Orally Disintegrating Tablets: A Short Review
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Abstract
This article summarizes the advantages of orally disintegrating tablets (ODTs) as well as critical issues during evaluation of ODTs such as bioequivalence and challenges and limitations of ODTs and finally present and the future of ODTs. ODTs have received ever-increasing demand and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water. When ODTs are put on tongue they disintegrate instantaneously, releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both, industry and academia. Their growing importance has been underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablet" as tablet that is to be place in the mouth where it disperses rapidly before swallowing. ODTs have some challenges but solutions to overcome these challenges were shown in this paper.

Keywords: Orodispersible; Orally disintegrating; Tablets; Fast; Advantages; Challenges; Bioequivalence; Biowaiver

Introduction
Oral drug delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, the most convenient and most economical method of drug delivery with the highest patient compliance [1,2]. Oral route is the most preferred route of administration and tablet and capsules are the most preferred dosage forms, but several limitations of that kind of dosage forms like choking and swallowing discomfort in geriatric and pediatric patients [3,4].

Orally disintegrating tablets have been developed and new ODT technologies compensate many pharmaceuticals and patients’ needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphasia [5]. Over the past three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance [6].

ODTs are being named as orodispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. There are some definitions that made by pharmacopeias and agency as follows: Orodispersible tablets have been placed in the mouth where they disperse fast before being swallowed and they are uncoated tablets. Orodispersible tablets disintegrate within 180 seconds when the disintegration tests have been conducted up to the test for disintegration of tablets [7,8].

Orally disintegrating tablets are intended to disintegrate fast in the mouth to provide dispersion before being swallowed where the active ingredient is intended for gastrointestinal delivery and/or absorption [9,10]. A solid dosage form containing active ingredients which disintegrates fast, usually within seconds, when put on the tongue. In addition to those definitions, FDA recommends that, orally disintegrating tablets should be considered as solid oral preparations that disintegrate fast in mouth, with an in-vitro disintegration time of approximately less than or equal to 30 seconds, when the disintegration test conducted to the United States Pharmacopeia (USP) disintegration test method or alternative [11,12].

Products of ODT technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding [6]. For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually [13]. Catalent Pharma Solutions (formerly Scherer DDS) in UK, Cima Labs in the US and Takeda Pharmaceutical Company in Japan are some of the initiators for the development of ODTs.

The first ODT which got approval from the US Food and Drug Administration (FDA) was a Zydis ODT formation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998 [14].
Bioequivalence of ODTs has some challenges but in this part basic solutions to overcome these challenges were given. Active pharmaceutical ingredients that are formulated as ODTs should be dispersed or dissolved in the saliva, then directly absorbed via oral mucosa and/or absorbed through the gastrointestinal system. When defining the dissolution test conditions to prove both of the in-vitro and in-vivo bioequivalence of two formulations, the physiological conditions of the mouth should be considered. pH, flow rate, volume of the saliva and targeted population are the important factors that should be considered.

There are several in-vivo studies for ODTs that conducted to prove bioequivalence of the ODTs, nevertheless BCS based biowaiver is also being considered for especially the active pharmaceutical ingredients are not absorbed via oral mucosa, but must be absorbed through the gastrointestinal system. But if this cannot be demonstrated, bioequivalence must be evaluated via in-vivo studies [25].

If the ODT test product is an extension to another oral formulation, a 3-period study is recommended in order to evaluate administration of the orodispersible tablet both with and without concomitant fluid intake. However, if bioequivalence between ODT taken without water and reference formulation with water is demonstrated in a 2-period study, bioequivalence of ODT taken with water can be assumed.

If the ODT is a generic/hybrid to an approved ODT reference medicinal product, the following recommendations regarding study design apply:

- If the reference medicinal product can be taken with or without water, bioequivalence should be demonstrated without water as this condition best resembles the intended use of the formulation. This is especially important if the substance may be dissolved and partly absorbed in the oral cavity. If bioequivalence is demonstrated when taken without water, also bioequivalence can be assumed with ODT taken with water.
- If the reference medicinal product is taken only in one way (e.g. only with water), bioequivalence should be shown in this condition (in a conventional two-way crossover design).
- If the reference medicinal product is taken only in one way (e.g. only with water), and the test product is intended for additional ways of administration (e.g. without water), the conventional and the new method should be compared with the reference in the conventional way of administration (3 treatment, 3 period, 6 sequence design). In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing 20 ml of water directly before applying the ODT on the tongue. It is recommended not to allow fluid intake earlier than 1 hour after administration.

