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### A REVIEW - FORMULATION & DEVELOPMENT OF ORODISPERSIBLE TABLET

**Pradip Sonwane M\*, Dr. Bhusnure O.G, Gaikwad V, Sayyed Sarfaraz Ali, Garkal Atul, Kamble Santosh**  
M. Pharmacy, CB Pharmacy College, Latur-413512.

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#### ABSTRACT

The oral route of drug administration is the most important method for administering drugs for systemic effects. Except in certain cases the parenteral route is not routinely used for self administration, e.g. insulin. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects. The parenteral route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow. Nevertheless it is probable that at least 90% of all drugs used to provide systemic effects are administered by the oral route. Oral route is presently the gold standard in the pharmaceutical industry where it is regarded as the safest, most economical and most convenient method of drug delivery resulting in highest patient compliance. Oral delivery of active ingredients include a number of technologies, many of which may be classified as Orodispersible tablets (ODTs). Usually, elderly people experience difficulty in swallowing the conventional dosage forms like tablets, capsules, solutions and suspensions because of tremors of extremities and dysphagia. 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. ODTs systems may offer a solution for these problems. Advancements in the technology arena for manufacturing these systems includes the use of freeze drying, cotton candy, melt extrusion, sublimation, direct compression besides the classical wet granulation processes. This has encouraged both academia and industry to generate new orally disintegrating formulations and technological approaches in this field. This article attempts at discussing the ideal characteristics, advantages and disadvantages, formulation aspects, formulation technologies and future potential of ODTs.

#### Corresponding author

##### **Pradip Sonwane M**

M.Pharmacy,  
CB Pharmacy College,  
Latur-413512

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## INTRODUCTION<sup>[1-8]</sup>

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to many other routes. Orodispersible tablets are also called as orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing. The United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrates, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. When put in the mouth, these dosage forms disintegrate instantly to release the drug, which dissolves or disperses in the saliva. Thereafter, the drug may get absorbed from the pharynx and oesophagus or from other sections of g.i.t as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form. The target populations for ODTs are pediatric, geriatric and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates. 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.

## Advantages Of Odt<sup>[9-10]</sup>

1. Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients.
2. Rapid drug therapy interventions.
3. Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
4. Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
5. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
6. Good solubility in water and saliva.
7. Free from bitter taste.
8. Dose lower than 20mg.
9. Small to lower molecular weight.
10. Partially non ionized to oral cavity at ph (6.8).
11. Ability to permeate oral mucosal tissues.
12. Ability to diffuse and partition into the epithelial of upper part of Git.

## Disadvantages Of Fast Dissolving Tablets<sup>[10-11]</sup>

1. Hygroscopic in nature.
2. Low amount of drug can be incorporated in each dose.
3. Some time it possesses mouth feeling
4. Highly fragile sometimes.
5. ODT requires special packaging for properly stabilization & safety of stable product.
6. Eating and drinking may become restricted

## Characteristics Of An Ideal Orodispersible Tablets [12]

Orally disintegrating drug delivery system should possess following characteristics:

1. Utilizes cost effective production method.
2. Require no water for oral administration.
3. Dissolve / disperse/ disintegrate in mouth in a matter of seconds.
4. Have a pleasing mouth feel and taste masking.
5. Less friable and have sufficient hardness.
6. Leave minimal or no residue in mouth after administration.
7. Manufacturing using conventional manufacturing method.

## CHALLENGES IN FORMULATION OF ODTs<sup>[13]</sup>

### 1. Disintegration time and mechanical strength

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there are chances that such fragile tablet will break during packing, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

## 2. Taste masking:

Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

Number of techniques are developed for masking the bitter taste of most of the drugs, that includes formation of pellets by extrusion, spheronization or mass extrusion<sup>14</sup>, coating of drug using a taste masking polymer<sup>15, 16</sup>, spray drying the drug dispersed in a polymeric solution<sup>17</sup>, complexation of drug by inclusion in cyclodextrin<sup>18, 19</sup>, drug-resinate complex formation<sup>20, 21</sup>, microencapsulation of drug by polymer<sup>22</sup>. Chandira R.M et al.<sup>23</sup> enhanced solubility of carvedilol by  $\beta$ - cyclodextrin as a complexing agent. Solubility studies were performed to investigate the drug carrier interaction. I.R. and D.S.C studies carried out to investigate any interaction and stability of formulation. Tablets were prepared by direct compression technique. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. It can be concluded that Carvedilol can be successfully complexed with Beta - cyclodextrin to prepare fast dissolving tablets in the ratio of 1: 4.

