Review Article

# A Brief Review on Oro-Dispersible Tablets: A Popular Growing Technology

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**Accepted on:** 06-05-2013; **Finalized on:** 31-07-2013.

**ABSTRACT**

Improved therapeutic efficacy and patient compliance are the two major requisites for the any drug delivery system to be successful. Oro-dispersible dosage forms especially Oro-dispersible tablets are growing popularity these days as these are more convenient and potentially safer alternatives to the traditional drug delivery systems. Apart from this, these Oro-dispersible tablets are offering 'market exclusivity' and extension of the patent life to the pharmaceutical manufacturers. These novel dosage forms especially tablets are formulated to get dissolved or disintegrated or dispersed in the saliva in few seconds without the help of water. These ODTs also overcame the difficulties for patients who are busy and are travelling, patients suffering from dysphagia (difficulty in swallowing), and dementia and in conditions of patients like pediatric, geriatric, bed-ridden. This article gives a brief review on the fabrication of Oro-dispersible tablets with a detailed concept of fabricating technologies, patented technologies as well as emerging trends or technologies.

**Keywords:** Fast disintegrants, Fast dissolving, ODTs, Oro-dispersible tablets.

## INTRODUCTION

As there are various routes of drug delivery systems to the body, the oral delivery is considered as one of the golden standard in the pharmaceutical industry where it is regarded as the safe, convenient, and most economical method of drug delivery having the patient compliance from the elderly. But difficulties have been aroused from pediatric, geriatric, bed-ridden, busy and travelling patients and also patients with dysphagia (difficulty in swallowing), dementia and in the cases of accessing of water. And as our society is getting aged, the Oro-dispersible tablets have been introduced with an objective to improve therapeutic efficacy and patient's compliance by overcoming the difficulties.[1] These novel type of tablets dissolve/disintegrate/ disperse in saliva within few seconds without water.

ODTs were defined as an solid dosage forms containing medicinal substances that disintegrate within a matter of seconds when placed upon the tongue. In the European Pharmacopoeia, ODTs were defined as Orodisperse that can be placed in the mouth where it disperses rapidly before swallowing. As a requirement in these regulations, the relative bioavailability (BA) of ODTs should be the same as that of conventional dosage forms after administering with or without water. United States Food and Drug Administration (FDA) defined ODTs as "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue".[2, 3]

Oro-dispersible tablets/Mouth dissolving tablets/ Oral fast disintegrating dosage forms can be used synonymously as fast dissolving tablets, fast-melts, rap melts, porous tablets or dispersible, quick dissolving or rapid disintegrating tablets.[4-7] United States Pharmacopoeia (USP) approved all the above terms as ODTs. And this dosage form begins to disintegrate immediately after coming in contact with the saliva, and the complete disintegration normally occurs within 30–50 seconds after administration.[8] The solution containing the active ingredient is swallowed, which is absorbed through the gastrointestinal epithelium to reach the target site to produce the desired effect.

In an survey conducted in Norway; among 6158 GP patients, approximately 26% patients reported that they do not take their prescribed medication as they had encountered problems in swallowing the conventional tablets. Often, the main complaints are the size, surface and taste of the tablets.[9,10] Oral FDTs had overcome some of these problems and also improved patient compliance. These FDTs have also been investigated for their potential in increasing the bioavailability of the poorly water soluble drugs through enhancing the dissolution profile of the drugs.[11,12] Moreover, pharmaceutical companies also had some commercial reasons for formulating these FDTs. As a drug reaches the end of its patent, the development and formulation of the drug into new dosage forms allows pharmaceutical companies to extend the patent life and 'market exclusivity'.[13] This allows pharmaceutical companies to increase profits in the long term by attracting new consumers through advertising and product promotion campaigns.

### Mechanism of drug release from MDTs[14]

- Swelling
- Wicking
- Deformation
- Particle repulsive forces

**Ideal characteristics of MDTs[15]**

- Should dissolve or disintegrate in the mouth rapidly without aid of water in matter of seconds.
- Should be compatible with taste masking.
- Should maintain physical integrity and possess no friable loss.
- Should have a pleasant mouth feel.
- Should leave minimum or no residue in the mouth after oral administration.
- Should exhibit low sensitive to environmental condition as temperature and humidity.
- Should allow high drug loading capacity.
- Should be adaptable and amenable to the existing processing and packaging machinery.
- Should allow the manufacturing of tablets using conventional processing & packaging equipments at low costs.

