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## Orally disintegrating tablets : formulation, preparation techniques and evaluation

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### ABSTRACT

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Formulation of a convenient dosage form for oral administration, by considering swallowing difficulty especially in case of geriatric and pediatric patient leads to poor patient compliance. To troubleshoot such problems a new dosage form known as orally disintegrating tablet (ODT), has been developed which rapidly disintegrate & dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form. In addition, patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders prefer such preparation because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in such type of dosage form. The popularity and usefulness of the formulation resulted in development of several ODT technologies for preparation. The current article is focused on ideal characteristics, advantages and disadvantages, formulation aspects, formulation technologies, evaluation of products and future potential. Various marketed preparations along with numerous scientific advancements made so far in this avenue have also been discussed.

**Key words:** API, Fast dissolving tablet, Oral route, Excipients, Oral dissolving tablet.

### INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (To accommodate various types of drug candidates) and most importantly, patient compliance (Sastry et al, 1997). Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture (Fasano et al, 2005). A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists. In similar fashion the oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of langerhans cells makes oral mucosa tolerant to potential allergens (Shojaei et al, 1998).

### Overview of Oral Mucosa

The anatomical and physiological properties of the oral mucosa have been extensively reviewed by several authors (Shojaei et al, 1998 & Gandhi et al, 1994). The oral cavity comprises

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the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Fig. 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells (Fig. 2).

The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss (Collins et al 1987). Beneath the epithelium are the basement membranes, lamina propria and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingival (gums) (Smart et al, 2004).

The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propria tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propria and a sub mucosa. The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces which are both keratinized and some non-keratinized (Collins et al, 1987). Table 1 depicted the advantages and disadvantages associated with utilizing the oral mucosa as a drug delivery site.

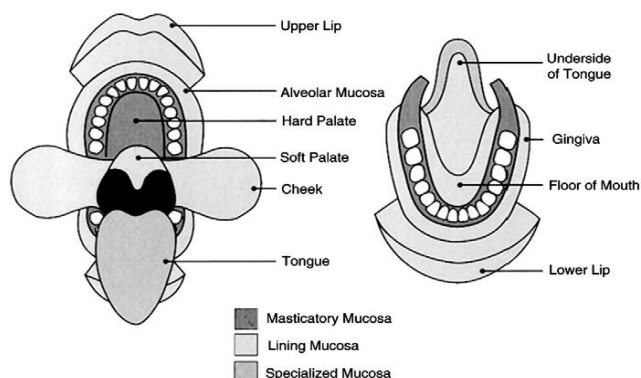


Fig. 1: Schematic representation of the different linings of mucosa in mouth (Squier et al, 2001)

## ORALLY DISINTEGRATING DOSAGE FORMS

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for ODDFs has enormously increased during the last

decade, particularly for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high incidence of ineffective therapy (Seager et al, 1998)

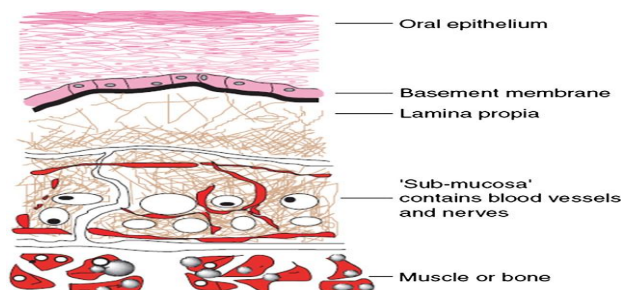


Fig.2: Schematic diagram of buccal mucosa (Smart et al, 2004)

Table1: The advantages and disadvantages associated with utilizing the oral mucosa as a drug delivery site (Sankar et al, 2011).

