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Review Article

ORALLY DISINTEGRATING TABLETS: A REVIEW

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ABSTRACT
Orally disintegrating tablets (ODTs) are gaining prominence as new drug delivery systems and emerged as one of the popular and widely accepted dosage forms, especially for the pediatric and geriatric patients. To obviate the problem of dysphagia and to improve patient compliance, ODTs have gained considerable attention as preferred alternatives to conventional tablet and capsule formulations. Various scientific techniques including freeze drying, moulding, spray drying, sublimation, direct compression, cotton candy process, mass extrusion, melt granulation etc. have been employed for the development of ODTs. These techniques render the disintegration of tablet rapidly and dissolve in mouth without chewing or additional water intake. The current article is focused on ideal characteristics, significant features, patented technologies, formulation aspects including the use of superdisintegrants. Various marketed preparations along with numerous scientific advancements made so far in this avenue have also been discussed.
KEYWORDS: Orally disintegrating tablets, Superdisintegrants, Disintegration, Enhanced bioavailability.

INTRODUCTION

Oral route of drug administration have wide acceptance, up to 50-60% of solid dosage forms are popular because of natural, uncomplicated, convenient, ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms being tablets and capsules, one important drawback of these dosage forms for patient is the difficulty to swallow. Swallowing of solid dosage forms like tablets and capsules and improper dosing of suspension and emulsion may produce difficulty for young children because of incomplete development of muscular and nervous system and elderly patients suffering from dysphasia, Parkinson's disorder and tremor. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled patients, patients who are uncooperative, or on reduced liquid intake plans or nauseated, patients having a persistent cough or a gag-reflex, and travelers who may not have access to water.[1]

To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.[2]

Fast dissolving tablets are gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a matter of seconds without the need of water or chewing. These are useful for pediatric, geriatric and also dysphagia patients, leading to improved patient compliance. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, fast dissolving drug formulations have been developed to overcome problems related to swallowing difficulties. When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration.[3]

Orally disintegrating 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 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 disperses readily and within 3 min in mouth before swallowing.

United States 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.[3]

An ideal oral fast disintegrating tablet should

Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.

- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable
- Leave minimal or no residue in mouth after administration
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipments.

Advantages of oral FDTs

- Administration to the patients who can not swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs starts from mouth, pharynx & oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Challenges confroting formulation of oral FDTs

i) Mechanical strength and disintegration time- Oral FDTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many Oral FDTs are fragile and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

ii) Taste masking- Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

iii) Mouth feel- The Oral FDT should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDT should be as small as possible. FDT should leave minimal or no residue in mouth after oral administration. Morever addition of flavours and cooling agents like menthol improve the mouth feel.

iv) Sensitivity to environmental conditions- FDT generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in a FDT are meant to dissolve in minimum quantity of water.

v) Cost- The technology used for a FDT 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.

Limitations to oral fast disintegrating tablets

- Drugs with relatively larger doses are difficult to formulate into FDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for FDT. Similarly patients with dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Selection of drug candidates for ODTs

Several factors must be considered while selecting an appropriate drug candidate for development of orally disintegrating dosage forms. The ultimate characteristics of a drug for dissolution in the mouth and pregastric absorption from ODTs include:

- Free from bitter taste.
- Dose lower than 20 mg.
- Small to moderate molecular weight.
- Good solubility in water and saliva.
- Partially nonionized at the oral cavity's pH.
- Ability to diffuse and partition into the epithelium of the upper GIT (log P >1, or preferably >2).
- Ability to permeate oral mucosal tissue.

In contrast, the following characteristics may render a drug unsuitable for delivery as an orally disintegrating dosage form

- Short half-life and frequent dosing.
- Very bitter or otherwise unacceptable taste because taste masking cannot be successfully achieved.
- Require controlled or sustained release.
- Combination with anticholinergics.

Wide range of drugs can be considered as a suitable candidate for such dosage forms. Various researchers have developed orally disintegrating dosage forms for different categories of drugs used in clinical therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, antiallergics, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, antiparkinsonism agents, antibacterial agents etc.

Ingredients to be used for FDDTs

Important ingredients that are used in the formulation of FDDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients.

Excipients balance the properties of the actives in FDDTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Binders keep the composition of these fast-melting tablets together during the compression stage. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast- dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used.

Role of super disintegrants

Use of disintegrants is the basic approach in development of MDTs. Disintegrants play a major role in the disintegration and dissolution of MDT. It is 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. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.

The optimum concentration of the superdisintegrant can be selected according to critical concentration of disinteg rant.Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if con centration of superdisintegrant is above critical Concentration, the disintegration time remains almost co nstant or even increases.

