ABSTRACT

Over the past three decades, Orally Disintegrating Tablet (ODT) has gained much attention as a preferred alternative to conventional oral dosage form such as tablet and capsules. This are also called as orodisperse, mouth dissolving, rapidly disintegrating, and fast melt system. This disintegrates in the mouth in seconds without chewing and the need of water which is advantageous mainly for pediatrics, geriatrics and patients having difficulty in swallowing tablets and capsules. Conventional preparation methods are spray drying, freeze drying, direct compression, Molding, and sublimation while new technologies have been developed for the production of orodispersible tablets. This review describes various formulation aspects, disintegrants employed and challenges in formulating ODTS, along with various exipients, evaluation tests and industrial applications in detail.

KEYWORDS: Orally disintegrating tablet; Super-disintegrant; Orodispersible tablets; Evaluation technique.

INTRODUCTION

Oral dosage forms like tablets and capsules possessing great problem of swallowing mainly for pediatrics, geriatrics, and bedridden, nauseous or non-compliant patients. Orally disintegrating dosage forms has to be placed in mouth and then get dispersed in saliva without the need of water.\(^1\)\(^-\)\(^2\) Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.\(^3\)\(^-\)\(^5\)
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. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%).

US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the ‘Orange Book’, an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. European Pharmacopoeia described orally disintegrating tablets as ‘uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed’ and as tablets which should disintegrate within 3 min. About 35% of the general population in addition to 30-40% of elderly institutionalized patients and 18-22% of all persons in long term care facilities suffer from dysphagia, i.e. difficulty in swallowing. Orally disintegrating tablets have been found to be the choice for Psychiatric as well as patient suffering from stroke, thyroid disorder, Parkinson’s diseases and multiple sclerosis, patients with nausea, vomiting and motion sickness.

Advantages of ODT

- Best for patient with oesophageal problems and have difficulties of deglutition tablets.
- High drug loading is possible.
- Rapid onset of action and may offer an improved bioavailability.
- Useful for pediatric, geriatric and psychiatric patients.
- Suitable during traveling where water is may not be available.
- No specific packaging required, can be packaged in push through blisters.
- Smooth mouth feel and pleasant taste.
- Conventional manufacturing equipment.
- Good chemical stability as conventional oral solid dosage form.
- Cost effective.

Characteristics of an ideal orally disintegrating drug delivery system

Orally disintegrating drug delivery system should possess following characteristics:

- Utilizes cost effective production method.
Require no water for oral administration.
Dissolve / disperse/ disintegrate in mouth in a matter of seconds.
Have a pleasing mouth feel and taste masking.
Less friable and have sufficient hardness.
Leave minimal or no residue in mouth after administration.
Manufacturing using conventional manufacturing method.

Choice of drug candidate \[14\]

Suitable drug candidate for orally disintegrating tablet should possess:
- No bitter taste.
- Good stability in water and saliva.
- Dose should be low as possible.

Unsuitable drug candidate for orally disintegrating tablet should include:
- Short half-life and frequent dosing.
- Drug having very bitter taste.
- Required controlled or sustained release.

Challenges in formulating ODTS

Palatability \[15-16\]

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient’s oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength \[17-19\]

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

Hygroscopicity \[20\]

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.
Amount of drug\textsuperscript{[15]}

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility\textsuperscript{[21]}

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet\textsuperscript{[22]}

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Excipients commonly used for ODT preparation.

It contains active principle, mixture of excipients comprising at least one disintegrant, a diluent, a lubricant, and, optionally, a swelling agent, a permeabilizing agent, sweeteners, and flavorings.

Some of the excipients employed are given in Table 1. Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers it will be advantageous to select ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethyl cellulose (HPMC), alone or in admixtures, and the most commonly acrylic polymers are used are the ammonio-methacrylate copolymer (Eudragit. RL and RS), polyacrylate (Eudragit. NE) and polymethacrylate (Eudragit. E). Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols, and, preferably, mannitol. The most common antistatic agents used are colloidal silica (Aerosil) precipitated silica (Sylod. FP244) micronized or non-micronized talc, maltodextrins, \( \beta \)-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium
stearyl fumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant.\[23\] An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling.\[24\]