Advantages	Disadvantages
1. Accessible	1. Permeability barrier of the oral mucosa
2. Self administrable	2. Saliva washes away drug
3. Oral mucosa repairs rapidly	3. Mastication and speech may dislodge
4. Different areas of the oral cavity have different permeability characteristics	4. Delivery device
5. Highly hydrated environment to dissolve drug	5. Requires formulation for agreeable taste
6. Sustained delivery possible	6. Highly enzymatic environment
7. Potential reduction of systemic side effects	7. Relatively small surface area
8. Avoid the hepatic first-pass effect	8. Risk of choking on or swallowing delivery device
9. High blood supply	
10. Fast systemic delivery possible	

In disease conditions such as motion sickness, sudden episodes of attacks of coughing and repeated emesis swallowing conventional solid dosage forms become difficult. Orally disintegrating dosage forms can serve as an effective alternative mode of drug delivery in such situations (Ghosh et al, 2005). When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva (Dobetti et al, 2001). Thereafter, the drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form (Brown et al 2001 & Deepak et al, 2004).

The novel technology of oral disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick dispersible tablets (Gupta et al, 2010). However, the function and concept of all these dosage forms are similar. Different orally disintegrating dosage forms are as follows:

1. Orally disintegrating tablets: It is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing (Gupta et al, 2010).
2. Fast dissolving films: The fear of taking solid tablets and the risk of choking for certain patient population still exists despite their short dissolution and disintegration time. It

consists of very thin oral strip, which releases the active ingredient immediately after uptake in to the oral cavity. It combines all advantages of tablets along with liquid dosage forms. This system is simply placed on patients tongue or any other mucosal surface, instantly wet by saliva; film rapidly hydrates and dissolves to release the medication (Vollmer et al, 2007).

3. Fast Caps: A new type of fast disintegrating drug delivery system based on gelatin capsules was developed. In contrast to conventional hard gelatin capsules, the fast caps consist of gelation of low bloom strength and various additives to improve the mechanical and dissolution properties of capsule shell. It includes several advantages like high drug loading, possible solid and liquid filling, and no compression of coated taste masked or extended release drug particles / pellets, good mechanical properties, simple manufacturing, mechanical stability and requirement of special packaging. (Bodmeier et al, 1999).
4. Medicated chewing gums: it is an attractive alternative for drug delivery system with several advantages including convenience for administration, mainly chewing gum is used to promising controlled release drug delivery system. These are mainly available currently for pain relief, smoking cessation, travel illness and freshening of breath.(Pandit et al, 2006).
5. Freeze-dried wafer: it is a quick-disintegrating, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. The saliva is swallowed and the drug is absorbed across the gastrointestinal tract (GIT). (Dobetti et al, 2001).

### ORALLY DISINTEGRATING TABLETS

The performance of ODTs depends on the technology used in their manufacture. The orally disintegrating property of these tablets is attributable to the quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation (Wilson et al, 1987).

#### Ideal characteristics of ODTs

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include (Kuchekar et al, 2003)

1. No water requirement for swallowing purpose but it should dissolve or disintegrate in the mouth usually within fraction of seconds.
2. Provide pleasant feeling in the mouth.

3. Be compatible with taste masking.
4. Be portable without fragility concern.
5. Leave negligible or no residue in the mouth after oral administration.
6. Exhibit low sensitivity to altered environmental conditions such as humidity and temperature.
7. Allow high drug loading.
8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.

#### Advantages of ODTs

1. ODT can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance (Wilson et al, 1987).
2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down (Fix et al, 1998).
3. ODT is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water (Fix et al, 1998).
4. Good mouth feel property of ODT helps to change the perception of medication (Allen et al, 1997).
5. As bitter pill particularly in pediatric patients (Wilson et al, 1987).
6. The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety (Indurwade et al, 2000).
7. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management (Wilson et al, 1987).
8. Suitable during traveling where water may not be available (Fix et al, 1998).
9. No specific packaging required can be packaged in push through blisters (Kuchekar et al, 2003).
10. Conventional manufacturing equipment (Kuchekar et al, 2003).
11. Cost effective (Wilson et al, 1987).
12. Good chemical stability as conventional oral solid dosage form (Allen et al, 1997).
13. New business opportunity like product differentiation, product promotion, patent extension and life style management (Wilson et al, 1987).
14. Allow high drug loading (Fix et al, 1998).
15. Provides rapid drug delivery from dosage forms (Allen et al, 1997).
16. Provide advantage of liquid medication in form of solid preparation (Shyamala et al, 2002)
17. Rapid drug therapy intervention (Wilson et al, 1987)
18. No chewing needed (Fix et al, 1998).