## 3. Sensitivity to environmental conditions:

ODTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in ODTs are meant to dissolve in minimum quantity of water.

## 4. Mouth feel:

ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODTs should be as small as possible. ODTs should leave minimal or no residue in mouth after oral administration. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.

## 5. Cost:

The technology used for ODTs should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

## TECHNIQUES USED IN PREPARATION OF ODTs

### 1. Freeze drying/ Lyophilization

Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drug in a water soluble matrix which is then freeze dried to give highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances<sup>24, 25</sup>. Freeze drying process normally consists of three steps: Material is frozen to bring it below the eutectic point. Primary drying to reduce the moisture around 4% w/w of dry product. Secondary drying to reduce the bound moisture up to required final volume.

#### *Advantages:*

More rapid dissolution than other available solid products.

#### *Disadvantages:*

High cost of the equipments & lack of physical resistance in blister packs.

Ahmed I.S. et al<sup>26</sup> prepared ODTs by freeze-drying an aqueous dispersion of Nimesulide containing a matrix former, a sugar alcohol, and a collapse protectant. Development of a lyophilized orally disintegrating tablet (ODT) enhanced the in vitro dissolution and in vivo absorption of Nimesulide, a drug with poor solubility and poor bioavailability. Bhojar P.K. et al<sup>27</sup> formulated rapid disintegrating tablet in the blister packs using Freeze Drying Method. Eudragit EPO polymer was used for complexation with drug Trimetazidine HCl for overcoming taste problem. The Lyophilization method was used to form the drug polymer complex in a tablet. 1:3 ratio of the drug to polymer was effectively masked the bitter taste of drug.

### 2. Spray drying

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 then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium<sup>28</sup>.

### 3. Molding

Tablets prepared by this method are solid dispersions. Molded tablets offer improved taste due to watersoluble sugars present in dispersion matrix. Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic 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°C under vacuum.

#### *Advantages:*

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is, in general made from water soluble sugars.

#### *Disadvantages:*

Moulded tablets do not possess great mechanical strength. Erosion & breakage occur during handling & opening of blister packages.

### 4. Sublimation

In this method a subliming material like (Ammonium bicarbonate, Ammonium carbonate, Urea, Benzoic acid, Naphthalene, camphor) is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores. Where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed Mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva 30.

#### *Advantage:*

Tablets dissolve in 10-20 sec. and exhibit sufficient mechanical strength.

Kumar R et al.<sup>31</sup> developed FDT with improved Haloperidol dissolution by sublimation of tablets containing camphor as subliming agent. Orodispersible tablets of haloperidol were prepared by wet granulation technique using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants. Camphor was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed into tablets. Alternatively, tablets were first prepared and later exposed to vacuum. Sublimation of camphor from tablets resulted in superior tablets as compared with the tablets prepared from granules that were exposed to vacuum. The results revealed that the tablets containing subliming agent had a good dissolution profile.

### 5. Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste 32/33

### 6. Direct Compression [35]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to:

#### **a) Superdisintegrants:**

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects 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.

