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# FAST FORWARD TO FASTER RELIEF: THE EVOLUTION OF ORAL DISINTEGRATING TABLETS

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***Abstract***

In the design of dosage forms, comforts of drug administration and patient conformity have considerable prominence. Recent and rising technologies can manufacture robust, versatile tablets with extraordinary taste masking and controlled release. Orally disintegrating tablets (ODTs) are solid dosage forms that disintegrate in the mouth in less than 60 s, and are thus swallowed without the need for water. Rapid disintegration of tablet cause quick dissolution and thus fast onset of action. ODTs are suitable dosage form for special populations like pediatrics, geriatrics, psychotic, dysphagic, bedridden patients, unconscious patients, young patients with under developed muscular and nervous system, patients with hand tremors problems and frequent traveller patients. It provides good stability, accurate dosing, easy manufacturing, decreased packaging size; self-administration is possible during the journey, as water is not required. ODTs are an economical method of drug delivery. ODTs are very important drug delivery system in cases where drug absorbed from buccal cavity. Various scientific techniques including spray drying, sublimation, freeze drying, molding, direct compression etc. have been employed for the development of ODTs. Today, ODTs are more widely available as over the counter products for the treatment of numerous diseases. The aim of this article is to review the advantages, limitations, formulation challenges, manufacturing techniques, patented technologies, marketed formulations and evaluation tests of ODTs.

***Keywords*:** Marketed formulation, ODTs, Patent, Tablet, Technology

## INTRODUCTION

Oral administration of drugs is preferred due to its ease of swallowing, distress avoidance, versatility and most significantly, patient compliance. The large number of patients find it difficult to swallow tablets and capsules, and do not take their medicines as prescribed. It is estimated that 50 % of the population affected by this problem, which finally results in a higher chance of noncompliance and ineffective therapy. For these reasons, tablets that can disintegrate in the oral cavity, have attracted enormous attention [1]. Solid dosage forms as oral tablets have the most considerable place among the entire pharmaceutical formulations [2].

Taste-masking is a crucial step in the formulation of an acceptable fast dissolving/disintegrating tablet (FDDT). Traditional tablet formulations generally do not solve the issues related to taste masking, because it is supposed that the dosage form will not disintegrate until it passes through the oral cavity. To eliminate the bitterness, the tablet can be prepared by adding flavors and sweetening agent or by sugar coating on the tablets. Many FDDT technologies combine unique types of taste masking as well [3-5]. ODTs technology, which makes tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. ODTs are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited bio-fluid [6, 7]. Orally disintegrating tablets are known by various names such as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, fast or rapid dissolving tablets, porous tablets, mouth dissolving tablets and rapimelts. The excipients used in ODT technology are usually hydrophilic in nature and can be selected on the basis of drug's physicochemical properties like hydrophilicity or hydrophobicity. If the active pharmaceutical ingredient is hydrophobic in nature, then dosage form is called disintegrating tablet whereas, if it is hydrophilic, then the dosage form is called fast dissolving tablet [8-10].

The ODT formulation defined by the Food and Drug Administration (FDA) as “a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue”. U.S. Food and Drug Administration approved Zydis, ODT formulation 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. Further a number of drugs have been approved by regulatory authorities for ODT formulations [11]. The aim of this article is to

review the advantages, limitations, formulation challenges, manufacturing techniques, patented technologies, marketed formulations and evaluation tests of ODTs.

**Advantages of ODTs**

The advantages of ODTs include [12-17]:

- No need of water to swallow the tablet.
- Compatible with taste masking and have a pleasing mouth feel.
- Can be easily administered to paediatric, elderly and mentally disabled patients.
- No residue in the oral cavity after administration.
- Manufacturing of the tablets can be done using conventional processing and packaging equipments at minimum cost.
- Allow high drug loading.
- Accurate dose can be given as compared to liquids.
- Dissolution and absorption of the drug is fast, offering a rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation.
- Some amount of drugs is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, thus reducing first pass metabolism, which offers improved bioavailability and thus reduced dose and side effects.
- No risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- ODTs are suitable for sustained and controlled release actives.
- Unit packaging.

**Limitations of ODTs**

It includes [18-20]:

- The tablets commonly have insufficient mechanical strength. Hence, conscientious handling is necessary.
- The tablets may leave an unpalatable taste and grittiness in the oral cavity if not formulated properly.
- Drugs which have large doses, can cause problems to formulate them into ODTs.
- Patients who simultaneously take anti-cholinergic drugs are not suitable candidates for ODTs.