**Salient features of MDTs[16]**

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Bioavailability of drug is increased as some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach.
- Pre-gastric absorption can results in improved bioavailability which results of reduced dosage with improved clinical performance through the reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided and thus provided improved safety.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action is required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stable for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.

**Advantages of MDTs[17,18]**

- Improved patient compliance.
- Rapid onset of action and may offer an improved bioavailability.
- Patient having difficulty in swallowing tablet can easily administer this type of dosage form.
- Useful for pediatric, geriatric and psychiatric patients.
- Suitable during traveling where water is may not be available.
- Gives accurate dosing as compared to liquids.
- Good chemical stability.
- Free of need of measuring, an essential drawback in liquids.

**Challenges of MDTs[19-23]**

- Ease of Administration
- Rapid disintegration
- Taste & Mouth feel effects
- Size of the dosage form
- Aqueous solubility
- Hygroscopicity
- Sensitivity towards environmental conditions viz., humidity & temperature
- Good mechanical strength
- Good package design
- Cost

**Formulation & Excipients used in MDTs[24]**

In formulating Mouth Dissolving Tablet/ Oral Dissolving Tablet, apart from drug, super disintegrants, additional excipients are likely to include a suitable flow aid and lubricant for tablet manufacture. Because the tablet is intended to dissolve in the mouth, MDTs often includes flavors and sweeteners to mask the taste of bitter actives. Finally, color may be added to the formulation to add elegance and to aid in identification of the final dosage.

In the formulation of MDTs/FDTs the most important additives are as follows:

***1. Diluents***

Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols & preferably mannitol.

### *2. Binders*

Generally, binders are used to keep the composition of tablets together with the drug during compression stage. The right selection of a binder or combination of binders is essential to maintain integrity and stability of the tablet. The temperature of the excipients should be preferably around 30-35$^0$C for faster melting property. Further its incorporation imparts smooth texture & disintegration characteristics to the system. Binders can be either liquid, semi solid or solid or mixtures of varying molecular weights such polyethylene glycol. Commonly used binders are cellulosic polymers, povidones, and polyvinyl alcohols.

### *3. Super disintegrants*

Mouth dissolving tablet requires faster disintegration and dissolution. In-order, to achieve faster disintegration, Super disintegrants is used in formulating ODTs. The super disintegrant used should be effective at low concentrations and have greater disintegrating efficiency and should be more effective intragranularly. The only problem is that it is hygroscopic therefore not used with moisture sensitive drugs.

Super disintegrants acts by swelling and due to swelling pressure exerted in the outer or radial directions, it causes the tablet to burst or accelerates the water absorption leading to enormous increase in the volume of granules to promote disintegration (Figure 1).

**Selection of Super disintegrants**

Although the super disintegrant primarily affects the rate of disintegration, when used at high levels, it can also affect the mouth feel, tablet hardness, and friability. Thus several factors must be taken into consideration while selecting a suitable super disintegrant.

A. Disintegration

The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressure necessary to provide rapid disintegration in the mouth.

B. Compactability

When manufacturing an ODT, it is desirable to have tablets with an acceptable hardness at a given compressional force to produce robust tablets that avoid the need to use specialized packaging while maximum production speed. Thus, a more compactable super disintegrant will produce stronger, less-friable tablets.

C. Mouth feel

To achieve patient compliance, MDTs must provide a palatable experience to the patient by masking the bitter nature of the drugs. Larger particles can results in a gritty feel effect so smaller particles are preferred.

D. Flow properties

Good flow and content uniformity are important to achieve the required dosage per unit. In a typical tablet formulation, super disintegrants are used at 2-5% w/w of the formula, which are significantly higher levels. At these higher levels, the flow properties of the disintegrant are most important because this makes a greater contribution to the flow characteristics of the total blend.