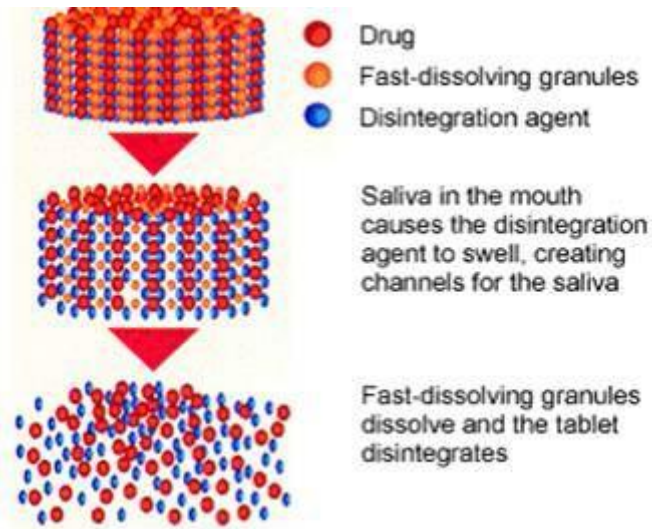


Fig. 1 Basic mechanism of Super disintegrants.

**MECHANISMS OF SUPERDISINTEGRANTS**

There are four major mechanisms for tablet disintegration as follows:

**1) Swelling**

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

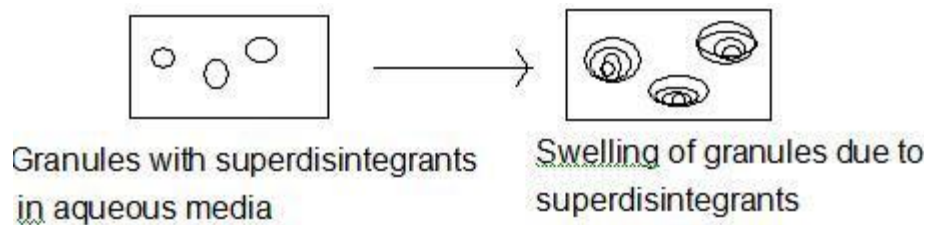


Fig. 2 Mechanism of superdisintegrants by swelling.

**2) Porosity and capillary action (wicking):**

Tablet in the aq. Media leads to penetration of the medium into tablet and thus replacement of air adsorbed resulting in weakening of intermolecular bond and breaking of tablet into fine particles.

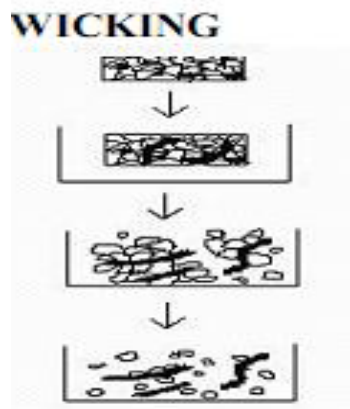
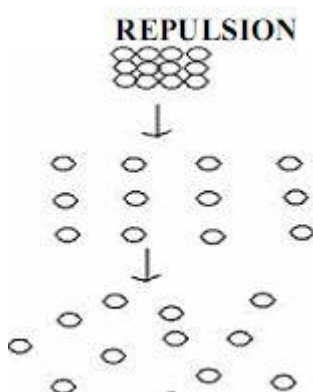


Fig. 3 Mechanism of superdisintegrants by Porosity and capillary action (wicking).

**3) Due to particle-particle repulsive forces:**

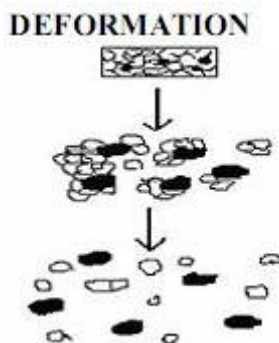
The electric repulsive forces b/w particles responsible for disintegration. It is secondary to wicking.



**Fig. 4 Mechanism of superdisintegrants due to particle repulsive forces.**

**4) Due to deformation:**

During tab. compression, disintegrated particles gets deformed and in contact with aq. media returns to normal structure (inc. in size). Eg: starch.



**Fig. 5 Mechanism of superdisintegrant due to deformation.**

**Table 1: List of common superdisintegrants.**

Superdisintegrants	Example of	Mechanism of action	Special comment
Crosscarmellose Ac-Di-Sol	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both	-Swells in two dimensions. -Direct compression or granulation
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked 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®	Crosslinked starch	-Swells 7-12 folds in <30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy® Calcium silicate	Natural super disintegrant	----- -Wicking action	-Does not contain any starch or sugar. Used in nutritional products. -Highly porous, -light weight -optimum concentration is between 20-40%

**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, lactitol, 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 mouthfeel.