**Difficulties with existing oral dosage form** [21-24]:

- The patient may suffer from tremors, therefore they may face difficulties to take a powder and liquid medication. In dysphasia, physical barriers and adherence to the esophagus may cause gastrointestinal ulceration.
- Ingestion of solid dosage forms like tablets and capsules can give rise to difficulties for young adults by causing hindrance in the development of muscular and nervous system.
- Liquid medicaments such as suspensions and emulsions are packed in multi-dose container: therefore content uniformity in each dose may not be maintained.
- Buccal and sublingual formulation may cause irritation of oral mucosa.

**Challenges in the formulation of ODTs** [25-27]:

- Mechanical strength and disintegration time: Disintegration time will extend if the mechanical strength is more, so a good cooperation between these two parameters is always necessary.
- Taste masking: Efficient taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.
- Mouth feel: The particles produced after disintegration of the ODT should be very small. ODT should not leave any residue in the mouth after oral administration. Addition of flavors and cooling agents like menthol enhance the mouth feel.
- Sensitivity to environmental conditions: ODTs should have low sensitivity to environmental conditions such as humidity and temperature.
- Cost: The technology adopted for an ODT should be acceptable in terms of cost of the final product.

The fast dissolving property of the ODTs requires rapid absorption of water into the tablet matrix, thus requires some standard approaches such as maximizing the porous structure of the tablet, incorporation of appropriate disintegrating agent and the use of water-soluble excipients in the formulation. Excipients used in ODTs contain at least one superdisintegrant, a diluent, a lubricant, a permeabilizing agent, sweeteners and flavourings. Type, examples and concentration of various excipients are presented in (Table 1).

**Table 1:** Type, examples and range in use (% in weight) of various excipients used in ODTs [28-31]:

| Type of the excipients | Examples | w/w (%) |
|---|---|---|
| Superdisintegrants | Croscarmellose sodium, crospovidone, sodium starch glycolate, microcrystalline cellulose, carboxy methyl cellulose, modified corn starch, polacrilin potassium etc. | 1-15 % |
| Binder | Polyvinylpyrolidone, polyvinyl alcohol, hydroxy propyl methylcellulose etc. | 5-10 % |
| Antistatic agent | Sodium laury lsulfate, sodium dodecyl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates etc. | 0-10 % |
| Diluents | Magnesium carbonate, calcium sulphate, magnesium trisilicate etc. | 0-85 % |

## APPROACHES FOR PREPARATION OF ODTs

Various preparation techniques have been developed on the basis of different principles, thus present different properties of ODTs by means of mechanical strength, stability, mouth feel, taste, swallowability, dissolution profile and bioavailability. Some of those technologies are patented. Basic pharmaceutical processes to manufacture ODTs are explained as follows:

### Spray drying

Spray drying methods are used to a great extent in pharmaceutical and biochemical procedures. Spray drying provides a rapid and economically efficient way to eliminate solvents and produces highly porous and fine powders. The formulations are compounded by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, croscarmellose sodium or sodium starch glycolate as disintegrating agent. An acidic material (e.g., citric acid) or alkali material (e.g., sodium bicarbonate) is used to improve disintegration and dissolution behaviour. Tablets prepared by the compression of spray dried powder, when immersed in an aqueous medium, showed a disintegration time of 20 s [32-34].

### Sublimation

Compressed tablet which contains highly water-soluble components can show slow dissolution behaviour, due to the low porosity of the tablets that reduces water penetration into the matrix. By conventional methods, volatile materials are compressed into tablets, these volatile materials can be removed by sublimation, which results in extremely porous structures. The volatile materials which can be used are ammonium carbonate, urea, ammonium bicarbonate, camphor and hexa methylene tetramine. In a few cases, thymol, menthol, camphor, an organic acid such as adipic acid and fatty acid such as arachidic acid, myristic acid, capric acid, and palmitic acid were used as the volatile materials and the sublimation temperature ranged from 40 ºC to 60 ºC. The disintegration time in the oral cavity was found to be about 25 s [35, 36].

### Freeze drying

Lyophilization process involves removal of solvents from a frozen drug solution or a suspension containing structure-forming excipients. The tablets formed by this process are usually very light and have highly porous structures that allow, rapid dissolution or disintegration. Lyophilization is done at very low temperature to eliminate the adverse thermal effects that may alter drug stability during processing. The freeze dried dosage form have relatively few stability concerns during its shelf life. The drying process may give rise to the glassy amorphous structure of excipients and drug substance [37, 38].