Other oral formulations such as orodispersible films, buccal tablets or films, sublingual tablets and chewable tablets may be handled in a similar way as for ODTs. Bioequivalence studies should be conducted according to the recommended use of the product [26]. However, as the BCS biowaiver is based on the intake of the tablet with a glass of water (i.e., solubility in 250 ml) and the orodispersible tablets are usually taken without water, it would seem appropriate that the solubility criterion should be amended accordingly. The dissolution method parameters (especially volume of the saliva) to characterize ODTs that simulate oral cavity have not yet been developed.

It is noteworthy that, the demonstration of BE without water is considered the worst case scenario and it is assumed that the formulation will be also equivalent with concomitant intake of water. However, such an assumption is questionable when either the test or the reference orodispersible tablet contains mannitol since the presence of water might increase the differences in absorption due to the osmotic effect of mannitol [27].
According to Ono et al. (2014) [28], the results of the present study suggest that the Biopharmaceutical classification system (BCS)-Biowaiver scheme (BWS) can be expanded to BCS class III drugs and ODTs. Furthermore, for BCS class III drugs with relatively high dose to solubility ratio, it is possible that the discrepancy of in vitro dissolution profiles does not necessarily translate to the bioinequivalence in vivo. The results of this study that includes dissolution studies at pH 1.2 and pH 6.8 of 6 active pharmaceutical ingredients, suggest that extension of the BCS-BWS to ODTs and IR formulations of BCS class III drugs is appropriate. Furthermore, for BCS class III drugs with relatively high dose to solubility ratio, clinical bioequivalence would be achievable even when two formulations showed different dissolution profiles in vitro.

However, Arieta et al. (2015) [29], defences like that EMA guideline states that the biowaivers are only applicable when comparing products with the same dosage form. In the case of ODTs, the product might be considered for a BCS-based biowaiver, which does not mean that it is actually possible, because it is not known how to define the volume of water for the solubility classification and the current dissolution methodology is questionable for a product that is going to be dispersed in the mouth without the intake of a glass of water. In the most optimistic case, BCS-based biowaivers of ODTs would be acceptable only between a test ODT and a reference ODT, not with different immediate release formulations, and the solubility classification should consider the administration instructions of the reference product, which should be identical for the test product.

The clinical study was designed as a single-dose, randomized sequence, open-label, 2-period crossover study. Healthy, non-smoking Chinese male volunteers were randomly assigned to receive 150 mg (administered as three 50-mg tablets) of either the test or reference formulation of flurbiprofen, followed by a 7-day wash-out period and administration of the alternate formulation. Test drugs were administered after a 12-hour overnight fast. Blood samples were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dosing. This single-dose study of flurbiprofen 150 mg (three 50-mg tablets of each formulation) found that the test (flurbiprofen 50-mg ODT) and reference (flurbiprofen conventional 50-mg tablet) products met the regulatory criteria for bioequivalence in these fasting healthy Chinese male volunteers. Both formulations were generally well tolerated [30].

In the other example, a total of 427 cancer patients receiving cyclophosphamide chemotherapy participated in this multicenter, double-masked, double-dummy, parallel-group, randomized study comparing the antiemetic efficacy and safety of an 8-mg conventional ondansetron tablet (OT, n = 212) taken twice daily with an 8-mg orally disintegrating ondansetron tablet (ODT, n = 215) taken twice daily for 3 days. In the primary efficacy analysis, complete or major control of emesis between days 1 and 3 was seen in 80% of OT and 78% of ODT patients. ODT provides greater choice and flexibility in the management of emesis and nausea. OT and ODT, 8 mg given twice daily for 3 days are both well tolerated and are of equivalent efficacy in preventing cyclophosphamide-induced emesis and nausea. ODT therefore represents an easy-to-administer, palatable, well-tolerated, and effective alternative to OT for cancer patients. It may be particularly useful in an ambulatory setting and is likely to be of particular benefit in patients who have difficulty swallowing a conventional tablet [31].

The study was open, randomized, two-period crossover trial with a 1-week washout period. Subjects were admitted to the hospital at 7 p.m. the day before the study and fasted 10 h before each drug administration. A single dose (8 mg) consisting of one Vonau® flash or Zofran® tablet according to the randomization plan was given to each subject in the fasting state for each treatment period. Fasting continued for 4 more hours after drug administration. The drug was administered with 240ml of water. Subjects were fed with standard meals 4 h (lunch), 7 h (snack) and 10 h (supper) after drug administration in each treatment.

