

## ORALLY DISINTEGRATING TABLET: FRIENDLY DOSAGE FORM

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### ABSTRACT

Orally disintegrating tablets (ODTs) have emerged as one of the popular and widely accepted dosage forms, especially for the paediatric and geriatric patients. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Among the dosage forms developed to facilitate ease of medication, the rapid disintegrating tablet (RDT) is one of the most widely employed commercial products.<sup>1</sup> As our society is becoming increasingly aged, the development of Fast- or mouth dissolving tablets have been formulated for paediatric, geriatric, and bedridden patients and for active patients who are busy and travelling and may not have access to water. Such formulations provide an opportunity for product line extension in the many elderly persons will have difficulties in taking conventional oral dosage forms (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Swallowing problems also are common in young individuals because of their underdeveloped muscular and nervous systems.<sup>2,3</sup> Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled, and patients who are uncooperative, on reduced liquid-intake plans, or are nauseated. In some cases such as motion sickness, sudden episodes of allergic attack or coughing, and an unavailability of water, swallowing conventional tablets may be difficult. This paper summarizes the formulation methods and drug formulation coming in market.

**KEYWORDS:** Orally disintegrating tablets, Superdisintegrants, Direct compression

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## **INTRODUCTION**

Orally disintegrating tablets or fast disintegrating tablet of the type of those intended to undergo disaggregation in the mouth in contact with the saliva in less than 60 seconds, preferably in less than 40 seconds, forming a suspension which is easy to swallow. It is better known by the phrase "orodispersible tablets". The common formulations in market are tablets or gel capsules. These forms, owing to their simplicity of use, are ideally suited to ambulatory treatment. However, certain patients, and especially the elderly, experience difficulties of deglutition which are such that it is difficult and, consequently, unpleasant for them to ingest tablets or gel capsules, even together with an intake of liquid. It is estimated that 50% of the population has difficulties in swallowing tablets or gel capsules. This problem results in the prescribed medicament not being taken and hence in the efficacy of the treatment being severely affected. So orodispersible tablets are easy administration for patients who have problems of deglutition or for those persons who would like to take their treatment without simultaneous ingestion of liquid.<sup>4</sup> ODTs also combine the advantages of both liquid and conventional tablet formulations allowing the ease of swallowing in the form of liquid. The advantages of these dosage forms are continuously and increasingly being identified in both pharmaceutical industries as well as in academia. The objective of present article is to highlight the development of ODTs, their significance, ideal characteristics, various techniques and aspects related to design and formulation, marketed preparations and future prospectives.<sup>5</sup>

## **ADVANTAGES OF ODTS**

1. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increases.
2. Pre gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
3. Ease of administration to patients who refuse to swallow a tablet, such as paediatrics, geriatric, mentally ill, disabled and uncooperative patients.
4. Convenience of administration and accurate dose as compared to liquids.
5. No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
6. Good mouth feel property of ODTs helps to change the psychology of medication as "bitter pill" particularly in paediatrics patients.
7. Ability to provide advantages of liquid medication in the form of solid preparation.
8. Rapid dissolution of drug and absorption, which may produce rapid onset of action<sup>5</sup>.

## **CHALLENGES IN FORMULATING ODTS**

### **Palatability**

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**

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-moulded 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<sup>6</sup>.

### **Hygroscopicity**

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**

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**

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**

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.

## **VARIOUS TECHNOLOGIES USED IN THE MANUFACTURE OF ODT**

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent & using highly water-soluble excipients in the formulation<sup>4</sup>. Following technologies have been used by various researchers to prepare ODT: -

- Freeze-Drying or Lyophilization
- Tablet Moulding
- Spray Drying
- Sublimation
- Direct Compression
- Cotton Candy Process
- Mass-Extrusion

### **Freeze-Drying or Lyophilization**

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells 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 aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped.

The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

### **Tablet Molding**

The preparation of ODT using molding technology employs water-soluble ingredients so that the tablet dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution.