### Molding

Molded tablets are made up of water-soluble ingredients. The powder mixture is sprinkled with a solvent (usually water or ethanol). The mixture is molded into tablets under pressure. Applied pressure should be lower than those used in conventional tablet compression. This process is also known as compression molding. Air drying can be used to remove the solvent. Due to lower pressure; a highly porous structure is created, that enhances the dissolution. The powder blend should be passed through a very fine screen, to improve the dissolution rate. Molded tablets disintegrate more rapidly and provide improved taste because of their highly water-soluble, sugar components. However, molded tablets generally do not have high mechanical strength. The chances of breakage of the molded tablets during tablet handling and opening of blister pockets, is very high. If the hardness enhancing agents are used in the formulation, decrease in disintegration rate is observed. Mechanical strength and good disintegration of the tablets can be improved by using non-conventional equipment and by using multistep processes [39, 40].

### Mass extrusion

The mass extrusion technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of softened mass through the extruder or syringe is carried out, to get a cylinder of the product which is then cut into even segments using a heated blade to form tablets [40, 41].

### Direct compression

Direct compression is the easiest and cost-effective tablet manufacturing process. This method can be applied to manufacture ODT by selecting appropriate combinations of excipients, which can provide fast disintegration and optimum physical resistance. Sugar-based excipients are widely used as bulking agents because of their aqueous solubility, sweetness, pleasing mouth feel, and

good taste masking. Tablets obtained by conventional compression method are less friable, but disintegrate more slowly. The compression method, with or without wet granulation, is a convenient and cost effective way to prepare tablets with sufficient structural integrity [42, 43].

## MARKETED FORMULATIONS

Large numbers of commercial products of different active drugs are available in the market [44]. Some of them are listed in (Table 3).

**Table 3:** Marketed formulations of ODTs

| Trade Name | Active Drug | Manufacturer |
|---|---|---|
| Felden fast melt | Piroxicam | Pfizer Inc., NY, USA |
| Ugesic | Piroxicam | Mayer organic Ltd. |
| Esulide MD | Nimesulide | Doff Biotech |
| Kazoldil MD | Nimesulide | Kaizen Drugs |
| Mosid MD | Mosapride | Torrent Pharma |
| Valus | Valdecoxib | Glenmark |
| Vomidon MD | Domperidone | Olcare lab |
| Claritin redi Tab | Loratidine | Schering Plough Corp., USA |
| Maxalt MLT | Rizatriptan | Merck and Co., NJ, USA |
| Zyprexia | Olanzapine | Eli Lilly., Indianapolis, USA |
| Pepcid RPD | Famotidine | Merck and Co., NJ, USA |
| Zofran ODT | Ondansetron | Glaxo Wellcome, Middlesex, UK |
| Zofer MD | Ondansetron | Sun Pharma |
| Ondem MD | Ondansetron | Alkem Pharma |
| Zoming-ZMT | Zolmitriptan | AstraZenecea, USA |
| Zeplar TM | Selegilline | Amarin Corp. London |
| Tempra Quiclets | Acetaminophen | Bristol Myers Squibb. USA |
| Febrectol | Paracetamol | Prographarm. France |
| Nimulid MDT | Nimesulide | Panacea Biotech. India |
| Torrox MT | Rofecoxib | Torrent Pharmaceuticals, India |
| Rofixx md | Rofecoxib | Cipla ltd. Mumbai ,India |
| Olanex Instab | Olanzapine | Ranbaxy Lab. Ltd, India |
| Romilast | Monteleukast | Ranbaxy Lab. Ltd, India |
| Zontec MD | Cetrizine | Zosta Pharma India |
| Lonazep MD | Olnazepine | Sun Pharma |
| Nime MD | Nimesulide | Maiden Pharma |
| Imodium lingual | Imodium | R.P. Scherer Corp., U.S.A |
| Pepcidin Rapitab | Pepcid | Merck & Co., U.S.A |
| Cibalginadue Fast | Ibuprofen | Novartis Consumer Health |
| Nurofen Flashtab | Ibuprofen | Boot healthcare |
| Hyoscyamine sulphate ODT | Hyoscyamine sulfate | Ethex Corporation |

## EVALUATION OF ODTS

### Precompression characterization of tablet

Prior to compression, the powder blends should be evaluated for their bulk and tapped density and from these values compressibility index and Hausner's ratio should be calculated, while the flow properties of powder blends should be assessed from the angle of repose [45].