### *4. Taste-masking agents*

Taste masking of the drug can be done by preventing the exposure of drug to the tongue rough processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulating in polymer systems or by complexation.

**Some of the approaches of taste-masking are**

a. Layering the drug onto inert beads using a binder followed by coating with taste-masking polymer.

b. Granulating the drug & coating with a taste-masking polymer.

c. Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.

d. Complexation using Inclusion complexes like cyclodextrins.

e. Psychological modulation of bitterness.

f. Coacervation to form micro capsulated drug within a polymer.

g. Formation of pellets by extrusion spheronization.

### *5. Sweeteners*

Sucrose and other natural sweeteners, such as sorbitol, can be used in ODTs, although artificial sweetening agents are customary. However, the applications of artificial sweeteners are restricted by Health regulations. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in the fast disintegrating tablet. Earlier cyclamates and cyclamic acid were the artificial sweeteners of the choice, but their use has now been restricted.

And some of the commonly used sweeteners are: Sorbitol, Mannitol, Hydrogenated starch hydrolysate, Maltitol solution, Maltitol, Xylitol, Erythritol, Glycerin, Sucrose, Fructose, Maltose etc.

### *6. Lubricants*

Commonly used lubricants are magnesium stearate, stearic acid, sodium stearyl fumerate, micronized polyoxyethylene glycol (Macrogol 6000), leucine and sodium benzoate.

### *7. Glidants*

Colloidal silica (Aerosil), precipitated silica, micronized/ non-micronized talc, maltodextrins etc are used as glidant.

**Techniques for formulating MDTs**

1. Melt Granulation

2. Phase transition

3. Sublimation

4. Tablet molding

A. Compression molding

B. Heat molding

C. No vaccum lyophilization

5. Freeze drying or Lyophilization

6. Mass extrusion

7. Spray drying

8. Direct compression

A. Super disintegrant

B. Sugar based excipients

9. Nanonization

10. Cotton candy process

A. Floss blend

B. Floss processing

C. Floss chopping & conditioning

D. Blend & Compression

11. 3-Dimensional printing (3-DP)

**1. Melt Granulation[25]**

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilises rapidly leaving no residues. The advantage of this technique when compared to the conventional granulation is that, no water or organic solvents are needed. As there is no drying step, the process consumes less time and uses less energy than in wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

**2. Phase transition[26]**

It is identified that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. MDTs by phase transition are prepared by heating sugar alcohols using erythritol (melting point 122°C), xylitol (melting point 93-95°C), trehalose (97°C), and mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

**3. Sublimation[27]**

The key for rapid disintegration of mouth dissolving tablets is the presence of a high porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec (Fig no.2: Schematic Diagram of Sublimation Technique for Preparation of MDTs. Even solvents like cyclohexane, benzene can be used as pore forming agents.

