A REVIEW ON: ORALLY DISINTEGRATING TABLETS

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Abstract
Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric, and psychiatric patients with dysphasia. Today, ODTs are more widely available as over-the-counter products for the treatment of allergies and cold and flu symptoms. Technologies used for manufacturing of orally disintegrating tablets are either conventional technologies or patented technologies. In conventional freeze drying, tablet molding, sublimation, spray drying etc. and in patented Zydis technology, Orasolv technology, Durasolv technology, Wowtab technology, Flashdose technology are important. Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. Evaluation of these tablets is done by following weight variation, friability, tensile strength, wetting time, water absorption ratio.

Keywords: ODT, Technology, Patients compliance, Mouth dissolving tablets, superdisintegrants.

INTRODUCTION
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. For these reason, tablets that can rapidly
dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. [1,2]

**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. [3]

**Ideal properties of ODTs**
The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function. An ideal ODT should meet the following criteria: [4]

- Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds
- Has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling
- Allow high drug loading
- Has a pleasant mouth feel
- Is insensitive to environmental conditions such as humidity and temperature
- Is Technologies used for manufacturing of orally disintegrating tablets adaptable and amenable to existing processing and packaging machineries

**Technologies used for manufacturing of orally disintegrating tablets**
The currently available technologies have been reviewed in the literature. The technologies are usually grouped according to the method used in making FDTs, such as:

- Freeze drying
- Molding and
- Compression

Compression is the most widely used method for making FDTs. Some methods are focused on unique granulation method such as spray-drying and flash-heating, to make shear form formulations; some are focused on selecting specific excipients such as water-insoluble calcium salt, specific disintegrant combination, and specific sugar combination; and some are focused on special treatment after compression, such as sublimation, sintering, and humidity treatments. Each method is examined in more detail below: [5-8]

**A. Freeze Drying**
Freeze drying (lyophilization) is a process in which solvent is removed from a frozen drug solution or a suspension containing
structure-forming excipients. The resulting tablets are usually very light and have highly porous structures that allow rapid dissolution or disintegration. When placed on the tongue, the freeze dried unit dissolves almost instantly to release the incorporated drug. The entire freeze drying process is done at non elevated temperatures to eliminate adverse thermal effects that may affect drug stability during processing. When stored in a dried state, the freeze-dried dosage form has relatively few stability problems during its shelf life. The freeze-drying process may result in a glassy amorphous structure of excipients as well as the drug substance, leading to the enhanced dissolution rate. Freeze drying, however, is a relatively expensive manufacturing process, and the formulation has poor stability at higher temperature and humidity.

B. Molding

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as compression molding.) Then the solvent can be removed by air-drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen.

Recently, the molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as heat molding) or by evaporating the solvent from a drug solution or suspension at ambient pressure (no vacuum lyophilization). Solid dispersion also can be used to make the tablets. The drug can remain discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to produce a solid solution or dissolve partially in the molten carrier while the remaining undissolved particles disperse in the matrix.

The characteristics of the tablets (such as disintegration time, drug dissolution rate, and mouth feel) vary based on the type of the dispersion or dissolution. Because of their water-soluble sugar components, molded tablets disintegrate more rapidly and offer improved taste. However, molded tablets typically do not have great mechanical strength. The chance of erosion and breakage of the molded tablets during tablet handling and opening blister pockets is high. If hardness enhancing agents are added to the formulation, the rate of tablet disintegration usually decreases. Mechanical strength and good disintegration of the tablets can be improved by using nonconventional equipment and/or multistep processes. Using a nonconventional approach, however, requires substantially larger investment in machinery. Compared with freeze-drying, molded tablets can be produced more simply and efficiently at an industrial scale, although disintegration
times may not be comparable to those of lyophilized forms.