The 90% confidence intervals for AUCO→t (89.3–107.2%), AUC0→∞ (89.7–106.0%) and C max (87.5–103.8%) are within the 80–125% interval, proposed by most regulatory agencies (FDA, EMEA, ANVISA). It was concluded that the two formulations are bioequivalent in their rate and extent of absorption and thus, may be used interchangeably, without any prejudice of therapeutic effect [32].

**Formulation Development of ODTs**

Selection of active pharmaceutical ingredient is one of the most important parameters to formulate ODTs. It should be dissolved in the oral cavity and absorbed. Also it shouldn't have bitter taste. It is better if it is in low dose, small to moderate molecular weight, good solubility in water and/or saliva, non-ionized property in pH 5.5-7.4 and ability to be absorbed via oral mucosa.

Excipient selection is important for disintegrating the tablet immediately and also important for masking bitter taste. Main excipient groups are diluents; disintegrants that have different disintegrate mechanisms, flavors, and taste masking agents, sweeteners, binders, lyoprotectants, glidants and lubricants. To accomplish the challenges, specific excipients can be used in different ranges.
Also selection of manufacturing method is as important as selection of Excipients. Because different technologies have various advantages and disadvantages. Some of those methods are patented. Those patented technologies are WOWTAB®, ORASOLV®*, DURASOLV® EFVDAS®, FLASHTAB® (main approach is conventional tablet processes with modifications), ZYDIS®, LYOC®, QUICKSOLV® (main approach is freeze drying method) and FLASHDOSE® (main approach is floss formation). In Table 1, some marketed ODTs and their manufacturing technologies, and major advantages were given [33-40].

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Local Brand Name</th>
<th>Category</th>
<th>Manufacturing Technology</th>
<th>Technological basis</th>
<th>Advantages of technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine (%)</td>
<td>Claritin (#)</td>
<td>Antihistaminic</td>
<td>Zydis®*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Mirtazapine (%)</td>
<td>Remeron (#)</td>
<td>Antidepressant</td>
<td>Orasolv®*</td>
<td>Compressed tablets</td>
<td>Effervescent disintegration</td>
</tr>
<tr>
<td>Olanzapine (%)</td>
<td>Zyprexa (%)</td>
<td>Antipsychotic; Serotonin-Dopamine Antagonist</td>
<td>Zydis®*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Ondansetron (%)</td>
<td>Zofran ODT (%)</td>
<td>Nootropic; Antiemetic; Serotonin-Receptor Antagonist</td>
<td>Zydis®*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Risperidone (%)</td>
<td>Risperdal (%)</td>
<td>Antipsychotic; Dopamine Receptor Antagonist; Serotonin-Dopamine Antagonist</td>
<td>Zydis®*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Rizatriptan (%)</td>
<td>Maxalt (%)</td>
<td>Antimigraine; Serotonin Receptor Agonist</td>
<td>Zydis®*</td>
<td>Lyophilization</td>
<td>Very fast disintegration (2-10 sn)</td>
</tr>
<tr>
<td>Tramadol (%)</td>
<td>Ultram (%)</td>
<td>Analgesic (Non-narcotic)</td>
<td>FlashDose®*</td>
<td>Cotton Candy Process</td>
<td>Effectively taste mask</td>
</tr>
<tr>
<td>Zolmitriptan (%)</td>
<td>Zomig (%)</td>
<td>Antimigraine; Serotonin Receptor Agonist</td>
<td>DuraSolv®*</td>
<td>Compressed tablets</td>
<td>Easy to formulate low dose of active ingredient and higher mechanical strength than Orasolv</td>
</tr>
<tr>
<td>Zolpidem (%)</td>
<td>Ambien (#)</td>
<td>Sedative/Hypnotic</td>
<td>FlashDose®*</td>
<td>Cotton Candy Process</td>
<td>Effectively taste mask</td>
</tr>
</tbody>
</table>

Table 1: Some ODTs in the market and name of patented ODTs technologies, their basis and advantages

Additionally recent innovator system called ‘SeDeM-ODT’ can be mentioned as an accessorily to the selection of excipients, that can be used in direct compression manufacturing method. ‘SeDeM-ODT’ is new and based on the earlier SeDeM expert systems that provide to predict compliance of powder blend to produce immediate release tablets by direct compression. One of major advantages of this expert system is that it avoids application of unnecessary inactive ingredients [41].