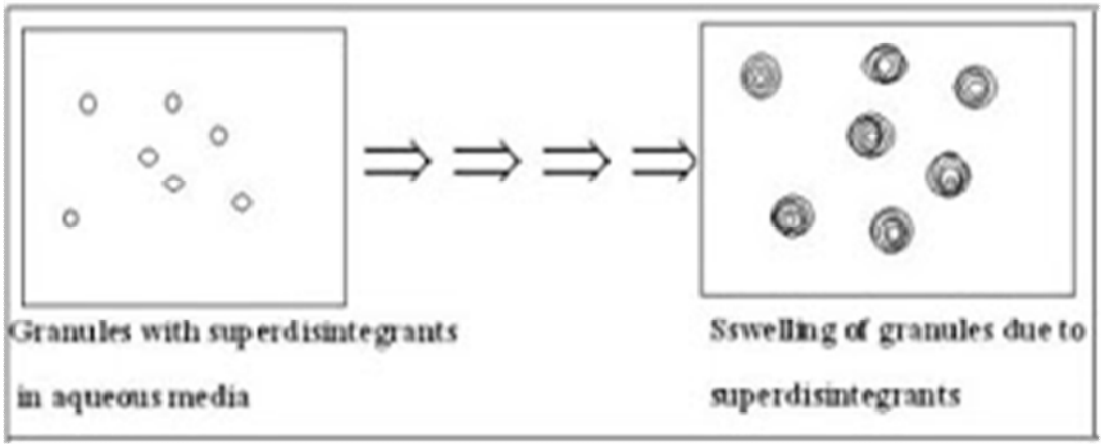


**Figure 1:** Mechanism of Super disintegrants

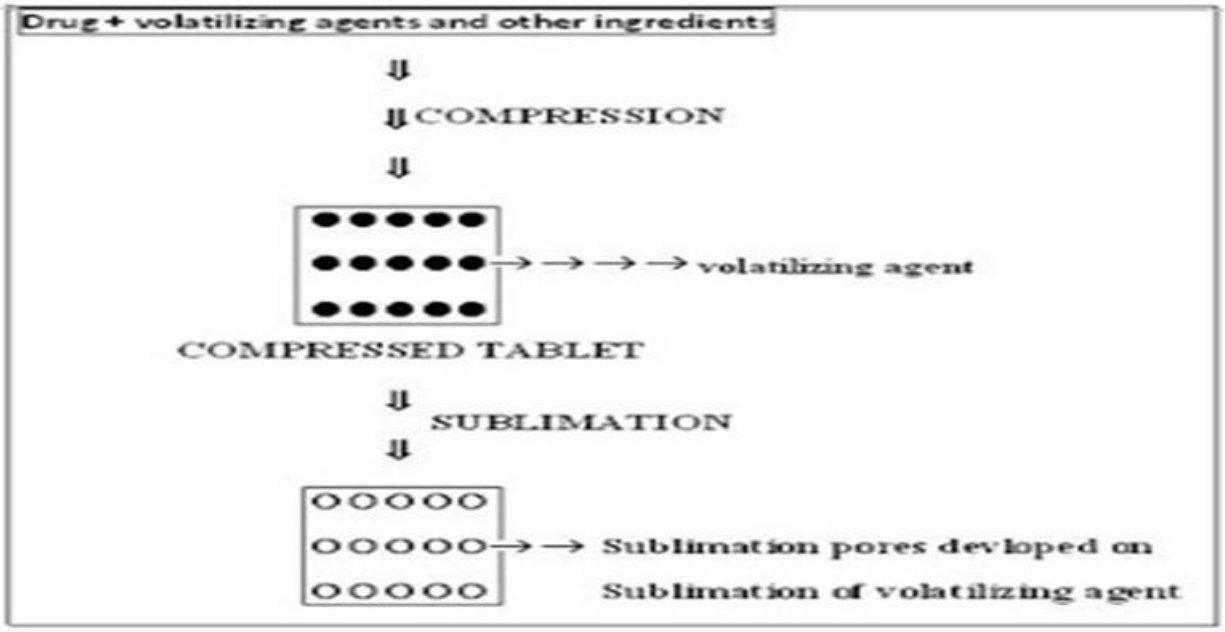


**Figure 2:** Schematic Diagram of Sublimation Technique for Preparation of MDTs

**4. Tablet moulding[28]**

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth.

Moulding process is of three types i.e., solvent method, heat method and No vacuum lyophilization.

***Solvent method*** involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in the molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. And this process is similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

***The heat molding process[29]*** uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

***No-vacuum lyophilization*** is done by evaporating the solvent from a drug solution or suspension at standard pressure. Unfortunately, moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablets often occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases.

**5. Freeze Drying[30]**

Freeze drying is the process in which water is sublimed from the product after it is frozen. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation.

The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped (Figure 3).

The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. And some of the Oral Dispersible Tablet (ODT)/ Fast Dissolving Tablet (FDT) excipients using this technique are mentioned in table 1.

***Freeze drying*** The major disadvantages of lyophilization technique are:

- Expensive and time consuming.
- Fragility makes conventional packaging unsuitable for these products.
- Poor stability under stress condition.

**6. Mass Extrusion[31]**

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened

mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

## 7. Spray Drying[32-34]

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets.

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 is then mixed with active ingredients and compressed into tablets.

Gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or Croscarmellose or crospovidone are used as super disintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a Super disintegrant like sodium starch glycolate & Croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

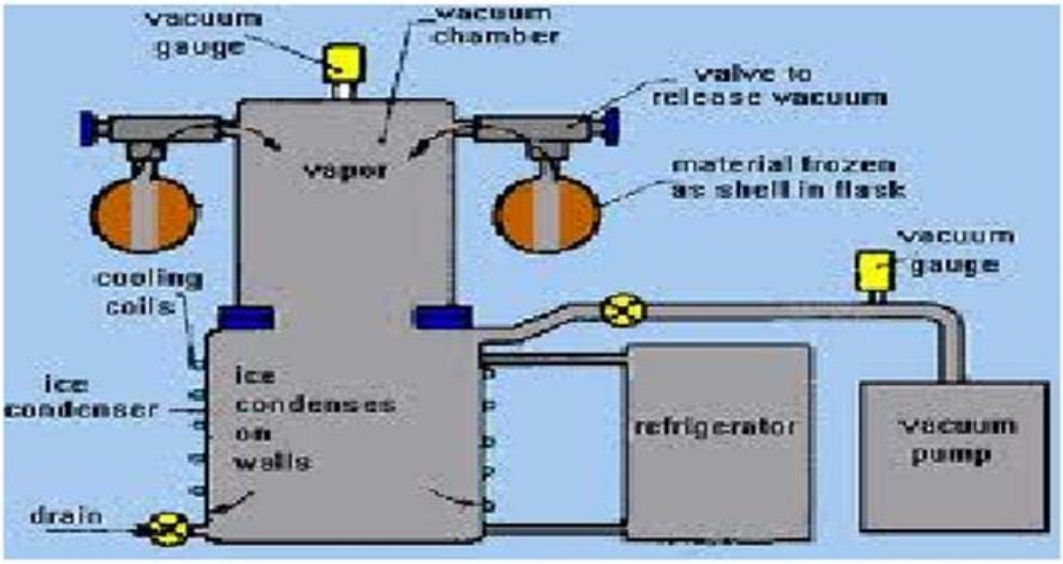


**Figure 3:** Freeze Dryer

**Table 1:** Oral Dispersible Tablet (ODT)/ Fast Dissolving Tablet (FDT) Excipients using Freeze drying

| Excipients | Use | Examples |
|---|---|---|
| Polymer | Strength and rigidity | Gelatin, alginate and dextrin |
| Polysaccharides | Crystalline, hardness and palatability | Mannitol and sorbitol |
| Collapse protectants | Prevents shrinking | Glycerin |
| Flocculating agents | Uniform dispersion | Xanthan gum and acacia |
| Preservatives | Prevent microbial and fungal growth | Parabens |
| Permeation enhancer | Transmucosal permeability enhancer | Sodium lauryl sulphate |
| pH adjusters | Chemical stability | Citric acid and sodium hydroxide |
| Flavors and sweeteners | Patient compliance | --- |
| Water | Porous unit formation | --- |

## 8. Direct Compression[35-39]

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and

hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

Direct Compression technique can now be applied to preparation of ODT because of the availability of improved excipients especially super disintegrants and sugar based excipients.

***(A) Super disintegrants***

In many orally disintegrating tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence the dissolution. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature.

***(B) Sugar Based Excipients***

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

- Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.
- Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

**9. Nanonization[40]**

In this process, the particles of the drug are reduced in the size to nanoparticles by milling the drug in the proprietary wet milling process. The agglomeration can be prevented by surface adsorption of the nanocrystals. These are then compressed & changed into a tablet. This technique is advantageous for less water soluble drugs. The bioavailability of the drug is increased as the disintegration time is reduced to a significant extent.

**10. Cotton candy process**

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process[41] involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. The candy floss matrix is grinded and blended with drug and excipients and then compressed to ODT. This process is more helpful for high doses of drug and also increases mechanical strength of tablet. But high temperature process limits the use of this process.

***A. (A) Floss blend***

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

***B. (B) Floss processing***

The floss formation machine uses flash heat & flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton candy' formation which consists of a spinning head (2000-3600 rpm) that flings the floss under centrifugal force & draws into long & thin floss fibers, which are usually amorphous in nature.[41]

***C. (C) Floss chopping & conditioning***

In this, fibers are converted into smaller particles in high shear mixer granulator. The partial crystallization is done by spraying ethanol (1%) on to the floss and subsequently evaporated it to impart improved flow & cohesive properties to the floss. This is called as Conditioning.