C. Compaction

Using a conventional tablet press to make fast-dissolving tablets is a very attractive method because of the low manufacturing cost and ease in technology transfer. However, the tablet press has been designed to make conventional tablets. When making conventional tablets, maintaining high tablet porosity is not a primary concern, and high compression force is used to ensure the tablet strength. Many strategies have been tried to achieve high porosity and adequate tablet strength using a tablet press. First, several granulation methods have been tried to obtain granules suitable for making FDTs. Wet granulation, dry granulation, spray drying, and flash heating methods have been tried. The second approach is to select special types of excipients as the main component for FDTs. The third approach is to compress tablets at low pressure and apply various after-treatments to the soft tablets.

The three most widely used approaches are described in detail below.

1. Granulation Methods

a. Wet Granulation

It is a process of producing FDTs by wet granulation in a fluidized bed. It was found that even with effervescent agents presented in the tablet with lower than 5%, quick disintegration times could be achieved. Furthermore, it was also found that fast disintegration time could be achieved using only the acid component of the effervescent couple. In the patent, the formulation includes polyalcohols (e.g., mannitol, xylitol, sorbitol, maltitol, erythritol, and lactitol), 1–30% of an edible acid, and an active ingredient as the dry mixture. This mixture was wet granulated with an aqueous solution of a water-soluble or water-dispersible polymer (e.g., poly(ethylene glycols), carrageenan, and ethylcellulose), which consisted of 1–10% of the final weight of the granule in a fluid bed. Granules with high porosity and low apparent density were obtained, and the tablets made by such granules had rapid disintegration times ranging from 3 to 30 seconds in the saliva developed an FDT for a poorly water-soluble active ingredient. First, nano particles were formed by mechanical grinding, precipitation, or any other suitable size reduction process. Those nanoparticles, less than 2 µm, were stabilized by surfactants. The particles were granulated with at least one pharmaceutically acceptable water-soluble or water-dispersible excipient using a fluid bed, and the granules were made into tablets. The tablets had complete disintegration or dissolution in less than 3 minutes.

b. Dry Granulation

Eoga and Valia disclosed a method of making FDTs by dry granulation. Higher density alkali earth metal salts and water-soluble carbohydrates usually do not provide quick disintegration and a smooth mouth feel. Low-density alkali earth metal salts and water soluble carbohydrates are also difficult to compress and caused inadequate content uniformity. For these reasons, low-density alkali earth metal
salts or water-soluble carbohydrates were precompacted, and the resulting granules were compressed into tablets that could dissolve fast. In this process, a powdered material with a density of 0.2–0.55 g/mL was precompacted to increase the density to 0.4–0.75 g/mL by applying a force ranging from 1 to 9 kN/cm. The resulting granules were compressed into tablets.\(^{[9]}\)

c. Melt Granulation
Abdelbary et al. described a new approach of preparing FDTs with sufficient mechanical strength, involving the use of a hydrophilic waxy binder (Superpolystate®, PEG-6-stearate) by melt granulation or wet granulation. Because Superpolystyrate\(^{\text{®}}\) is a waxy material with a melting point of 33–37 °C and a hydrophilic to lipid balance (HLB) value of 9, it will not only act as a binder and increase the physical strength of tablets but also help the disintegration of the tablets. In case of melt granulation, granules were prepared in a high-speed blade mixer at 40–44 °C, according to the conventional hot-melt procedure. For wet granulation, an oil-in-water emulsion of Superpolystyrate\(^{\text{®}}\) was used as the granulating agent. Then, granules were blended with croscarmellose, aspartame, and magnesium stearate and compressed into tablets. The melt granulation FDTs had better hardness results than the wet granulation FDTs. The disintegration times of melt granulation tablets; however, was more than 1 minute.\(^{[10]}\)

