

Orodispersible Tablet- A Novel Drug Delivery System

Sharad A More*, Dr. S. K. Mohite.

Department of Quality Assurance, Rajarambapu College of Pharmacy, Kasegaon, Sangli .

ABSTRACT

Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. One such approach is oral disintegrating tablets (ODTs). ODTs are a solid unit dosage form, which disintegrates or dissolves rapidly in the mouth without the general requirement for swallowing, the chewing and water. Yet, dysphasia is the most common disadvantage of conventional tablets. To overcome such problems, certain innovative drug delivery systems, like 'Mouth Dissolving Tablets' (MDT) have been developed. These are novel dosage forms which dissolve in saliva within a few seconds, when put on tongue. Such MDTs can be administered anywhere and anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients.

Keywords: Oral disintegrating tablets, mechanism of action superdisintegrant, evaluation test for ODT, ODTs preparations, patented technologies.

INTRODUCTION

Drug Delivery Systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms . Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis . Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which result results in a high incidence of noncompliance and Ineffective therapy . It has been reported that dysphagia (difficulty in swallowing) is common Among all age groups and more specific with pediatric, geriatric population along with Institutionalized patients and patients with nausea. Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid Swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way. The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts. However of all the above terms, United States Pharmacopoeia (USP) approved these

dosage forms as ODTs. Recently, European Pharmacopoeia has used the term “orodispersible tablet” for tablets that disperse readily and within three minutes before swallowing.

United States Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medicinal substances 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 . Fast dissolving tablets are also called as mouth dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva⁵. The faster the drug into solution, quicker the absorption and onset of clinical effect. 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 significantly greater than those observed from conventional tablets dosage form.

Mouth Dissolving Tablet (MDT)

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

Ideal Properties Of MDT

Mouth Dissolving Tablet should

- a. Not require water or other liquid to swallow.
- b. Easily dissolve or disintegrate in saliva within a few seconds.
- c. Have a pleasing taste.
- d. Leave negligible or no residue in the mouth when administered.
- e. Be portable and easy to transport.
- f. Be able to be manufactured in a simple conventional manner within low cost.
- g. Be less sensitive to environmental conditions like temperature, humidity etc.

Advantages Of MDT

- a. No need of water to swallow the tablet.
- b. Can be easily administered to pediatric, elderly and mentally disabled patients.
- c. Accurate dosing as compared to liquids.
- d. Dissolution and absorption of drug is fast, offering rapid onset of action.
- e. Bioavailability of drugs is increased¹⁰as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down into the stomach.
- f. Advantageous over liquid medication in terms of administration as well as
- g. transportation.
- h. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
- i. Free of risk of suffocation due to physical obstruction when swallowed.

Drug selection criteria

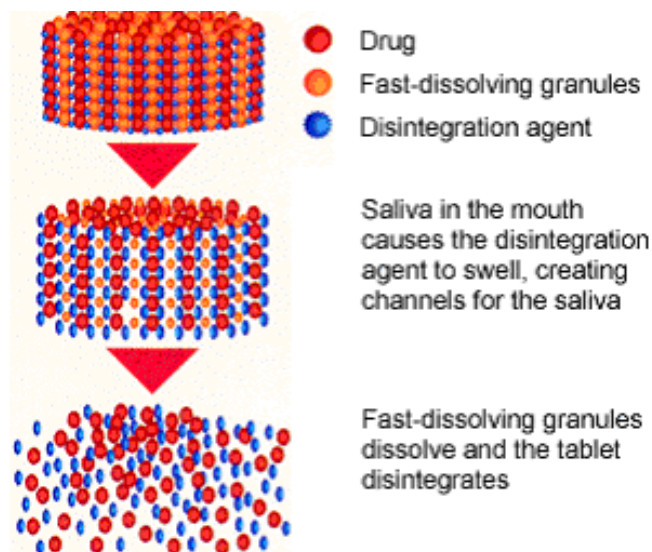
The ideal characteristics of a drug for oral dispersible tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for ODT.

Mechanism Of Action Of Disintegrants

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

- By Capillary Action
- By Swelling
- Because Of Heat Of Wetting
- Due To Release Of Gases
- By Enzymatic Action
- Due To Disintegrating Particle/Particle Repulsive Forces
- Due To Deformation



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.

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 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 separate fraction of formulation.