19. Adaptable and amenable to existing processing and packaging machinery (Wilson et al, 1987)
20. Rapid onset of action (Bradoo et al, 2001)

### Disadvantages of ODTs

1. ODT is hygroscopic in nature so must be kept in dry place (Devrajan et al, 2003)
2. Some time it possesses mouth feeling (Chang et al, 2000).
3. It also shows the fragile, effervescence granules property (Chang et al, 2000)
4. ODT requires special packaging for proper stabilization & safety of stable product (Devrajan et al, 2003)

### MECHANISMS OF ODTs

ODTs involve the following mechanisms to achieve the desired fast dissolving characteristics (Sahoo et al, 2010):

1. Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.
2. Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.
3. There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug. The mechanisms are-
  - ❖ High swellability of disintegration
  - ❖ Chemical reaction
  - ❖ Capillary action

### FORMULATION ASPECTS OF ODTs

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. This includes both the pharmacologically active ingredients (drug) and the excipients (additives).

A. Selection of drug candidate: Several factors may be considered while selecting an appropriate drug candidate for development of orally disintegrating tablets. The ultimate characteristics of a drug for dissolution in mouth and pregastric absorption from fast dissolving tablets include (Reddy et al, 2002)

1. Free from bitter taste
2. Dose lower than 20mg
3. Small to moderate molecular weight
4. Good solubility in water and saliva
5. Partially unionized at oral cavity pH
6. Ability to diffuse and partition in to the epithelium of upper GIT ( $\log > 1$ , or preferably  $> 2$ )
7. Ability to permeate oral mucosal tissue.

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient. Researchers have formulated ODT for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These

include neuroleptics, cardiovascular agents, analgesics, antiallergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction (Kushekar et al, 2003)

In contrast, the following characteristics may render unsuitable for delivery as an orally disintegrating tablet:-

1. Short half life and frequent dosing.
2. Very bitter or otherwise unacceptable taste because taste masking cannot be successfully achieved.
3. Require controlled or sustained release.
4. Combination with anticholinergics.

B. Selection of excipients: Mainly seen excipients in ODT are as follows at least one disintegrant, a diluent, a lubricant, and optionally, a swelling agent, sweeteners, and flavoring agents etc. Ideal bulk excipients for orally disintegrating dosage forms should have the following properties (Bansal et al, 2003):

1. Disperses and dissolves in the mouth within a few seconds without leaving any residue.
2. Masks the drug's offensive taste and offers a pleasant mouth feel.
3. Enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature.

The role of excipients is important in the formulation of fast-melting tablets. The temperature of the excipients should be preferably around 30–35°C for faster melting properties. Detail of excipients is given in table 2 & 3.

**Table 2:** Excipients to be used for the preparation of ODTs (Liang et al, 2001)

Excipients	Function	Examples
<b>Superdisintegrant</b>	Increases the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the super disintegrant	Crospovidone, Microcrystalline cellulose, sodium starch glycolate, sodium carboxy methyl cellulose, pregelatinized starch, Carboxy methyl cellulose, and modified corn starch. Sodium starch glycolate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable
<b>Flavors</b>	Increases Patient compliance and acceptability	Peppermint flavor, 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 agents include, vanilla, citrus oils, fruit essences.
<b>Sweeteners and sugar based excipients</b>	This is another approach to manufacture ODT by direct compression. Sugar based excipients acts as bulking agents. These exhibits high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel.	Artificial sweeteners like Aspartame, Sugars derivatives. Bulking agents like dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol
<b>Surface Active agents</b>	Reduces interfacial tension and thus enhances solubilization of FDT	Sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens),

