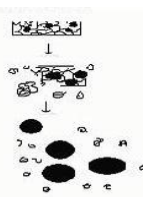
Microcrystalline cellulose and low substituted hydroxyl propyl cellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch Glycolate, Crospovidone and Crosscarmellose are some of the popular superdisintegrants. The list of commonly used Superdisintegrants with their description is shown in Table 1.

Mechanism of Superdisintegrants¹⁰

There are four major mechanisms for tablet disintegration as follows:



WICKING



SWELLING

Fig. 1.0: Disintegration by wicking and swelling process

Disintegration properties can be promoted wet ability and dispensability of the system and thereby increase the disintegration and dissolution^{20,21,22}. The optimum concentration of super disintegrants can be selected according to critical concentration of disintegrant. Below this concentration the tablet disintegration time is inversely proportional to the concentration of superdisintegrants, where as if concentration of superdisintegrants incorporated in tablet is above the critical concentration, the disintegration time remains approximately constant or even increases.

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

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 table ting conditions. For these types of disintegrates 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. The wicking and swelling process of disintegration is Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrants attempts to explain the swelling of tablet made with non swellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

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. This may be a mechanism of starch and has only recently begun to be studied. Disintegration of tablets by deformation and repulsion

Sugar-based Excipients

Sorbitol, Mannitol, dextrose, xylitol, fructose, maltose, isomalt and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar based materials.

Table 1 List of super disintegrants

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose®	Cross linked	Swells 4-8 folds	Swells in two
Ac-Di-Sol®	Cellulose	in < 10 seconds,	dimensions, used for
Nymce ZSX®		acts by swelling	direct compression
Primellose®Solutab®		and	or granulation
Vivasol®L-HPC		wicking both	
Crospovidone	Cross linked	Swells very little	Water insoluble and
Crospovidone M®	PVP	and returns to	spongy in nature so
Kollidon®		original size after	get porous tablet
Polyplasdone		compression	
		but act by	
		capillary action	
Sodium starch	Cross linked	Swells 7-12 folds	Swells in three
Glycolate	Starch	in < 30 seconds	dimensions and high
Explotab®			level serve as sustain
Primo gel			release matrix
Alginic acid NF	Cross linked	Rapid swelling in	Promote
Satialgine®	alginic acid	aqueous medium	disintegration
		or wicking action	in both dry or wet
			granulation
Soy polysaccharides	Natural		Does not contain any
Emcosoy®	superdisintegrants		starch or sugar, used
			in
			nutritional products
Calcium silicate		Wicking action	Highlyporous, 20-40%

Using acid treated yeast cell wall

Natural materials should be useful as pharmaceutical additives from the perspective of resource utilization and safety. Acidified brewers yeast cell wall (AYC) has been examined with respect to novel applications as it can be used as an aqueous coating material for tablets and granules. In accordance with these properties of AYC, AYC maintains the baggy structure of the original yeast. In water, AYC is dispersed as independent particles with a surface hydrogel layer. Water is included within the structure unlike other polymers.

Using hydroxyl waxy binders

This work describes a new approach to prepare fast dissolving tablets with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder (Superpolystate®, PEG-6-stearate). 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.

Patented Technologies for Fast Dissolving Tablets^{13, 14,15,16,17.}

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 materials 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 crystalline, 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. 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, oligo saccharides) 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.

Table 2 List of commercially available Orodispersible/FDT tablets

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
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegiline	Amarin Corp., London, UK
Tempra Quiclets	Acetaminophen	Bristol Myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, 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 Fast melt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA

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