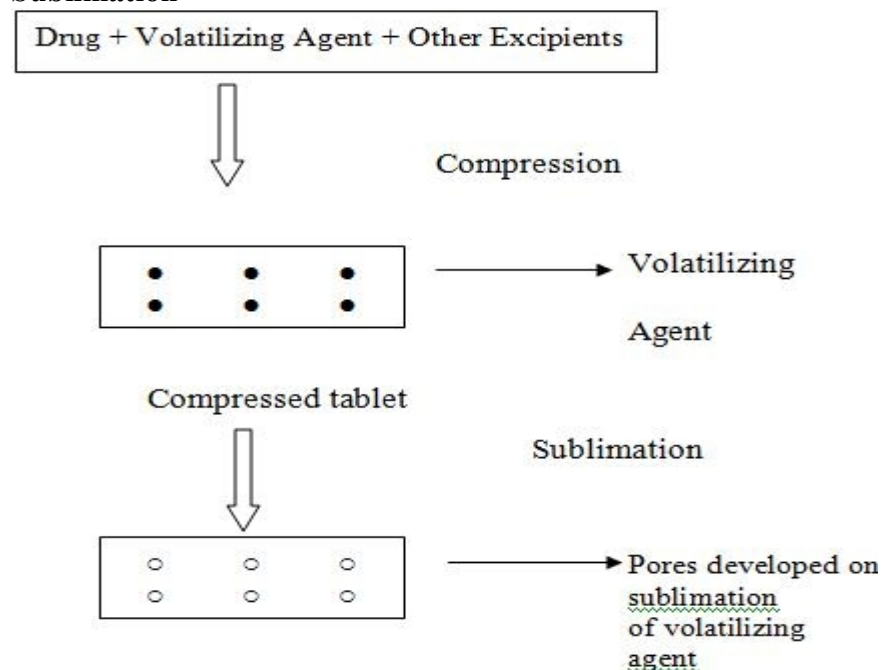
The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30° under vacuum. The mechanical strength 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. To overcome this, Van Scoik incorporated taste masked drug particles. 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 lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture. Masaki uses an agar solution as a binding agent and a blister packaging as well as a mold to prepare an intrabuccally fast disintegrating tablet.

### **Spray Drying**

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing ODT. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or cross carmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. Allen and Wang have reported this technique for preparing fast dissolving tablets. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & crosscarmellose 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.

### **Sublimation**

The key to rapid disintegration of ODT is preparation of a porous structure in the tablet matrix. To generate such a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and ophthalmic 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. Even solvents like cyclohexane, benzene can be used as pore forming agents. Vacuum drying technique has been very often used by researchers to sublime the volatile ingredients and thus maximize the porous structure in the tablet matrix. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

**Sublimation****Cotton Candy Process**

The cotton candy process is also known as the “candy floss” process and forms the basis of the technologies such as Flash Dose (Fuisz Technology). An ODT is formed using a candy floss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallized to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently compressed into ODT. However the high processing temperature limits the use of this technology to thermo stable compounds only.

**Mass-Extrusion**

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 tablets. The dried cylinder can also be used to coat granules for bitter drugs and there by achieve.

**Direct Compression**

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants & sugar based excipients.

**(a) Superdisintegrants**

Disintegrants are substances or mixture of substances added the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants<sup>(4,5)</sup>. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1 – 10 % by weight relative to the total weight of the dosage unit. In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution<sup>8</sup>.

**Selection of Superdisintegrants**

Factors to be considered for selection of superdisintegrants<sup>9</sup>:

- It should produce rapid disintegration(hydrophilic) when tablet meets saliva in the mouth
- It should be compactable enough to produce less-friable tablets.

- It can able to produce good mouth feel to the patient. Thus, small particle sizes are preferred to achieve patient compliance.
- It should has good flow since it improve the flow ability of the total blend.