***D. (D) Blending & Compression***

The chopped & conditioned floss fibers are blended with drug & other excipients and compressed into tablets. Exposure of the dosage forms to elevate temperature and humidity conditions ($40^0$C & 85% RH for 15mins) improve the mechanical strength of tablets due to expected crystallization of floss material that results in binding & bridging, to improve the structural strength of the dosage form.[43]

**11. 3-Dimensional Printing[44]**

3-Dimensional Printing is a rapid prototyping technology. Prototyping involves constructing specific layers that uses powder processing & liquid binding materials. A novel fast dissolving drug delivery device (DDDD) with loose powders in it was fabricated using the 3-DP process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3-DP system. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared by using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting large pore size & large pore volume.

**Evaluation of MDTs**

***Thickness[45]***

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using

filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

***Weight uniformity test***[45]

If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test. 20 tablets were selected at random and average weights were determined. Then individual tablets are weighed and the individual weight was compared with the average (table 2).

$$\text{Calculate the average weight of tablets} = \frac{\text{Total weight of tablets}}{\text{Number of tablets}}$$

$$\text{Average weight of tablets (X)} = \frac{(X1+X2+X3+.....+X20)}{20}$$

**Table 2:** As per I.P Limits of Weight variation

| Average weight(mg) | Percentage deviation |
|---|---|
| 80 or less | 10.0 |
| >80 &<250 | 7.5 |
| 250 or >250 | 5.0 |

***Hardness test***[45]

Hardness of MDTs tablets were evaluated by using "Monsanto hardness tester". Tester consists of a barrel containing a compressible spring held between two plungers. Lower plunger is placed in contact with tablet & a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a guage in the barrel to indicate the force.

***Friability (F)***[45]

Roche friability is used to measure the friability of the tablets .It rotates at rate of 25 rpm.10 tablets are weighed collectively and placed in the chamber of friabilator. In the friabilator, the tablets are exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4min), the tablets are taken out from the friabilator and intact tablets are again weighed collectively.

Percentage friability is determined by using the formula,

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

Where,

W1 = weight of tablets before test

W2 = weight of tablets after test

***Content Uniformity test***[46]

Ten tablets were used in this test, where each one was crushed and transferred into a 100 ml volumetric flask. The flasks were brought to volume by phosphate buffer pH 6.8. The flasks were placed onto a sonicator till complete dissolution; 1 ml of the solution was filtered through a Millipore filter of 0.45 µm pore size then introduced into a 25 ml volumetric flask which was completed to volume by phosphate buffer. The absorbance of the solution was measured using a UV-visible spectrophotometer against the blank buffer. The tablets meet the test if the mean drug content lies within the specified range of the labeled potency.

***In- vitro* Disintegration test**

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen which was immersed in water bath at 37 ± 2$^0$C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the Pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.

***Modified Dissolution apparatus for Disintegration time***[47]

Three tablets per batch were evaluated for disintegration time by employing a modified dissolution apparatus. Instead of the disintegration apparatus described in JP XII, a modified dissolution apparatus (JP XII paddle method) was employed (figure 4). Simulated salivary fluid (900 ml), maintained at 37±0.5 $^0$C was stirred with a paddle at 100 rpm. Disintegration time was recorded when all the fragments of the disintegrated tablet passed through the screen of the basket.

***In-vitro dispersion test***[48]

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. *In- vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in-vitro* dispersion time was performed.

***Wetting time***[49]

Ten milliliters of water soluble dye, eosin solution is added to petridish containing five circular filter papers of 10 cm diameter. Tablets were carefully placed on the surface of the filter paper and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results were presented as mean value of three determinations (± SD).