As established in previous reviews, direct compression is the most preferred manufacturing method to produce ODTs. By using ‘SeDeM-ODT’ expert system, many excipients can be evaluated. The ‘SeDeM-ODT’ expert system has 12 parameters (bulk density, tapped density, inter-particle porosity, Carr index, cohesion index, Hausner ratio, angle of repose, powder flow, loss on drying, hygroscopicity, particle size, homogeneity index ) which classified into 5 factors (dimensions, compressibility, flowability/powder flow, lubricity/stability, lubricity/dosage) to determine the index of good compression (IGC). That complies to analyse the suitability of 43 excipients for direct compression manufacturing method [42].

Some tests are being conducted to prove the quality of ODTs. But the most critical tests are disintegration and dissolution tests to prove in-vitro equivalence of the formulation. There are some compendial and non-compendial methods for disintegration test and there are different limitations for those tests. Frequently disintegration tests are being conducted to USP current edition. Dissolution tests are usually being conducted at pH 1.2 and pH 6.8 to simulate oral and pregastric absorption. But sometimes different mediums can be chosen up to APIs pKa. In Table 2, Dissolution test conditions and limits and disintegration test limits for some ODTs were given [25].

Advantages of ODTs

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations. It provides the convenience of a tablet formulation, and also allows the ease of swallowing as the liquid formulation.

Others are:
- Not requirement of water or other liquid to swallow.
- Easily dissolution or disintegration in saliva within a few seconds.
- Pleasing taste.
- Leave in trace amount or no residue in the mouth when administered.
- Being portable and easy to transport.
- Being able to be manufactured by direct compression method with low cost.
- Can be easily administered to children, old and mentally disabled patients.
- Accurate dosing as compared to liquids.
- Dissolution and absorption of drug is fast, offering rapid onset of action.
Bioavailability of drug is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva transferring down into the stomach.

First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.

Free from risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.

Suitable for sustained/controlled release actives.

Allows high drug loading [45-52].

### Dissolution Test Conditions and Limits

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Apparatus</th>
<th>Speed (RPMs)</th>
<th>Medium</th>
<th>Volume (mL)</th>
<th>Recommended Sampling Times (minutes)</th>
<th>Limits</th>
<th>Disintegration Test Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam II (Paddle)</td>
<td>II</td>
<td>50</td>
<td>70 mM Potassium Phosphate Buffer, pH 6.0</td>
<td>500</td>
<td>2, 5, 10, 15 and 20</td>
<td>NLT 70%</td>
<td>NMT 60 s (Test 1)</td>
</tr>
<tr>
<td>Carbidopa/Levodopa II</td>
<td>II</td>
<td>50</td>
<td>0.1 N HCl</td>
<td>750</td>
<td>5, 10, 15, 30, and 45</td>
<td>NLT 75% (both for 2 APIs)</td>
<td>NMT 60 s</td>
</tr>
<tr>
<td>Lansoprazole (delayed release) II</td>
<td>II</td>
<td>75</td>
<td>Acid Stage: 0.1 N HCl; Buffer Stage: Phosphate Buffer, pH 6.8 with 5 mM Sodium Dodecyl Sulfate</td>
<td>500, 900 (Acid), 60 (Acid), 10, 20, 30 and 45 (Buffer)</td>
<td>Not applicable in pharmacopoeia</td>
<td>Not applicable in pharmacopoeia</td>
<td></td>
</tr>
<tr>
<td>Loratadine I (Basket)</td>
<td>I</td>
<td>50</td>
<td>SGF without enzyme</td>
<td>900</td>
<td>2, 4, 6 and 10</td>
<td>NLT 80%</td>
<td>Not applicable in pharmacopoeia</td>
</tr>
<tr>
<td>Mirtazapine II (Paddle)</td>
<td>II</td>
<td>50</td>
<td>0.1 N HCl</td>
<td>900</td>
<td>5, 10, 15, 20 and 30</td>
<td>NLT 80%</td>
<td>NMT 60 s</td>
</tr>
<tr>
<td>Olanzapine II (Paddle)</td>
<td>II</td>
<td>50</td>
<td>0.1 N HCl</td>
<td>900</td>
<td>10</td>
<td>NLT 80%</td>
<td>NMT 10 s (Test 1)</td>
</tr>
<tr>
<td>Ondansetron II (Paddle)</td>
<td>II</td>
<td>50</td>
<td>0.1 N HCl (deaerated)</td>
<td>900</td>
<td>10</td>
<td>NLT 80%</td>
<td>NMT 10 s</td>
</tr>
<tr>
<td>Risperidone II (Paddle)</td>
<td>II</td>
<td>50</td>
<td>0.1 N HCl</td>
<td>500</td>
<td>5, 10, 15</td>
<td>NLT 80%</td>
<td>NMT 30 s (Test 1)</td>
</tr>
</tbody>
</table>

Table 2: Dissolution test conditions and limits and disintegration test limits for some ODTs [43,44]

### Challenges and Limitations for ODTs

- Drugs with relatively larger doses are difficult to formulate into ODTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug [53].