d. Spray Drying
Spray drying methods are widely used in pharmaceutical and biochemical processes. Spray drying provides a fast and economical way of removing solvents and producing highly porous, fine powders. Allen and Wang produced a particulate support matrix for use in making FDTs by a spray-drying technique. The components included supporting agents composed of two polypeptide components of the same net charge (preferably nonhydrolyzed and hydrolyzed gelatin), a bulking agent (mannitol), and a volatilizing agent. To maintain the net charges of the polypeptide components, an acidifying or alkalinizing agent was included. The mixtures of the above components were spray dried to obtain porous granules. The reason to use polypeptide components of the same charge was that molecules would repel each other even after spray drying, so porous and low-bulk-density particles could be formed. By incorporating a volatilizing agent (ethanol in most cases), the surface tension of the droplets was further reduced during spray drying, and more pores and channels were created. The dissolution rate of the matrix was further increased when combined with a bulking agent. A minimal amount of an effervescent agent was optionally included to further accelerate the dissolution rate. To aid in keeping the tablets intact during handling, a thin coating of polymeric material could be applied externally. This coating should not inhibit the capillary uptake of water during dissolution. Active ingredients can be microencapsulated or nanoencapsulated to further achieve taste masking.\(^{[11]}\)

2. Direct Compression
From the pharmaceutical manufacturer’s point of view, direct compression is the
simplest and most cost-effective tablet manufacturing procedure. Pharmaceutical companies can use conventional manufacturing equipment and commonly available ingredients. This method can be applied to manufacturing FDTs by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility and sweetness, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations. [12]

PATENTED TECHNOLOGIES

1. Zydis technology
Zydis was the first marketed technology developed by R.P.Scherer, Inc. for formation of new generation tablets. Zydis, the best known of the fast dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolve in a matrix composed of two components, a saccharide e.g. mannitol and a polymer. When Zydis units are kept in the mouth the freeze dried structure disintegrates instantaneously and does not require water for swallowing. Polymers such as gelatin, dextran or are incorporated to impart strength during handling. Mannitol or sorbitols are incorporated, to obtain crystallanity, elegance and hardness. Flocculating agents (e.g., xanthan gum and acacia) to provide uniform dispersion of drug particles; preservatives (e.g., parabens) to prevent microbial growth; permeation enhancers (e.g., sodium lauryl sulphate) to improve transmucosal permeability; pH adjusters (e.g., citric acid) to optimize chemical stability; flavours and sweeteners to improve patient compliance. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Gums prevent the sedimentation of dispersed particles in manufacturing process. Collapse protectants like gelatin prevents the shrinkage of Zydis units during freeze-drying process or on long term storage. The product is very light weight and fragile, and must be dispensed in a special blister pack. [13, 14]

2. Orasolv technology
OraSolv was Cima's first fastdissolving/disintegrating dosage form. In this system active medicament is taste masked, contains disintegrating agent. The disintegration of ODT in the mouth is cause by the action of an effervescent agent, activated by saliva. The amount of effervescent agent is in general about 20-25% of the total weight of the tablet. The widely used effervescent disintegration pair usually includes an acid source (citric, tartaric, malic, fumaric, adipic and succinics) and carbonate source (sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate). The microspheres are loosely compressed to maintain the integrity of the coating. The major disadvantage of the OraSolv...
formulations is its mechanical strength. For that reason, Cima developed a special handling and packaging system for OraSolv. Manufacturing requires a controlled environment at low relative humidity and protection of the final tablets with moisture impermeable blisters.\cite{13,15}

3. Durasolv technology
Durasolv is CIMA’s second generation fast dissolving or disintegrating tablet formulation to produce stronger tablets for packing in conventional blisters or bottles. Durasolv has much higher mechanical strength due to use of the higher compaction pressure during tabletting. One disadvantage of Durasolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to high pressure during compaction. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter tasting drugs to the patient taste buds. So this technology is good for tablets having low amount of active ingredients.\cite{16}

4. Wow tab technology
The WOW in the WOWTAB signifies the tablet is to be given without water. This technology utilizes sugar and sugar-like excipients. The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. The two different saccharides are those with high moldability like maltose, mannitol, sorbitol, and oligosaccharides (good binding property) and low moldability like lactose, glucose, mannitol, xylitol (rapid dissolution). Tablets produced from this technology will have sufficient hardness to maintain the physical characteristics of the dosage form during production until it comes in contact with moisture such as saliva in mouth. Due to the significant hardness the WOWTAB formulation is more stable to the environment than the Zydis and Orasolv. Erythritol was found to be the best sugar for this type of formulation, showing rapid disintegration which is unaffected by tablet hardness.\cite{13,17}