**Advantages-:**

It is cost effective due to low manufacturing cost, conventional equipments and limited number of processing steps.

**Disadvantages-:**

Differences in particle size and bulk density b/w the drug and diluents may lead to stratification within the granulation.

Large dose may present problem if it is not easily compressible by itself. Avani RG et al<sup>36</sup> formulated orodispersible tablet of ondansetron hydrochloride (HCl) by direct compression using sodium starch glycolate and croscarmellose as super disintegrant. These tablets were evaluated for weight variation, mechanical strength, *in-vitro* disintegration time, *in-vivo* disintegration time, and wetting time and drug release characteristics. Hardness and friability data indicated good mechanical strength of tablet. The results of *in-vitro* disintegration time and *in-vivo* disintegration time indicated that tablet dispersed rapidly in mouth within 3-5sec. It was confirmed that superdisintegrants addition technique is a useful method for preparing oro dispersible tablet by direct compression method. Sharma s et. al<sup>37</sup> prepared fast-dissolving tablets (FDT) of promethazine theoclate by direct-compression method using Ac-Di-Sol, sodium starch glycolate and crospovidone in different concentrations. Different types of evaluation parameters for tablets were used. Tablets containing Ac-Di- Sol showed super organoleptic properties, along with excellent in-vitro and in-vivo dispersion time and drug release, as compared to other formulations. Jain C.P. et. al<sup>38</sup> have prepared fast dissolving tablets of valsaetan using different superdisintegrants by direct compression method. Prepared FDTs were evaluated for physico-chemical properties and in-vitro dissolution and concluded that the drug released from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing crospovidone.

**7. Phase transition process**

FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol [39]

**8. Cotton Candy Process**

This process utilizes a unique spinning mechanism to produce floss-like crystalline structure. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to improve flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength. However, high-process temperature limits the use of this process<sup>40,53</sup>

**9. Nanonization [54]**

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique<sup>41</sup>. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poor water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence 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)<sup>32</sup>.

**IMPORTANT PATENTED TECHNOLOGIES IN ODTs****1. Zydys**

ZYDIS (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of fast disintegrating dosage forms. There are approximately 12 marketed products, including lorazepam, piroxicam, loperamide, loratidine, enalapril<sup>42</sup>. This drug delivery system consists of freeze-dried tablets having active drug designed to rapidly disintegrate in the mouth.<sup>43</sup> The freeze-dried tablet is made by lyophilizing a suspension or solution of drug containing various excipients such as polymer, polysaccharides, preservatives, Ph adjusters, flavors, sweeteners, and colors, which is then filled in blisters. Freeze drying occurs in the blisters, which are then sealed and further packaged. Some of the advantages of the Zydys system include fast disintegration time. Some of the disadvantages include low throughput, high cost of goods, and limited taste masking.

## 2. OraSolv, DuraSolv, and PakSolv

OraSolv and DuraSolv are CIMA's core ODT tablet based technologies. The ingredients contained in the technology include polyols as fillers, disintegrant, which may include an effervescence couple, flavor, sweetener, and lubricant. The drug may be taste masked if required typically utilizing a fluid bed coating process. The tableting process includes direct compression, and can accommodate a wide range of potency from less than 1 mg to as high as 500 mg. Tablets manufactured with OraSolv technology should contain an effervescence couple along with microparticles of drug within a rupturable coat.<sup>44</sup> The tablets manufactured are compressed at a low hardness that promotes fast disintegration. The dosage forms need to be packaged in foil-foil aluminum blisters with a dome shape that impact physical protection and impermeability to moisture. This constitutes the PakSolv Technology.<sup>45</sup> PakSolv is a "domeshaped" blister package that prevents the vertical movement of the tablet within the depressions, because the diameter of the lower portion of the dome is too narrow to accommodate the tablet. PakSolv also offers light, moisture, and child resistance. Tablets manufactured with DuraSolv technology

## 3. Lyoc

Lyoc technology is owned by Cephalon Corporation. CIMA is a subsidiary of Cephalon, and currently manages the Lyoc R&D efforts. This was the first freeze-drying-based technology introduced for ODTs. The process involves preparation of a liquid solution or suspension of the drug containing fillers, thickening agents, surfactants, non-volatile flavoring agents, and sweeteners.<sup>47</sup> This homogenous liquid is then deposited in blister cavities and subjected to freeze drying.