<b>Binder</b>	Maintains integrity of dosage form prior to administration	sorbitan fatty acid esters (Spans), polyoxyethylene stearates, Polyvinylpyrrolidone(PVP), Polyvinylalcohol(PVA)
<b>Color</b>	Enhances appearance and organoleptic properties of dosage form	Hydroxy propyl methylcellulose(HPMC) Sunset yellow, Amaranth, Red iron oxide
<b>Lubricants</b>	Lubricant helps reduce friction and wear by introducing a lubricating film between mechanical moving parts of tablet punching machine	Stearic acid, Magnesium stearates, Zinc stearate, calcium stearate, talc, polyethylene glycol, liquid paraffin, magnesium lauryl sulfate, colloidal silicon dioxide.
<b>Fillers</b>	Enhances bulk of dosage form	Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide

**Table 3:** Superdisintegrants to be used for the preparation of ODTs (Bhowmik et al, 2009)

Name	Composition	Mechanism of action	Special comment
Crosscarmellose Ac-Di-Sol Nymce ZSX Primellose@Solu tab Vivasol L-HPC	Cross linked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crospovidone Crospovidone M Kollidon Polyplasdone	Cross linked PVP	Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab Primogel	Cross linked starch	Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine	Cross linked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy	Natural super disintegrant	-Does not contain any starch or sugar. Used in nutritional products	
Calcium silicate	-Wicking action		Highly porous, Optimum concentration is between 20-40%

## TECHNIQUES FOR PREPARATION OF ODTs

The techniques used to manufacture ODTs can be classified as:-

- 1) Conventional techniques
- 2) Patented techniques

### Conventional Techniques

The various conventional technologies are developed for the preparation of Orally Disintegrating drug delivery system that are Freeze drying, Spray drying, Molding, Phase transition process, Melt granulation, Sublimation, Mass Extrusion, Cotton Candy Process, Direct compression (Meyers et al, 1995 & Makino

et al, 1993). Detail of all these conventional techniques is given in **table 4**.

### Patented Techniques

Rapid-dissolving characteristic of ODTs is generally attributed to fast penetration of water into tablet matrix resulting in its fast disintegration. Several technologies have been developed on the basis of formulation aspects and different processes and resulting dosage forms vary on several parameters like mechanical strength, porosity, dose, stability, taste, mouth feel, dissolution rate and overall bioavailability. **Table 5** represents the list of unique patented technologies, their advantages, disadvantages, and **Table 6** represents the patented technology and their branded products.

### EVALUATION OF ODTs

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends (Reddy et al, 2002). There are many formulation and process variables involved in mixing and all these can affect the characteristics of blends produced (Kushekar et al, 2003).

**A. Evaluation of blends before compression:** The various characteristics of blends to be tested before compression are (Kushekar et al, 2003 & Shyamala et al, 2002):

**1. Angle of repose:** Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$$\tan \theta = h/r$$

Where h and r are the height of cone and radius cone base respectively. Angle of Repose less than 30 ° shows the free flowing of the material.

**Bulk density:** Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using following formula:

$$\text{Bulk density} = \text{Weight of the powder} / \text{Volume of the packing.}$$

**Tapped density:** It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be calculated by using following formula:

$$\text{Tapped Density} = (\text{Weight of the powder} / \text{volume of the tapped packing})$$