5. Cotton candy technology
This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. The cotton candy process also known as the candy floss process. A mouth dissolving tablet is formed using candy floss or shear form matrix. It involves the formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallised to have improved flow properties and compressability. This candy floss matrix is then milled and blended with active ingredients, excipients and subsequently compressed to ODT. This process can accommodate larger drug doses and offer improved mechanical strength. However, high process temperature limits the use of this process.\cite{16,17}

6. Oraquick technology
The Oraquick fast dissolving/disintegrating tablets formulation utilizes a patented taste masking technology. This taste masking process does not utilize solvents of any kind, so leads to faster and more efficient production.
During processing low-heat is produced so this technique is suitable for heat sensitive drugs. KV pharmaceuticals also claims that the matrix that surrounds and protects the drug powder in microencapsulated particle is more pliable. This technique gives tablets with good taste masking and quick dissolution in matter of seconds. [18]

7. NanoCrystal technology
NanoCrystal™ Fast dissolving technology provides for: Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix. Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded As Safe) ingredients, filled into blisters, and lyophilized. This method avoids manufacturing process such as granulation, blending and tableting which is more advantages for highly potent and hazardous drugs. For fast dissolving tablets, Elans proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase dissolution rate. [19]

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

1. 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 test.

2. 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%).

3. 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 procedure. [20]

Five circular tissue papers of 10 cm 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 ratio the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, R can be the determined according to the following equation.

\[ R = 100 \frac{(Wa - Wb)}{Wb} \]
4. 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.

5. Disintegration test

The time for disintegration of ODTs is generally <1 min and actual the disintegration time that patients can experience ranges from 5 to 30 s. 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.

6. 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.

Counseling points for ODTs [21]

Pharmacists are in the ideal position to become familiar with the various technologies, and educate their patients on what to expect upon taking their first dose. The majority of patients receiving ODT formulations have little understanding of this new dosage form. Patients may be surprised when tablets begin to dissolve in the oral cavity. They might expect a faster onset of therapeutic action. Clarification from the pharmacist can avoid any confusion or misunderstanding. 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 disintegration/dissolution and decrease the bioavailability of the product. Although chewable tablets have been in the market for some time, they are not the same as the new ODTs. Patients for whom chewing is
difficult or painful can use these new tablets easily. ODTs 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 ODTs for effervescent tablets. Pharmacists may wish to stress the difference between the use of ODTs and effervescent tablets. ODT formulations are more susceptible to degradation via temperature and humidity. Some of the newest ODT formulations are dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such formulations to ensure they are not exposed to high levels of moisture or humidity. As with most drugs, patients should be advised to avoid storing ODTs in the medicine cabinet in the bathroom. Pharmacists have been alerted to exercise additional care when dispensing new prescriptions for ODT formulations. Most such products are available in the same strengths as traditional dosage forms. Prescribing physicians must make an additional notation for the dispensing of an ODT. A physician may also mistakenly believe the drug brand name is Zydis, for example, without identifying a specific drug. Verification with the prescribing practitioner may be necessary in some cases and can clear up any confusion.  

**Industrial Applications**

Industrial applications include the following:

- To develop an orally disintegrating dosage forms and to work with existing disintegrants
- To further improvise upon the existing technology of ODTs
- To optimize the blend of disintegrants or excipients to achieve ODTs
- To select and develop proper packaging material and system for enhanced stability of the product and also develop a cost-effective product
- To arrive at various taste-masking agents and prepare palatable dosage forms thereby increasing patient compliance
- To develop disintegrants from different polymers which are used as coating materials by certain modifications and use them for formulating ODTs.

**Future Prospects**

These dosage forms 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. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide.
Conclusion
Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms. The target population has expanded to those who want convenient dosing anywhere, anytime, without water. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand. By paying close attention to advances in technologies, pharmaceutical companies can take advantage of ODTs for product line extensions or for first-to-market products. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for ODTs in the days to come.

References
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