## 4. Flashtab:

Flashtab tablet matrix consists of a swellable agent (modified starch or microcrystalline cellulose) and a super disintegrant (crospovidone or croscarmellose). The system may also contain, depending on the need, a highly water-soluble polyol with binding properties such as mannitol, sorbitol, maltitol, or xylitol, instead of the swellable agent as mentioned before. <sup>48</sup> The active is taste masked by direct coating. Tablets manufactured using this technology produce durable tablets in which the excipients are first granulated using wet or dry granulation process, then the coated drug is mixed with the excipient granules and compressed into tablets that can be handled and packaged using conventional processing equipment. Tablets for blister packaging can withstand the pressure used to push the tablet out of the lidding foil of the blister card. Tablets containing hygroscopic material can also be blister packaged, by using high-quality polyvinyl chloride or aluminum foils, which provide a higher degree of moisture protection than ordinary polyvinyl chloride or polypropylene foils.

## 5. Flash Dose:

Fuisz technologies was the inventor of the FlashDose technology.<sup>[49]</sup> It is now owned by Biovail. FlashDose tablets are manufactured utilizing SHEARFORM matrix in which material containing substantial amounts of fibrous polysaccharides, which are processed by simultaneous action of flash melting and centrifugal force, are compressed to form fine sugar fibers. FlashDose tablets containing a matrix of these sugar fibers disintegrate very rapidly upon contact with saliva, with disintegration times of a few seconds. The tablets produced by FlashDose are hydrophilic and highly porous, owing to relatively low compression during the pressing of the tablets. For taste masking, Fuisz uses its own patented, single-step, solvent-free process, termed "CEFORMTM technology," which produces uniform microspheres with a very narrow particle size distribution. The resulting tablets produced by this process are soft, friable, and highly moisture sensitive. They require specialized packaging materials and processes to protect them from external humidity and mechanical abrasion.

## 6. Wow tab:

Wow tab technology is patented by Yamanouchi Pharmaceutical Co.<sup>50</sup> WOW means "Without Water". In this process, combination of low mouldability saccharides with hardness 0-2 kg and high mouldability saccharides with hardness more than 2 kg is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide e.g. lactose, glucose, and mannitol and granulated with a high mouldability saccharide e.g. Maltose, Oligosaccharides and compressed into tablet. **7. Pharmaburst technology:** Pharmaburst™ is a "Quick Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system which involves a dry blend of a drug, flavors, and lubricant then followed by compression into tablets which then dissolve within 30-40 seconds. Tablets manufactured by this methodology have sufficient strength can be packed in blister packs and bottles<sup>51</sup>.

## 8. Frosta™:

Akina owns Frosta technology. The technology incorporates manufacture of highly plastic granules using a plastic material, a material enhancing water penetration, and a wet binder.<sup>52</sup> These granules can then be compressed into tablets at low pressure, thus enabling fast disintegration upon administration. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.



**9. Quicksolv technology:**

Quicksolv (Janssen Pharmaceutica, Beese, Belgium). In the Quicksolv formulation, the matrix compositions are dissolved in the solvent (usually water), and then this solution is frozen. At the temperature the first solvent will remain in the solid form, and then the frozen solution contacts the second solvent which is usually, ethanol, menthol, or acetone. Thus, the first solvent is removed after a few hours of contacting the second solvent to result in a usable matrix. The final product disintegrates almost instantly. This method is claimed to prevent or to reduce the incidence of cracking during the final preparation, having uniform porosity and also the adequate strength for handling 53.

**10. Nanocrystal technology [54]:**

This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.