### **Superdisintegrants**

Crospovidone, Microcrystalline cellulose, sodium starch glycolate, sodium carboxy methyl cellulose, pregelatinized starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycolate has good flow ability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

### **(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, maltitol, 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. Mizumito *et al* have classified sugar-based excipients into two types 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 maltitol) exhibit high mouldability and low dissolution rate. Mouldability is defined as the capacity of the compound to be compressed/molded. The mouldability of type 1 saccharide can be improved by granulating it with type 2 saccharides. WOWTAB technology used in Benadryl fast melt tablets uses this technique. Most commercial ODTs have been developed using mannitol as the bulk excipient of choice. Mannitol is overwhelmingly preferred over lactose because of its extremely low hygroscopicity, excellent chemical and physical compatibility, good compressibility and better sweetness. ODT formulators prefer to use a directly compressible mannitol, which enables the preparation of robust tablets that can withstand processing and transportation. Specially textured directly compressible, spray-dried, or granulated mannitol excipients have been designed to meet these needs. These excipients under defined manufacturing conditions gives a highly porous structure and friable exterior structure which helps in faster disintegration of ODT, they also provide a satisfactory mouth feel and so suitable for use in preparation of harder ODT by direct compression at low pressure.

### **(c) Other Excipients**

**Flavours:** Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil thyme oil, oil of bitter almonds. Flavoring agnets include, vanilla, citrus oils, fruit essences

**Sweeteners:** Aspartame, Sugars derivatives

**Fillers:** Directly compressible spray dried Mannitol, Sorbitol, Xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, and aluminium hydroxide.

**Surface active agents:** Sodium doecyl sulfate, sodium lauryl sulfate, poly oxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), poly oxyethylene stearates.

**Lubricants:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

### **Evaluation of ODTs**

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

### **Hardness**

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers.

### **Friability**

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

### **Wetting time and water absorption ratio**

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a Petri dish. Ten millilitres of water soluble dye solution is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the Petri dish is noted (Wb). The wetted tablet from the Petri dish is taken and reweighed (Wa)'. The water absorption ratio

R can be the determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

### **Moisture uptake studies**

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a desecrator over calcium chloride at 37°C for 24h. The tablets were then weighed and exposed to 75% relative humidity; at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desecrator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

### **Disintegration test**

The time for disintegration of ODTs is generally <1min and actual disintegration time that patience can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents.

### **Dissolution test**

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile<sup>30,12</sup>.

### **Industrial Applications**

- To develop an orally disintegrating dosage forms and to work with existing disintegrants.
- To further improve 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<sup>12</sup>.

### **Future Prospects**

These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Should next generation drugs are predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favoured 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**

ODTs offer numerous significant advantages over conventional dosage forms because of improved efficacy, bioavailability, and rapid onset of action, better patient compliance and acceptance. Pediatric and geriatric patients are primary concerns, as both the groups find these dosage forms convenient to administer as compared to the conventional dosage forms. ODTs can be prepared in several ways and product performance depends upon the drug suitability and excipients selection in the delivery system. Due to the availability of various formulation techniques, good patient compliance and huge potential, several products have already been commercialized. Furthermore, market size and popularity of these dosage forms will surely expand in future. It is also emphasized that newer scientific and technological innovations should be undertaken for the emergence of promising and versatile dosage form with novel performance and characteristics.

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**Table 1: List of commercially available ODTs**

<b>Name of the Product</b>	<b>Active Ingredients</b>
Imodium Lingual	Imodium
Pepcidin Rapitab	Quick releasing antiulcer preparation of pepcid
Mosid – MT	Mouth melt tablet of Mosapride citrate.
Calritin Reditabs	Immediate Dissolving formulation of Calritin
Nimulid – MD	Nimesulide
Zyrof Meltab	Rofecoxib
Claritin Reditab	micronized loratadine
Feldene Melt	piroxicam (10 or 20 mg),
Maxalt-MLT	rizatriptan (5 or 10 mg), peppermint flavour
Pepcid RPD	famotidine (20 or 40 mg),
Zyprexa Zydis	olanzapine (5, 10, 15 or 20 mg),
Zofran ODT	ondansetron (4 or 8 mg), strawberry flavor
Remeron Soltab	mirtazepine (15, 30, or 45 mg), orange flavor