**Table 1: Name and weight percentage of different excipients**\[24\]

<table>
<thead>
<tr>
<th>Name of the excipients</th>
<th>% tage used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disintegrant</td>
<td>1 to 15%</td>
</tr>
<tr>
<td>Diluent</td>
<td>0 to 85%</td>
</tr>
<tr>
<td>Binder</td>
<td>5 to 10%</td>
</tr>
<tr>
<td>Antistatic Agent</td>
<td>0 to 10%</td>
</tr>
</tbody>
</table>

**Super-disintegrants and ODT**

Super-disintegrant plays the major role in orodispensible tablet. Caramella et al. found that disintegration efficiency is based on the force-equivalent concept (the combined measurement of swelling force development and amount of water absorption).\[25-26\] Force equivalence expresses the capability of a disintegrant to transform absorbed water into swelling (or disintegrating) force.\[27\] The optimization of tablet disintegration is commonly done by mean of the disintegration critical concentration. Below this concentration the tablet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increased.\[28\] Recently few ion exchange resins (e.g. Indion 204, 234) are found to have super-disintegrant property and are widely used in pharmaceutical industry.\[29\] Some of the super disintegrants employed are discussed in Table 2.

**Table 2: Some super disintegrants employed in orally disintegrating tablet.**\[30-31\]

<table>
<thead>
<tr>
<th>Superdisintegrants</th>
<th>Nature</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosspovidon</td>
<td>Crosslinked homo polymer of N-vinyl-2-pyrrolidone</td>
<td>Both swelling and wicking</td>
</tr>
<tr>
<td>Crosscarmellose sodium</td>
<td>Cross linked form of sodium CMC</td>
<td>Swelling</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Crosslinked low substituted carboxymethyl ether of poly-glucopyranose</td>
<td>Water uptake followed by rapid and enormous swelling</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Sodium salt of alginic acid</td>
<td>Swelling type</td>
</tr>
<tr>
<td>Effervescent mixture</td>
<td>Citric acid, tartaric acid, sodium bicarbonate</td>
<td>Effervescence</td>
</tr>
<tr>
<td>Acrylic acid derivative</td>
<td>Poly (Acrylic acid)super porous gel</td>
<td>Wicking type</td>
</tr>
<tr>
<td>NS-300</td>
<td>Carboxy methyl cellulose</td>
<td>Wicking type</td>
</tr>
</tbody>
</table>
Formulation aspect in developing ODT

Orally Disintegrating tablets are formulated utilizing several processes, which differ in their methodologies. Various processes employed in formulating of ODTs include, Freeze drying, Spray drying, Molding, Phase transition process, Melt granulation, Sublimation, Mass Extrusion, Cotton Candy Process, Direct compression. There are several commercial products available in indian market for ODTs that are given in Table 3.

Table 3: Orally disintegrating tablet products available in Indian market.[32]