**Table 4:** Conventional techniques used for the preparation of ODTs.

S.No	Techniques	Method and characteristics of prepared ODTs
1	<b>Disintegrant addition</b>	Involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For e.g. MCC and sodium starch glycolate are used in formulation of Efavirenz, Crystalline cellulose (AvicelPH-102) and low substituted HPEC used in oxybutinin and pirenzepine formulation. Crospovidone used in galanthamine HBr. Crospovidone (3% w/w) and croscarmellose Na (5% w/w) used in prochlorperazine maleate formulation. <b>Characteristics:</b> similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability
2.	<b>Freeze Drying or Lyophilization</b>	The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into 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. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. Finally the blisters are packaged and shipped. <b>Characteristics:</b> The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability. Dose incorporated:- insoluble 400mg Water soluble drug loading:- 60mg <b>Advantages of Freeze drying</b> <ul style="list-style-type: none"> <li>• Tablets produced by this technique possess very low disintegration time.</li> <li>• Render tablets with great mouth feel due to fast melting effect.</li> <li>• Provides immediate dissolution (5 sec).</li> <li>• Increases absorption and bioavailability of drug.</li> <li>• Lyophilization is useful for heat sensitive drug that is thermo labile substances.</li> <li>• Tablets prepared by lyophilization disintegrate rapidly in less than 5 sec due to quick penetration of saliva in pores when placed in oral cavity.</li> </ul> <b>Disadvantages of freeze drying</b> <ul style="list-style-type: none"> <li>• Relatively expensive and time consuming process.</li> <li>• The product obtained is poorly stable and fragile, sensitive to humidity rendering conventional packaging unsuitable.</li> <li>• Very poor physical resistance,</li> <li>• High cost of production,</li> <li>• Low dose of water-soluble drugs</li> </ul>
3	<b>Moulding</b>	Water-soluble ingredients with a hydro alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. <b>Characteristics:</b> Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased. <b>Advantages :</b> Very rapid dissolution (5–15 s) <b>Disadvantages :</b> High cost of production , Weak mechanical strength Possible limitations in stability
4	<b>Sublimation</b>	Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, and hexamethylenetetramine were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. <b>Characteristics:</b> Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc. <b>Advantages:</b> Good physical resistance & highly porous structure <b>Disadvantages:</b> Harmful residual adjuvant, Extra equipments for heating, Not applicable to volatile and heat sensitive drugs
5	<b>Spray-Drying</b>	By hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating agent and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution. (Mishra DN.et al) <b>Characteristics:</b> Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium
6	<b>Mass Extrusion</b>	Involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. <b>Characteristics:</b> The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.
7	<b>Direct compression</b>	Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. <b>Characteristics:</b> It is most cost effective tablet manufacturing technique. <b>Advantages</b> <ul style="list-style-type: none"> <li>• Requires fewer unit operations compared with wet Granulation (shorter processing time and lower energy consumption)</li> <li>• Fewer stability issues for actives that are sensitive to heat or moisture</li> <li>• For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, Norfloxacin.</li> <li>• Fewer excipients may be needed in a direct compression Formula.</li> </ul> <b>Disadvantages</b> <ul style="list-style-type: none"> <li>• Issues with segregation – these can be reduced by matching</li> <li>• The particle size and density of the active drug substance with excipients</li> <li>• In general, the drug content is limited to approximately 30% or approximately 50 mg</li> <li>• Not suited for poorly flowing drug compounds</li> <li>• Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing</li> </ul>
8	<b>Cotton candy process</b>	Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT. <b>Characteristics:</b> It can accommodate high doses of drug and offers improved mechanical strength.
9	<b>Compaction</b> <b>a) Melt granulation</b>  <b>b) Phase-transition process</b>	Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. <b>Characteristics:</b> It melts in the mouth and solubilizes rapidly leaving no residue. Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. <b>Characteristics:</b> The compatibility increased and so sufficient hardness gained by the formulation.