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

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 finepar ticles. Water uptake by tablet depends upon hydrophilicit y 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.

By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling.

Tablets with high porosity show poor disintegration due t o 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 di sintegration is again slows down.

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.

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 ofpressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. Asthese disintegrants are highly sensitive to small chang es in humidity level and temperature, strict control of env ironment is required during manufacturingof the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fractio n 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 th e volume of granules to promote disintegration.

Techniques for preparing fast dissolving tablets

Many techniques have been reported for the formulation of Fast dissolving tablets or
Orodispersible tablets.

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion
7. Nanonization
8. Cotton Candy Process
9. Fast Dissolving Films

Freeze-Drying or Lyophilization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. 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. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Molding

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients

(e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents

Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

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 tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (up to 200 mg of drug per unit).

Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. A matrix known as 'floss', with a combination of excipients, either alone or with drugs is prepared by using shear form technology. Like cotton-candy fibers floss is fibrous material made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and poly-dextrose can be transformed into fibers at 30–40% lower temperature than sucrose. Due to this modification thermo labile drugs can be safely incorporated into the formulation. This process results in a highly porous product 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:

(a) Floss blend: - The floss mix is prepared by blending the 80% sucrose in combination with mannitol/dextrose and 1% surfactant. The surfactant maintains the structural integrity of the floss fibers by acting as crystallization enhancer. This process helps in retaining the dispersed drug in the matrix, thereby minimizes the migration out of the mixture.

(b) 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.

(c) Floss chopping and conditioning: - In this step fibers are converted into smaller particles in a high shear mixer granulator. The partial crystallization is done by spraying ethanol (1%) onto the floss and subsequently

evaporated it to impart improved flow and cohesive properties to the floss. This is called Conditioning.

(d) Blending and compression: - Finally, the chopped and conditioned floss fibers are blended with the drug and other excipients and compressed into tablets. Exposure of the dosage forms to elevated temperature and humidity conditions (40 °C and 85% RH for 15min) improves the mechanical strength of tablets due to expected crystallization of floss material that result in binding and bridging, to improve the structural strength of the dosage form.

Fast Dissolving Films

It is a newer developing front in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, CMC, HPMC, HEC, HPC, PVP, PVA etc.), drug and other taste masking ingredients are dissolved in non-aqueous solvent to prepare non-aqueous solution, which on evaporation of solvent forms a film. Resin adsorbate or coated micro particles of the drug can be incorporated into the film if the drug is bitter. This film when placed in mouth, melts or dissolves rapidly and release the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 sec with instant drug delivery and flavored tast

COUNSELING POINTS FOR FDDTS

Pharmacists are in the ideal position to become familiar with the different technologies, and educate their patients on what to expect upon taking their first dose. The majority of patients receiving FDDT preparations have little understanding of this new dosage form. Patients may be surprised when tablets begin to dissolve in the mouth. They might expect a faster onset of therapeutic action. Clarification from the pharmacist can avoid any confusion or misunderstanding. As with all dosage form technologies, some patient populations are better served by their use than others. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. 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. Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation. Decreased volume of saliva may slow the rate of dissolution/disintegration and decrease the bioavailability of the product.

Although chewable tablets have been on the market for some time, they are not the same as the new FDDTs. Patients for whom chewing is difficult or painful can use these new tablets easily. FDDTs can be used easily in children who have lost their primary teeth, but do not have full use of their permanent teeth.

Patients may mistake fast-dissolving/disintegrating for effervescent tablets. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets.

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Table 1: Marketed preparation of ODTS

Trade name	Active drug	Manufacturer
Zontec MD	Cetrizine	Zosta pharma India
Zofer MD	Odansetron	Sun pharma
Vomidon MD	Domperidon	Olcare lab
Valus	Valdecoxib	Glen mark
Ugesic	Piroxicam	Mayer organic Ltd.
Torrox MT	Rofecoxib	Torrent pharma
Romilast	Moontelukast	Ranbaxy Labs Ltd
Rofixx MD	Rofecoxib	Cipla Ltd
Ondem MD	Ondansetron	Alkem pharma
Olanex istab	Olanzapine	Ranbaxy Labs Ltd
Nimulid MDT	Nimesulide	Panacea biotech
Nime MD	Nimesulide	Maiden pharma
Mosid MD	Mosapride	Torrent pharma
Lonazep MD	Olanzapine	Sun pharma
Kazoldil MD	Nimesulide	Kaizen drugs
Esulide	Nimesulide	Doff biotech