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domray MD</td>
<td>Domperidone</td>
<td>Ray remedies</td>
</tr>
<tr>
<td>Velrid MD</td>
<td>Domperidone</td>
<td>Shreyam health care</td>
</tr>
<tr>
<td>Vomidon MD</td>
<td>Domperidone</td>
<td>Olcare lab</td>
</tr>
<tr>
<td>Zotacet MD</td>
<td>Cetirizine Hcl</td>
<td>Zota pharma</td>
</tr>
<tr>
<td>Olanex instab</td>
<td>Olanzapine</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Manza RDT</td>
<td>Olanzapine</td>
<td>Manp pharma(Orchid)</td>
</tr>
<tr>
<td>Romilast</td>
<td>Montelukast</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Torrox MT</td>
<td>Rofecoxib</td>
<td>Torrent</td>
</tr>
<tr>
<td>Ziflam</td>
<td>Rofecoxib</td>
<td>Kopran</td>
</tr>
<tr>
<td>Doloroff</td>
<td>Rofecoxib</td>
<td>Indoco</td>
</tr>
<tr>
<td>Rofaday MT</td>
<td>Rofecoxib</td>
<td>Lupin</td>
</tr>
<tr>
<td>Dolib MD</td>
<td>Rofecoxib</td>
<td>Panacea</td>
</tr>
<tr>
<td>Orthoref MD</td>
<td>Rofecoxib</td>
<td>Biochem</td>
</tr>
<tr>
<td>Rbcx-25 MD</td>
<td>Rofecoxib</td>
<td>Shalman pharma</td>
</tr>
<tr>
<td>Roffec MD</td>
<td>Rofecoxib</td>
<td>Excare lab</td>
</tr>
<tr>
<td>Roftab MD</td>
<td>Rofecoxib</td>
<td>Olcare lab</td>
</tr>
<tr>
<td>Zofex-25 MD</td>
<td>Rofecoxib</td>
<td>Zota pharma</td>
</tr>
<tr>
<td>Valus</td>
<td>Valdecoxib</td>
<td>Glenmark</td>
</tr>
<tr>
<td>Nency MD</td>
<td>Nimesulide</td>
<td>Zenon health care</td>
</tr>
<tr>
<td>Nexus MD</td>
<td>Nimesulide</td>
<td>Lexus</td>
</tr>
<tr>
<td>Nimex MD</td>
<td>Nimesulide</td>
<td>Mexon health care</td>
</tr>
<tr>
<td>Nimez MD</td>
<td>Nimesulide</td>
<td>Zota pharma</td>
</tr>
<tr>
<td>Nisure MD</td>
<td>Nimesulide</td>
<td>Suzen pharma</td>
</tr>
<tr>
<td>Nimulid MD</td>
<td>Nimesulide</td>
<td>Panacea</td>
</tr>
<tr>
<td>Olnim MD</td>
<td>Nimesulide</td>
<td>Olcare lab</td>
</tr>
<tr>
<td>Sulbid MD</td>
<td>Nimesulide</td>
<td>Alpic remedies</td>
</tr>
<tr>
<td>Topmide</td>
<td>Nimesulide</td>
<td>Antigen health care</td>
</tr>
<tr>
<td>Nimpain MD</td>
<td>Nimesulide</td>
<td>Prompt cure pharma</td>
</tr>
<tr>
<td>Mosid MT</td>
<td>Mosapride</td>
<td>Torrent</td>
</tr>
</tbody>
</table>
Freeze drying

In freeze-drying drug physically trapped in a water soluble matrix, which is freeze-dried to produce a tablet that dissolve rapidly in less than 5 sec when placed in mouth. Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drug in a water soluble matrix which is then freeze dried to give highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in less than 5 sec due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances.\textsuperscript{33-34}

Ahmed et al. prepared lyophilized tablet using freeze drying technique. The lyophilized tablet prepared by dispersing drug Ketoprofen in aqueous solution of highly water soluble carrier consisting of gelatin, glycine and sorbitol in blister packs and then subjected to lyophilillation in blister packs. It was found that the increase in solubility of ketoprofen from lyophilized tablet matrix was nearly three times greater than solubility of the plain drug which was due to supersaturation generated by amorphous form of drug.\textsuperscript{35}

Spray drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 sec when immersed in an aqueous medium.

Allen et al. used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 sec.\textsuperscript{36}

Molding

Tablets prepared by this method are solid dispersions. Molded tablets offer improved taste due to water-soluble sugars present in dispersion matrix.
Moulding is done by two methods

a. Compression molding: The manufacturing process involves compressing a powdered mixture previously moistened with solvent (usually ethanol or water) into mould plates to form a wetted mass. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

b. Heat molding: A molten matrix in which drug is dissolved or dispersed can be directly molded into orodispersible tablets. The tablets prepared using heat molding process involves settling of molten mass that contain a dispersed or dissolved drug.\[^{37}\] In this process, the suspension or solution of drug, agar and sugar is prepared and then poured into the blister packaging. The agar solution is then solidified at room temperature to form a jelly and dried at 30°C under the vacuum. Developed orally disintegrating tablets was found to improve the mouth feel due to the presence of the water soluble sugars.\[^{38}\]

c. No vacuum lyophilization: This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

Molded tablets had less mechanical strength. Drug can be present as micro particles or discrete particles dispersed in the matrix. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength. They possess highly porous structure which is supposed to increase their disintegration and dissolution rates.\[^{39}\]

Compaction

A. Melt Granulation

Abdelbary et al. prepared orally disintegrating tablet by incorporating a hydrophilic waxy binder PEG 6-stearate (Superpolystate®) in the formulation. It has melting point of 33-37°C and HLB value of 9. It acts as a binder and increases the physical resistance of tablet. It helps for fast disintegration of tablet when place in mouth and leaving no residue in oral cavity.\[^{40}\]