10	<b>Nanonization</b>	Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs. <b>Characteristics:</b> It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).
11	<b>Fast Dissolving Films</b>	Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs. <b>Characteristics:</b> It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).
12	<b>Tableting (standard)</b>	<b>Advantages:</b> <ul style="list-style-type: none"> <li>• Low cost of production</li> <li>• Use of standard equipment/materials</li> <li>• High dose</li> <li>• Good physical resistance</li> </ul> <b>Disadvantages:</b> <ul style="list-style-type: none"> <li>• Significant effects of the size and hardness of the tablets on disintegration property</li> </ul>
	<b>Tableting (effervescent)</b>	<b>Advantages:</b> <ul style="list-style-type: none"> <li>• Use of standard equipment</li> <li>• High dose Good physical resistance</li> <li>• Pleasant effervescent mouth feel</li> </ul> <b>Disadvantages:</b> <ul style="list-style-type: none"> <li>• Operating in controlled low humidity</li> <li>• Need of totally impermeable blister</li> </ul>
	<b>Tableting (Humidity Treatment)</b>	<b>Advantages:</b> <ul style="list-style-type: none"> <li>• Good physical resistance.</li> <li>• Pleasant mouth feel</li> </ul> <b>Disadvantages:</b> <ul style="list-style-type: none"> <li>• Extra equipments for humidification and drying</li> <li>• Possible limitations in stability</li> <li>• High cost of production</li> <li>• Not suitable for moisture sensitive compounds</li> <li>• Fragile before humidity treatment</li> </ul>

**Compressibility index:** The Compressibility Index of the blends is determined by compressibility index. Compressibility Index can be calculated by using following formula:

$$\text{Compressibility Index (\%)} = [(TD-BD) \times 100] / TD$$

**Hausner's ratio:** A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using following formula:

$$\text{Hausner's ratio} = (\text{Tapped density} \times 100) / (\text{Poured density})$$

Hausner's ratio <1.25 – Good flow = 20% **compressibility index**  
1.25 – Poor flow = 33% **compressibility index**

**Void Volume:** The volume of the spaces is known as the void volume "V" (Yoshio .et al) and is given by the formula

$$V = V_b - V_p$$

Where,  $V_b$  = Bulk volume (volume before tapping)

$V_p$  = True volume (volume after tapping)

**Porosity:** The porosity  $\epsilon$  of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by following formula:

$$\epsilon = (V_b - V_p) / V_p = 1 - V_p/V_b$$

**Table 5:** Different Patented techniques for preparation of ODTs (Takagi et al, 2005 & Modi et al, 2006)

S. No.	Technique	Advantages	Disadvantages
1	<b>Zydis</b>	Quick dissolution, Self-preserving and increased bioavailability.	Expensive process, poor stability at higher Temperature and humidity.
2	<b>Orasolv</b>	Taste-masking is twofold, quick Dissolution.	Low mechanical strength
3	<b>Durasolv</b>	Higher mechanical strength than Orasolv, Good rigidity.	Inappropriate with larger dose.
4	<b>Flashtab</b>	Only conventional tableting technology	—
5	<b>Wow tab</b>	Adequate dissolution rate and hardness.	No significant change in bioavailability
6	<b>Oraquick</b>	Faster and efficient production, appropriate for heat-sensitive drugs	--
7	<b>Ziplet</b>	Good mechanical strength, satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg).	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution.
8	<b>FlashDose</b>	High surface area for dissolution	High temperature required to melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity.

Porosity is frequently expressed in percentage and is given as:

$$\% \epsilon = (1 - V_p / V_b) \times 100$$

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

**B. Evaluation of Tablets:** All the formulated ODTs were subjected to the following quality control tests (Shyamala et al, 2002, Bradoo et al 2001, & Makino et al, 1993):

**Weight variation:** The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation. **Table 9** depicted USP Specification for uniformity of weight.

**Table 6:** Patented technology and their branded products (Modi et al, 2006).

S. No.	Technology	Process involved	Patent owner	Drugs (Brand name)	Used
1	Zydis	Lyophilization	R.P.Scherer Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)	
2	Quicksolv	Lyophilization	Jansen Pharmaceutical	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-tab)	
3	Flashtab	Lyophilization	Ethypharm	Ibuprofen (Nurofen Flashtab)	
4	Lyoc	Multiparticulates Compressed tablets	Farmlyoc	Phloroglucinol Hydrate (Spasfon Lyoc)	
5	Orasolv	Compressed Tablets	Cima Labs Inc.	Paracetamol (Temptra Quicklets), Zolmitriptan (Zolmig Repimelt)	
6	Durasolv	Molding	Cima Labs Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)	
7	RapiTab	Compressed Tablets	Schwarz Pharma	--	
8	Wow tab	Compressed Molded Tablets	Yamanouchi Pharma Technologies, Inc.	Famotidine (Gaster D)	
9	Fast melt	Molding	Élan Corp.	--	
10	Ziplets	Molding	Eurand	Ibuprofen (Cibalgina Fast)	Due
11	FlashDose	Cotton-candy process	Fuisz Technology Ltd.	Tramadol (Relivia dose)	HCl Flash
12	Oraquick	Micromask taste Masking	KV Pharm. Co., Inc.	Hyoscyamine Sulfate ODT	
13	Advatab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetirizine, AdvaTab Paracetamol	