E. 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.

F. Due To Disintegrating Particle/Particle Repulsive Forces

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

Researchers found that repulsion is secondary to wicking.

G. Due To Deformation

Hess had proved that 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.

Preparation of MDT

1. Freeze-drying or lyophilization
2. Sublimation
3. Spray drying
4. Moulding
5. Mass extrusion
6. Direct compression

1. Freeze-drying or lyophilization

The tablets prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve rapidly when come in contact with saliva. In this process, water is sublimated from the product after freezing. First of all, the material is frozen to bring it below its eutectic point. Then primary drying is carried out to reduce the moisture to around 4% w/w of dry product. Finally, secondary drying is done to reduce the bound moisture to the required volume.

2. Sublimation

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method

3. 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. Allen and Wang used this technique to prepare mouth-dissolving tablets, which disintegrated within 20 s.

4. Moulding

Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on whether and to what extent it dissolves in the wetted mass. The drug can exist as discrete particles or micro particles in the matrix. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion.

5. 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.

6. Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially Tablet disintegrants and sugar-based excipients. Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution.

EVALUATION OF ODTs

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness:

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers.

Friability:

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration

properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet.

The wetting time of the tablets can be measured by using the simple procedure²⁹. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added 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 is noted as the wetting time.

For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (W_b). The wetted tablet from the petridish is taken and reweighed (W_a). The water absorption ratio,

R can be the determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

Moisture uptake studies:

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation.

Ten tablets from each formulation were kept in a dessicator over calcium chloride at 37°C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Disintegration test:

The time for disintegration of ODTs is generally <1min and actual disintegration time that patient can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents.

Dissolution test:

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile.

In-vitro dispersion time:

Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C, Time required for complete dispersion of a Tablet was measured.

Future prospects of MDT

Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. In addition, MDTs may be suitable for the oral delivery of drugs such as protein and peptide based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Because drugs delivered in MDTs may be absorbed in the pregastric sites of highly permeable buccal and mucosal tissues of the oral cavity, they may be suitable for delivering relatively low molecular weight and highly permeable drugs. Future possibilities for improvements in MDTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from MDTs have yet to be fully realized.

List of products categorized by technology

ZYDIS PRODUCTS:

Claritin Reditab *micronized loratadine (10 mg)*, citric acid, gelatine, mannitol, mint flavour.

Feldene Melt *piroxicam (10 or 20 mg)*, gelatine, mannitol, aspartame, citric anhydrous.

Maxalt-MLT *rizatriptan (5 or 10 mg)*, gelatine, mannitol, aspartame, peppermint flavour.

Pepcid RPD *famotidine (20 or 40 mg)*, gelatine, mannitol, aspartame.

Zyprexa Zydis *olanzapine (5, 10, 15 or 20 mg)*, gelatine, mannitol, aspartame, methylparaben sodium, propylparaben sodium.

Zofran ODT *ondansetron (4 or 8 mg)*, aspartame, gelatine, mannitol, methylparaben sodium, propylparaben sodium, strawberry flavour.

Dimetapp Quick Dissolve Children's Cold and Allergy Tablets (OTC)

ORASOLV PRODUCTS:

Remeron Soltab *mirtazepine (15, 30, or 45 mg)*, aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavour.

Tempra FirstTabs *acetaminophen (80 or 160 mg)*, inactive ingredients including mannitol (currently available in Canada).

Triaminic Softchew (OTC)

DURASOLV PRODUCTS:

NuLev *hyoscyamine sulfate (0.125 mg)*, aspartame, colloidal silicon dioxide, crospovidone, mint flavouring, magnesium stearate, mannitol, microcrystalline cellulose

Zomig ZMT *zolmitriptan (2.5 mg)*, mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid, anhydrous, colloidal silicon dioxide, magnesium stearate, orange flavour

WOWTAB PRODUCTS:

Benadryl Allergy & Sinus Fastmelt (OTC)

Children's Benadryl Allergy & Cold Fastmelt (OTC)

Marketed Products of MD

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	Zyodus, 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
Olanex Instab	Olanzapine	Ranbaxy Labs Ltd., New Delhi, India
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Mosid-MT	Mosapride citrate	Torrent Pharmaceuticals, Ahmedabad, India
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Maxalt MLT	Rizatriptan	Merck and Co., NJ, U.S.A
Zelapar TM	Selegiline	Amarin Corp., London, UK

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