***In-vitro Dissolution studies***[50, 51]

*In-vitro* dissolution studies of the mouth dissolving tablets were performed according to USP XXIII Type-II dissolution employing a paddle stirrer at 50 rpm using 900 ml of simulated salivary fluid pH 6.8 at 37±0.5°C as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals and replaced immediately with equal

volume of fresh medium. The samples were filtered through 0.22 mm membrane filter disc and analyzed for drug content by measuring the absorbance by UV-Visible spectrophotometer. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates.

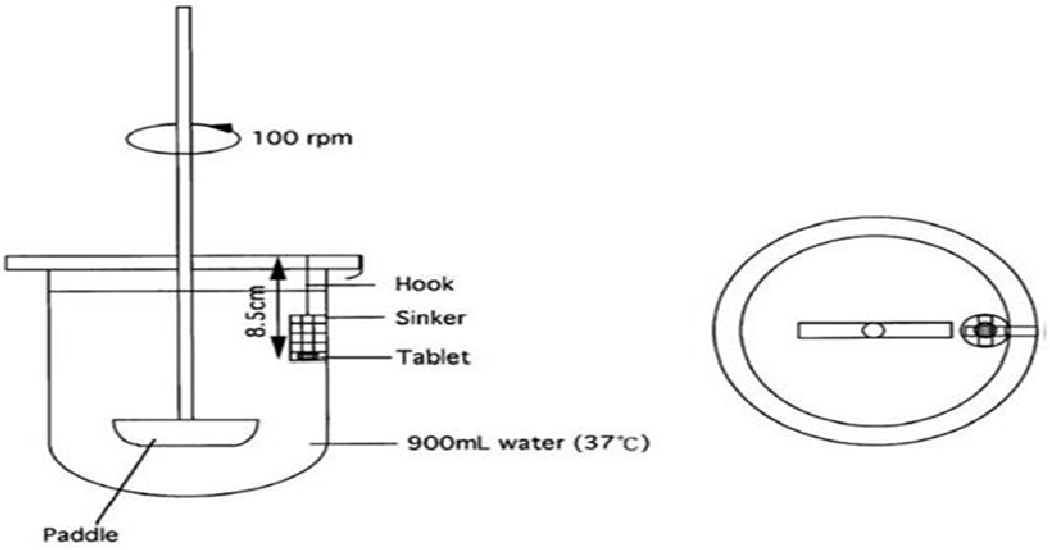


**Figure 4:** Schematic view for Modified Dissolution apparatus for Disintegration time

***Particle packaging index (PPI)***[52]

Particle packaging index was calculated on FDTs compressed to its maximum extend by modifying the method. It is a indicator of compactness of powder. The particle packaging index is a ratio of density of tablet to density of particles. Density of tablets (tablet) was determined using the following formula;

$$\rho tablet = \frac{Wtablet}{\Pi r2t}$$

Where.,

$W_{tablet}$= weight of tablet,

r = radius of tablet

t = thickness of tablet

Density of particles was determined by n-hexane displacement method.

***Moisture Uptake Studies***[53]

Ten tablets from each formulation were kept in desiccator over calcium chloride at 37$^0$C for 24 h. Then the tablets were weighed and exposed to 75% relative humidity (using saturated sodium chloride solution) at room temperature for 2 weeks. One tablet without super disintegrant as control was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded. The results were presented as mean value of three determinations (± SD).

***Tablet Porosity Measurement***[53]

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration.

This instrument is based on the capillary rise method phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure differences across the interface is given by the Washburn equation II , where the pressure drop is inversely related to the pore size (perpendicular radius).

$$\Delta P = (2v/r) \cos \Theta$$

Where.,

V= surface tension of the liquid

r= Perpendicular radius

Θ= Angle of contact between the liquid & capillary walls

Pore radius is calculated from the equation using experimental data obtained in the form of P.

In this test, the contact angle between mercury and tablet is kept at 140$^0$ and the surface tension at the interface of mercury and the tablet is 0.486N/m. Pore size in the range of 0.06-360µm can be efficiently measured by this technique.

Otherwise, Tablet porosity can also be calculated by

$$\varepsilon = 1\text{-}m/(p_t v)$$

Where.,

$P_t$= true density

m & v= weight & volume of the tablet

Tablets prepared by spray drying, lyophilization & cotton candy process generally possess high porosity & therefore, have extremely low disintegration time.