Perissutti et al. developed the orally disintegrating tablets of Carbamazepine by melt granulation technique. The granules were prepared by using polyethylene glycol (PEG-4000) as a melting binder and lactose monohydrate as hydrophilic filler without using solvents or water. The dissolution profiles of granules containing crosspovidone as an intragranulating agent were found to be superimposable to those prepared without it. Also, the extragranular addition of a small amount of crosspovidone gave rise to a further increase in disintegration rate and dissolution performances.\[^{41}\]
B. Phase Transition Process

The combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, is important for making orally disintegrating tablets without any special apparatus. Here, tablet produced by compressing the powder containing two sugar alcohols of high and low melting point and subsequently heating at temperature between their two melting points. Orally disintegrating tablets were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

Kuno et al. studied the effect of preparation method on the properties of orally disintegrating tablets manufactured using phase transition of sugar alcohol. Before heating process, tablet did not have sufficient hardness because of low compatibility but after heating, increase in interparticular bonding or binding surface area occurs which then increased tablet hardness.\(^{[42]}\)

C. Sublimation

This technique is based on the use of volatile ingredients (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc.) to other tablet excipients and the mixture is then compressed into tablets. Entrapped volatile material is then removed via sublimation, which leads to formation of a porous structure. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 sec in saliva. Several solvents like cyclohexane, benzene etc. can also be used as pore forming agents. Orodispersible tablets with highly porous structure and good mechanical strength have been developed by this method.

Koizumi et al. prepared highly porous compressed tablets. They used mannitol as a tablet matrix material while camphor as subliming agent. Camphor was removed by subliming in vacuum at 800C for 30 min to develop pores in the tablets.\(^{[43]}\)

Makino et al. described a method of producing a fast dissolving tablet using water as a pore forming material. They used a mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc) which then moistened with water (1-3 %w/w) and compressed into tablets. Then water was removed, yielding highly porous tablet.\(^{[44]}\)
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 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 masked their bitter taste. [45]

Cotton candy process
This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to improve flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength. However, high-process temperature limits the use of this process. [46]

Direct compression
Direct compression is the easiest way to manufacture tablet in low manufacturing cost. The basic principle involves addition of disintegrants and/or water soluble excipients and/or effervescent agents. Superdisintegrants in optimum concentration (about 2-5%) are mostly used so as to achieve rapid disintegration along with the good mouth feel.

Bi et al. examined the disintegrant property of mixture of microcrystalline cellulose and low substituted hydroxy propyl cellulose (MCC: L-HPC) for orally disintegrating tablet and found that shortest disintegration time was observed in the range of ratio of MCC: L-HPC (8:2 to 9:1). [47] Cousin et al. prepared orally disintegrating tablet using carboxymethyl cellulose as disintegrating agent and swelling agent consisting of modified starch or microcrystalline cellulose. The tablets disintegrate in the mouth in less than 60 sec. [48]

Gillis et al. prepared a fast-dissolving tablet of Galanthamine hydrobromide which comprise of diluent which is a spray dried mixture of lactose monohydrate and microcrystalline cellulose in the ratio of 75:25, a cross linked polymeric disintegrant such as crosspovidone and a direct compression process was used for preparation of fast dissolving tablets. [49]
Gattani et al. prepared Ondansetron mouth dissolving tablet using treated agar as a superdisintegrating agent and found that tablets with treated agar powder had disintegration rate comparable to other superdisintegrants.\textsuperscript{[50]}

**Ziplets technology**

Recently Eurand (Pessano con Bornago, Italy) developed the Ziplets technology, which can be used with water insoluble compounds as both bulk actives and as coated microparticles (the latter containing soluble and/or insoluble drugs). Coated granules are easy alternative for laboratory purpose. It was found that the addition of a suitable amount of a water-insoluble organic excipient combined with one or more effective disintegrants imparted an excellent physical resistance to the ODT, and simultaneously maintained optimal disintegration, even at low compression forces and tablet hardnesses.\textsuperscript{[51]} In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in a much longer disintegration time. As the soluble components dissolve on the tablet's outer layer, the rate of the water diffusion into the tablet core decreases because of the formation of concentrated viscous solutions.\textsuperscript{[52]}

**ODT evaluation of special concern**

Crushing strength and friability can be assessed as stated in pharmacopoeias. But some tests are of special concern and these include the following:

**Wetting time and water absorption ratio**

Wetting time of ODT is carried out by using the method given by Bi et al. (1996). In this method a piece of tissue paper folded twice in a small culture dish (internal diameter =6.5 cm) containing 6 ml of water. A tablet is placed on the paper, and the time for complete wetting is measured.\textsuperscript{[44]} The wetted tablet is then weighed and the water absorption ratio was calculated using Eq. (1)

$$ R = \frac{(Wb - Wa)}{Wa} $$

Where $Wa$ and $Wb$ are the weights before and after water absorption, respectively.