**Table 7:** Angle of repose as an indication of powder flow properties.

S. No.	Angle of Repose (°)	Type of Flow
1.	< 20	Excellent
2.	20 – 30	Good
3.	30 – 34	Passable
4.	> 34	Very Poor

**Table 8:** Relationship between % compressibility index and flow ability.

S. No.	% compressibility index	Type of Flow
1.	5-12	Excellent
2.	12-16	Good
3.	18-21	Fair to Passable
4.	23-35	Poor
5.	33-38	Very Poor
6.	< 40	Very Very Poor

**Table 9:** USP Specification for uniformity of weight.

S.No.	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	More than 324	5

**Hardness:** The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm<sup>2</sup> is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc.

**Friability test:** Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. The percentage of friability can be calculated using the formula

$$\% \text{ Friability} = [(W1-W2)100]/W1$$

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

**Disintegration test:** The USP disintegration apparatus contains six glass tubes that are “3 long, open at the top, and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 °C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

**Mechanical strength:** Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important



parameters for the determination of mechanical strength. Crushing Strength or Tablet Tensile strength is the force required to break a tablet by compression in the radial direction, it is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet is measured by using Pfizer hardness testers. Tensile strength for crushing (T) is calculated using equation

$$T = 2F / \pi \cdot d \cdot t$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet respectively.

**Uniformity of dispersion:** Keep the Two tablets in 100ml water and stir gently for 2 minutes. The dispersion is passed through 22 meshes. The tablets will consider passing the test if no residue remained on the screen.

**Wetting time:** The wetting time of the tablets is measure by using a simple procedure. Place the five circular tissue papers of 10 cm diameter in a petridish containing 0.2% w/v solution (3ml). A tablet is carefully placed on the surface of the tissue paper. The time require for develop blue color on the upper surface of the tablet is noted as the wetting time.

**Water absorption ratio:** A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determine by using following formula

$$R = 100 \times W_a - W_b / W_b$$

Where,  $W_b$  is the weight of tablet before water absorption

$W_a$  is the weight of tablet after water absorption

**Taste/ Mouth sensation:** Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch is tested for the sensation by placing the tablet on the tongue. The healthy human volunteers are used for evaluation of mouth feel. Taste evaluation is done by a panel of 5 members using time intensity method. Sample equivalent to 40 mg i.e. dose of drug is put in mouth for 10 seconds and record taste instantly and then after 10 secs, 1, 2, 4 and 6 minutes. Volunteer's opinion for the taste is rated by giving different score values i.e. 0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful.

**In -Vivo disintegration test:** In-vitro disintegration time is measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation are randomly selected and in vitro dispersion time is carried out. (Shirai et al, 1993)

**In-Vivo disintegration test:** The test is carried out on 2 or 3 tablets in the mouth and the time in second taken for complete disintegration of the tablet is measured.

**In-Vitro dissolution test:** In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer pH 6.8, 900 ml is used as dissolution medium which maintained at  $37 \pm 0.5^\circ\text{C}$ . Withdraw aliquot of dissolution medium (10 ml) at specific time intervals (2 min) and filter. The amount of drug dissolved is determined by suitable analytical technique. (Cirri et al, 2005)

**Stability Studies:** The optimized formulation of ODTs is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics.

## FUTURE POTENTIAL

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 favored for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide.