**Table 3:** Patented technologies of Orally Disintegrating Tablets

| Name of the Patented ODT technology | Patentee / Manufacturing company | Manufacturing technique | Products |
|---|---|---|---|
| Zydis[54] | Catalent pharma solutions | Lyophilization | Grazax®<br>(A Grass pollen allergy vaccine) |
| Lyoc[55] | Farmalyoc | Lyophilization | Wafers |
| QuickSolv[55] | Janssen pharmaceutica | Lyophilization | Tablets |
| Nanocrystal[56] | Elan, King of Prussia | Spray drying | Nanoparticles, Nanocrystals |
| OraSolv[57] | CIMA labs | Modified direct compression | |
| DuraSolv[58] | CIMA labs | Modified direct compression | |
| Ora Vescent[59] | CIMA labs | Modified direct compression | FENTORA® |
| EMP[60] | Elmed-Eisai | Wet processing | |
| WOW TAB[61] | Yamanouchi pharmaceutical co. | Granulation followed by compression | |
| Frosta[62] | Akina | Granulation followed by compression | |
| Easy Tec[63] | Antarus | Granulation followed by compression | |
| Flash Dose[64] | Biavail corporation | Molding / Cotton candy process | Nurofen meltlet<br>(a new form of Ibuprofen) |
| FlashTab[65] | Prographarm Laboratories | Granulation followed by compression | |
| Ora Quick[66] | KV Pharmaceuticals | Taste-masking technology, Micromask | |
| Solu Tab DR[67] | Takeda Pharmaceutical company | | Pravacid delayed release ODTs<br>(Lansoprazole) |
| Orexo AB[68] | Meda pharma | | Sublimox<br>(Sublingual tablet of Zolpidem) |
| Sa Tab<br>Adva Tab/ Ziplet ™ 70 | Sato pharmaceuticals | Moistening & Drying<br>Modified Direct compression | Microcaps/Diffucaps®<br>(taste masked/CR drug particles)<br>Advatab granules<br>(rapidly dispersing microgranules)<br>Hata's tablet press<br>(Matsui Ex-Lub system) |
| Microcaps[71] | Eurand corporation | Coacervation process | |
| Shearform[72] | Fuisz | Flash heat process | EZ Chew tablets |
| Dispersible tablet[73] | Lek, Yugoslavia | | |
| Pharmaburst[73] | SPI Pharma, New castle | Dry blending followed by compression | |
| Quick-Dis[74] | Lavipharm | | Quick-Dis™ (Films) |
| Ceform[75] | | | Microspheres |

**Emerging Technologies in ODTs**

Many emerging technologies had been come into existence apart from the above mentioned patented technologies. Aprecia is the exclusive pharmaceuticals, nutraceuticals, and cosmetics licensee from the Massachusetts Institute of Technology (MIT) of their 3DP-related patent estate. ZipDose™ is a versatile fast-dispersing dosage form enabling high-dose and/or multidrug products with fast flashing times, unique taste-masking options, and IR/ER combinations.[76] Alpex's ODT based on a patented taste-masking and tableting technology comprising taste-masked drug particles. Dainippon Sumitomo Pharma received the approval by the FDA for ODT formulations of Amlodipine indicated for the treatment of hypertension/angina pectoris. The product is produced using the company's proprietary formulation technology SUITAB, the ODTs. FastOral1 technology from CLL Pharma consists of preparing ODTs comprising one or more drugs dispersed in an excipient mixture (e.g., trehalose, vinyl pyrrolidone–vinyl acetate copolymer.[77]

## CONCLUSION

A more recent breakthrough technology that accelerated market introduction of pharmaceutical products is in the form of ODTs. These ODTs had emerged as an advanced alternative to the traditional drug dosage forms. These ODTs have better patient acceptance, compliance with improved biopharmaceutical properties, improved efficacy & better safety. Increasing demand and patient acceptance had been seen with ODTs from all the age groups which had taken as an advantage by the pharmaceutical companies to develop many more technologies and to commercialize the available drugs into ODTs.

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**Source of Support:** Nil, **Conflict of Interest:** None.