**Disintegration test**

The time for disintegration of ODTs is generally less than one minute and actual disintegration time that patient can experience ranges from 5-30 sec. The standard procedure of performing disintegration test for these dosage forms has several limitations.
and they are not suitable for the measurement of very short disintegration times. The method needs to be modified for ODTs as disintegration is required without water; thus the test should mimic disintegration in salivary contents. A modified dissolution apparatus is applied to an ODT with a disintegration time that is too fast to distinguish differences between tablets when the compendial method is used. A basket sinker containing the tablets is placed just below the water surface in a container with 900 mL of water at 37°C, and a paddle rotating at 100 rpm is used. The disintegration time is determined when the tablet has completely disintegrated and passed through the screen of the sinker.[53]

A single cylindrical glass tube comparable to rigid glass tube, compared to the rigid basket-rack assembly supporting six tubes, with 35-mm inner diameter and 90 mm length, was constructed. The medium consists of water at a temperature between 15 and 25°C. Only one tablet at a time was tested and considered disintegrated when completely dispersed fragments were obtained.[54]

Various scientists[55] have developed new in vitro methods that allow an accurate determination of disintegration test. The disintegration test is performed using a texture analyzer instrument. In this test, a flat-ended cylindrical probe penetrates into the disintegrating tablet immersed in water. As the tablet disintegrates, the instrument is set to maintain a small force for a determined period of time. The plots of some distance traveled by the probe generated with the instrument’s software provide disintegration profile of the tablets as a function of time. The plot facilitates calculation of the start and end-point of the tablet disintegration.

**Dissolution test** [56]

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 M Hcl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counterparts. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used.
Moisture uptake studies

Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic. Ten tablets from each formulation are kept in a desiccator over calcium chloride at 37°C for 24 h. The tablets are then weighed and exposed to 75% RH at room temperature for two weeks. The required humidity (75% RH) is achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as control (without superdisintegrant) is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded.

Clinical studies

In vivo studies have been performed on oral fast-disintegrating dosage forms to investigate their behavior in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Zydis’s residence time in the mouth and stomach, and its transit through the esophageal tract, was investigated using gamma-scintigraphy. Its dissolution and buccal clearance was rapid, the esophageal transit time and stomach emptying time were comparable with those of traditional tablets, capsules, or liquid forms. A decreased intersubject variability in transit time was also observed. Zydish also showed good therapeutic efficacy and patient acceptability - particularly in children or when easy administration and rapid onset of action were required (such as for patients undergoing surgery).

The fastdisintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability. Increased bioavailability and improved patient compliance were observed in Lyoc formulations for different drugs such as phloroglucinol, glafenine, spironolactone, and propyphenazone. Using Zydis, all the drugs that can be absorbed through the buccal and esophageal mucosa exhibited increased bioavailability and side-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism. Finally, the suitability of ODTs for long-term therapy was also assessed. Lyoc formulations containing aluminum were positively tested in patients with gastrointestinal symptoms.
Patient counseling for ODTs[70]

ODT developed offers significant advantages for various group of patients, but the majority of patients receiving ODT have little understanding of this novel drug delivery systems. 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
Orally disintegrating drug delivery system may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics which have limited bioavailability when administered by conventional tablets and get 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
The ODTs have potential applications over convectional dosage forms with their improve patient compliance and convenience, bioavalability and rapid onset of action. 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. ODT administration is easy for patients who have problems of deglutition or for those persons who would like their treatment without simultaneous ingestion of liquid. In addition of the above advantages it gives pharmacokinetic parameters which are equivalent to those obtainable with existing tablets or gel capsules. Orally Disintegrating tablets are prepared by various technologies and so formulation scientists have more alternatives to choose the best technology according to the specific drug profile. 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. Thus ODTs may be developed for most of the available drugs in near future.

REFERENCES