**Table 10:** Marketed Preparations of ODTs

S.No	Name of the Product	API	Name of company
1.	Imodium Lingual	Imodium	Janssen
2.	Pepcidin Rapitab	Pepcid	-
3.	Mosid – MT	Mosapride citrate.	Torrent
4.	Calritin Reditabs	Micronized Loratadine	Schering plough Corp., USA
5.	Nimulid – MD	Nimesulide	Panacea
6.	Zyrof Meltab	Rofecoxib	-
7.	Feldene Melt	Piroxicam	Pfizer
8.	Maxalt-MLT	Rizatriptan Benzoate	Merck
9.	Pepcid ODT	Famotidine	Famotidine Merck
10.	Zyprexa Zydis	Olanzapine	Eli Lilly
11.	Zofran ODT	Ondansetron	GSK
12.	Remeron Soltab	Mirtazepine	-
13.	Imodium Instant melts	Loperamide HCl	Janssen
14.	Romilast	Montelukast	Ranbaxy
15.	Olanex instab	Olanzapine	Ranbaxy
16.	Zomig ZMT and Rapimelt	Zolmitriptan	Astra Zeneca
17.	Zotacet MD	Cetirizine HCl	Zota Pharma

18.	Valus	Valdecocixb	Glenmark
19.	Torrox MT	Rofecocixb	Torrent
20.	Rofaday MT	Rofecocixb	Lupin
21.	Orthoref MD	Rofecocixb	Biochem
22.	Nulev	Hyoscyamine sulfate	Schwarz Pharma
23.	Klonopin Wafers	Clonazepam	Roche
24.	Kemstro	Baclofen	Schwarz Pharma
25.	Zeplar TM	Selegiline	Amarin Corp., London
26.	Tempera Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
27.	Febrectol	Paracetamol	Prographarm, Chateaufneuf, France
28.	Benadryl Fast melt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA
29.	Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceuticals
30.	Risperdal MTab	Risperidone	Janssen pharmaceuticals
31.	Spasfon Lyoc	Phloroglucinol hydrate	Farmalyoc
32.	Nurofen Flash Tab	Ibuprofen	Ethypharm
33.	Tempera Quicklets	Paracetamol	Cima Labs
34.	Zolmig Repimelt	Zolmitriptan	Cima Labs
35.	Gaster D	Famotidine	Yamanouchi Pharma Tech. Inc.
36.	Cibalgina Due Fast	Ibuprofen	Eurand International
37.	Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd
38.	Hyoscyamine sulfate ODT	Hyoscyamine sulfate	KV Pharma. Co., Inc.
39.	Abilify Discmelt	Aripiprazole	Otsuka America/ Bristol-Myers Squibb
40.	Allegra ODT	Fexofenadine	Sanofi Aventis
41.	Aricept ODT	Donepezil	Eisai Co.
42.	Clarinx Redi Tabs	Desloratadine	Schering-Plough
43.	Alavert Quick dissolving tablets	Loratidine	Wyeth
44.	Clonazepam ODT	Clonazepam	Par Pharmaceuticals
45.	FazaClo	Clozapine	AzurPharma
46.	Jr. Tylenol Meltaways	Acetaminophen	McNeil Consumer Healthcare
47.	Klonopin Wafers	Clonazepam	Roche

## CONCLUSION

The ODTs have potential advantages over conventional oral dosage forms as they improved patient compliance; convenience, rapid onset of action and bioavailability which drawn the attention of many manufactures. The pediatric and geriatric populations are the primary ones whose problems are easily targets by ODTs, as both the groups found it difficult to swallow conventional tablets. ODTs are to maximize the porous structure of the tablet matrix and incorporate super disintegrating agents in optimum concentration so as to achieve rapid disintegration and instantaneous dissolution of the tablet along with good taste masking properties and excellent mechanical strength. Many drugs can be incorporated in ODT especially unpalatable drugs. The research is still going on. More products need to be

commercialized to use this technology properly. Thus ODT may be developed for most of the available drugs in near future.

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