### Angle of repose

The frictional forces in loose powder or granules can be measured by the angle of repose. This is the angle between the surface of a pile of powder or granules and the horizontal plane. It is determined by the funnel method. Pour the blend through a funnel, that can be raised vertically to a maximum cone height (h). The radius of the heap (r) should be measured. The angle of repose is calculated by following formula:

$$\tan \Theta = \frac{h}{r}$$

### Bulk density and tapped density

An accurately weighed amount of powder should be introduced in 100 ml measuring cylinder. Note the initial volume, then the cylinder should be tapped 100 times on a plane hard surface and tapped volume of packing should be recorded [46]. Bulk density (BD) and tapped density (TD) should be calculated using following formula:

$$BD = \frac{\text{weight of powder}}{\text{volume of packing}}$$

$$TD = \frac{\text{weight of powder}}{\text{tapped volume of packing}}$$

BD = weight of powder/ volume of packing
TD = weight of powder/tapped volume of packing

**Carr's index (Compressibility)**
Compressibility index of powder can be determined by following formula [47]:

$$\text{Carr's index (\%)} = \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}}$$

**Hausner's ratio**
Hausner's ratio is an index of ease of powder flow. It is calculated by the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

**Post compression characterization of tablets**

**Weight variation test**
Individually weigh 20 tablets, which are selected at random and calculate the average weight.

**Tablet hardness**
Monsanto hardness tester can be used to determine the crushing strength.

**Tablet Friability**
Weigh twenty tablets of formulation and subject them to abrasion by employing a Roche friabilator at 25 rpm for 4 min. Weigh the tablets and compare with their initial weights to obtain percentage friability.

$$\text{\% Friability} = \frac{(W1 - W2) \times 100}{W1}$$

Where W1 = Weight of tablets before test (initial weight)
W2 = Weight of tablets after test (final weight)

**Thickness**
The diameter and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by screw gauge. Tablet thickness should be controlled within a ± 5 % variation of a standard value. In addition, the thickness must be controlled to facilitate packaging. The thickness in millimeters (mm) should be measured individually for ten preweighed tablets using screw gauge. The average thickness and standard deviation should be reported [48].

***In vitro* disintegration time**
For this test, six tablets are employed in water at 37 ºC using a tablet disintegration tester. The time required for disintegrating the tablets and passing completely through the sieve is recorded.

***In vitro* dissolution study**
The release rate of drug from ODTs is determined using USP dissolution testing apparatus 2 (paddle method). The dissolution test is performed using 900 ml of 0.1 N HCl at 37±0.5 ºC at 100 rpm.

**Wetting time**
Use a piece of tissue paper (10.75×12 mm), fold it twice and place it in a culture dish (d= 6.5 cm) containing 6 ml of water. Put a tablet on the paper and record the time required for complete wetting.

***In vitro* dispersion time**
Put the tablets in 10 ml of phosphate buffer solution (pH 7.4) at 37±0.5 °C. Measure the time required for complete dispersion of tablets [49].

**Water absorption ratio (R)**
Note the weight of the tablet prior to placement in the petri dish (Wb) utilizing a digital weighing balance. Note the weight of the tablets after wetting (Wa). Water absorption ratio, R, can be determined according to the following equation:

$$R = 100 \times \frac{Wa - Wb}{Wb}$$

where Wb and Wa are tablet weights before and after water absorption, respectively [50].

## CONCLUSION

All the available ODTs technologies work on the primary concept, to maximize the porous structure of the tablet matrix to achieve speedy tablet disintegration in the buccal cavity along with good taste-masking properties and satisfactory mechanical strength. Future challenges for many ODT manufacturers include reducing costs by finding ways to manufacture with conventional equipment, varieties in packaging, enhanced mechanical strength and taste-masking potential. Hence, demand by patients and the accessibility of various technologies have increased the acceptance of oral disintegrating tablets, which in turn prolongs the patent life of a drug. The techniques and technologies described in this article represent how recent developments in formulation and processing technologies make the efforts to achieve mouth dissolving tablets. One can consider the emergence of more novel technologies for ODTs in the coming days. Thus ODTs will have tremendous scope as a delivery system for most of the drugs in the near future.

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