**11. Zipllets/advatab55 :**

This technology is patented by Pessano con Bornago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles.

**PREFORMULATION STUDIES [56- 59]:**

Angle of Repose, Bulk Density, Tapped Density, Void Volume, Porosity, Compressibility characteristics (Carr's and Hausner index).

**1) Angle of Repose:**

The angle of repose was determined by the funnel method suggested by Newman. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

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

$$\theta = \tan^{-1} h/r \quad \text{Therefore}$$

Where:

$\theta$  = Angle of repose,

h = height of the cone

r = Radius of the cone base

Angle of Repose less than 30 ° shows the free flowing of the material.

**Table 2: Angle of Repose as an Indication of Powder Flow Properties.**

Sr. No.	Angle of Repose	Type of Flow
4	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very poor

**2) Bulk Density:**

Specific bulk volume or reciprocal of bulk density is called bulkiness or bulk. Bulkiness increases with a decrease in particle. The bulkiness can be calculated by the following formula,

$$\text{Bulkiness} = 1/Db$$

$$Db = M/Vb$$

Where,

Db = Bulk Density

M = Weight of sample in gm

Vb = Bulk volume (untapped volume)

**3) Tapped Density**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in abulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where,

M = is the mass of powder

Vt = is the tapped volume of the powder.

**4) Void Volume:**

The volume of the spaces is known as the void volume “v” and is given by the Formula,

$$V = Vb - Vt$$

Where,

Vb = Bulk volume (volume before tapping)

Vt = True volume (volume after tapping)

**5) 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:

$$\epsilon = Vb - Vt / Vb = 1 - Vt/Vb$$

Porosity is frequently expressed in percentage and is given as:

$$\% \epsilon = (1 - Vt/ Vb) \times 100.$$

**6) Carr's index (or) % compressibility**

It indicates powder flow properties. It is expressed in percentage and is give:

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where,

Dt= is the tapped density of the powder and

Db= is the bulk density of the powder.

**EVALUATION OF ORODISPERSIBLE TABLETS****1. Tablet thickness:**

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. Thickness was recorded using vernier calliper.

**2. Weight variation<sup>60</sup>:**

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in Table 3.

Table 3: Weight Variation Specification as per IP.

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

**3. Friability<sup>61</sup>:**

Friability Attempts for decreasing the disintegration time increase the friability of ODTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100$$

Limit- less than 1%

**4. Hardness (Crushing strength)<sup>[62]</sup> :**

Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. 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.

**5. 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

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

Where,

W<sub>b</sub>= is the weight of tablet before water absorption

W<sub>a</sub>= is the weight of tablet after water absorption

**6. 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.

**7. Wetting time:**

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water containing Eosin, a water-soluble dye, is added to petridish. 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 a wetting time.

**8. Disintegration time<sup>63</sup>:**

According to the European pharmacopoeia the fast disintegrating or Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. However it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. To overcome these problems, several new methods have been proposed. One of these methods uses a Charge Couple Device (CCD) camera or texture analyzer to evaluate the disintegration time of tablets. In another method, a modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature at 37°C and a magnetic stirrer. DT is noted at 25 rpm. One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted.

**9. In vivo disintegration time 64:**

In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth.

**10. 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.

### 11. Dissolution test [65]:

The dissolution method for oral disintegrating tablets is the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used. The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets.

### ROLE OF PHARMACISTS IN DISPENSING FDT [63]:

As Pharmacists are in the ideal persons to know about recent technologies, thus have opportunity to educate the patient for effective treatment. It is responsibility of pharmacists to keep up -todate on potential drug-food interactions of medications, especially today's new drugs, so that they may counsel properly to the patients. The majority of patients receiving FDDT preparations have little understanding of this new dosage form.

### FUTURE PROSPECTS

The oral drug delivery market remains the largest segment of the overall drug delivery market, presently valued at \$49 billion, and growing at a rate of 10% each year<sup>67</sup>. Fast dissolving drug delivery has received ever-increasing demand during last decade, and the field has become a rapidly growing area in the pharmaceutical industry. 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 be 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 autoinjectors. 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

The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. 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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