  The application for technologies used for ODTs is limited by the amount of drug into each unit dose. The drug dose must be lower than 400mg for insoluble drugs and 60mg for soluble drugs [54].

  However Flashdose technology can accommodate larger drug doses and offers improved mechanical strength. Orasolv® technology can accommodate a wide range of active pharmaceutical ingredient from 1 mg to 500 mg [38].

- Mechanical strength - ODTs are made of porous or soft molded matrices in order to allow its disintegration in mouth. This makes tablet friable and handling becomes difficult.

  Orodispersible tablets with highly porous structure and good mechanical strength have been developed by sublimation method. Also Durasolv® has much higher mechanical strength than Orasolv due to the use of higher compaction pressures during compression.

- Palatability - ODTs are intended to be dissolved in mouth. Most of the drugs have bitter taste. Bitter taste can be masked with enough sweetener and flavors.

  Specifically, methods of taste masking include lipophilic vehicles, coating with polymers, carbohydrates, lipids or proteins complexation with cyclodextrins or ion-exchange resins, formation of salts, use of salting out layers and solid dispersions [55].

  OraQuick utilizes its own patented taste masking technology i.e. MicroMask®. In MicroMask® technology, taste-masking process is done by incorporating drug into matrix microsphere [56].

- Drugs in form of ODTs are hygroscopic in nature and hence need to be protected from humidity [57]. To overcome humidity problem special working facilities can be designed by simple methods and special air-conditioning systems can be set up.

  Size of tablet 7 and 8 mm are easy to swallow while tablets of size 8mm are easy to handle. Hence, tablet sizes which are both easy to handle and swallow are difficult to achieve. For the patient compliance, to make the swallowing easier, round shape punches having optimum dimensions can be used.

- Drug candidates should be stable both in water and in saliva, should not ionize at oral cavity pH and should be able to permeate oral mucosal tissue to diffuse and partition in upper GI epithelium (logP > 1, or preferably > 2, not have short half-life) [58]. To optimize solubility problem of the active pharmaceutical ingredient some solid buffers and surfactants can also be chosen.
• ODT requires special packaging for proper stabilization and safety of stable product [40,41].

Future of ODTs

ODT technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. “supergenerics” for veterinary or human application [17-21].

Some new quality control methods can be developed to determine the technological aspects of orally disintegrating tablets to define the characteristics of ODTs [25].

Protein and peptide-based therapeutics that used via oral route, have limited bioavailability when administered by immediate release tablets. Those kinds of products usually degrade immediately in gastrointestinal system. The developments of improved oral protein delivery Technology by ODTs, that dispersed and/or dissolved in the saliva, are very promising for the delivery of high molecular weight protein and peptide [38].

It would be an innovative improvement in the ODT technology when development of ODTs with controlled release properties that can deliver drugs which has short half-lives like 12–24 hours. The added convenience and compliance of such formulations will be used more immensely [39].

In addition, the ability to formulate drugs in large doses will bring another important technological advance. In general, the ODT formulations require large amounts of excipients, and having large doses of drug will only make the final formulation too big to handle. ODT formulations that require fewer excipients than the drug itself will be a break through [41].

ODT technologies are in progress, but development of formulation of ODTs that contains lipophilic active pharmaceutical ingredients is a challenge. New ODT technology should be developed to find a solution for this problem [57].

As far as seen in the literature there is not much delayed release ODTs in the market. Controlled release ODTs and/or in line with the purpose system and/or fixed dose combination ODT technologies can be developed as a next generation.

Conclusion

As a conclusion orally disintegrating tablets have many advantages compared with the other oral dosage forms, such as better bioavailability, better patient compliance, and improved efficacy. Nevertheless formulation challenges such as limited tablet weight, disintegration time, friability, manufacturing technology, and packaging should be considered. Orally disintegrating tablets may be evaluated as a first choice for pediatrics and geriatrics – situations that parenteral cannot be used especially for central nervous system, gastrointestinal system disorders and pain.

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