



---

## Review Article

---

### ORODISPERSIBLE TABLETS: A COMPREHENSIVE REVIEW

Pooja Arora\*, Vandana Arora Sethi

Lloyd Institute of Management and Technology Plot No.2 Knowledge Park-2, Greater Noida-201306 (U.P).

\*Corresponding Author: Email [vandana.sethi@gmail.com](mailto:vandana.sethi@gmail.com)

(Received: November 10, 2012; Accepted: January 12, 2013)

#### ABSTRACT

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.

**Keywords:** Dysphagia, Formulation technologies, Orodispersible tablets, Pharmaceutical industry.

#### INTRODUCTION

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<sup>1</sup>.

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.<sup>2</sup> 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 disintegrants, 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<sup>3-6</sup>. 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<sup>7</sup>.

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<sup>8</sup>.

#### **Advantages Of Odt<sup>9, 10</sup>**

- 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.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.

#### **Disadvantages Of Fast Dissolving Tablets<sup>10, 11</sup>**

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

#### **Characteristics Of An Ideal Orodispersible Tablets<sup>12</sup>**

Orally disintegrating drug delivery system should possess following characteristics:

- Utilizes cost effective production method.
- Require no water for oral administration.

- Dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel and taste masking.
- Less friable and have sufficient hardness.
- Leave minimal or no residue in mouth after administration.
- 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.

Bhoyar 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>.

#### Advantages:

Rapid disintegration of tablets.

Masareddy R<sup>29</sup> et al studied the effect of co-processed excipient bases in formulation of orodispersible tizanidine HCl tablets by direct compression method. Co-processed excipient of microcrystalline cellulose with SSL-hydroxypropylcellulose was prepared using spray drier in 1:1, 1:2 and 1:3 ratio. Formulated tablets were evaluated for hardness, friability, *in vitro* disintegration time and *in vitro* drug release. Granules obtained by spray drying technique were found to be more spherical which improved its flow property and was supported by scanning electron microscope studies. Inclusion of co-processed excipient base in formulation of orodispersible tablets enhanced disintegration significantly.

### 3. Molding

Tablets prepared by this method are solid dispersions. Molded tablets offer improved taste due to water-soluble 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 posses 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 <sup>30</sup>.

**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 croscarmellose sodium as superdisintegrants. Camphor was sublimed from the

granules by exposing the granules to vacuum. The porous granules were then compressed in to 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 <sup>32, 33</sup>.

**Advantage:** Mask bitter taste by coating the granules.

Mansing G. Patil et al<sup>34</sup> prepared orally disintegrating tablets of Tramadol hydrochloride for achievement of quick onset of action of the drug. An attempt was to prepare bitterless orally disintegrating tablet using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules and tablet was prepared using superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate. The extrusion technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymeric carrier while shaping the composite material to form a pharmaceutical product. The drug release from orally disintegrating tablets increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone.

#### 6. Direct Compression<sup>35</sup>

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 by using the super disintegrants.

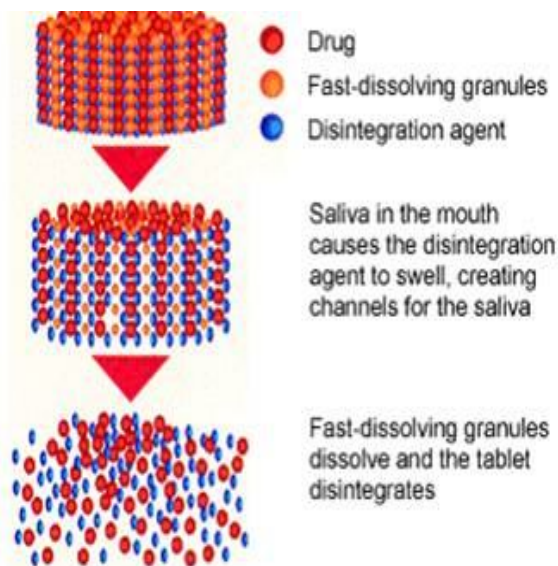


Fig. 1 Basic mechanism of Super disintegrants.

## 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.

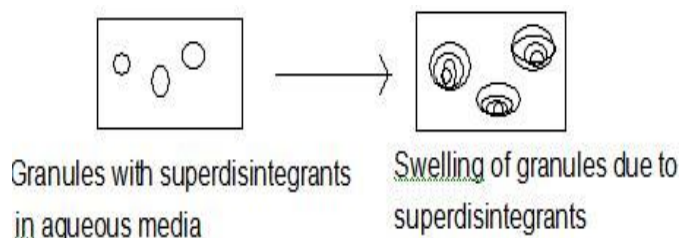


Fig. 2 Mechanism of superdisintegrants by swelling

### 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.

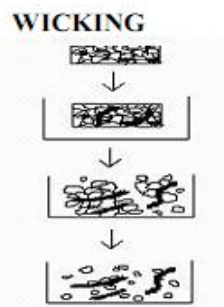


Fig. 3 Mechanism of superdisintegrants by Porosity and capillary action (wicking).

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

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

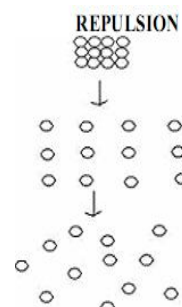


Fig. 4 Mechanism of superdisintegrants due to particle-particle repulsive forces

### 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.

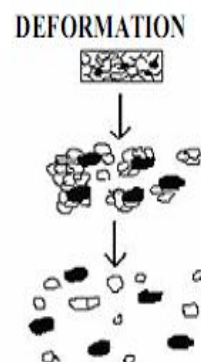


Fig. 5 Mechanism of superdisintegrant due to deformation

**Table 1:** List of common superdisintegrants<sup>35</sup>

Superdisintegrants	Example of	Mechanism of action	Special comment
<b>Crosscarmellose®</b>  <b>Ac-Di-Sol®</b>	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation
<b>Crosspovidone</b> <b>Crosspovidon M®</b> <b>Kollidon®</b> <b>Polyplasdone®</b>	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
<b>Sodium starch glycolate</b> <b>Explotab® Primogel®</b>	Crosslinked starch	-Swells 7-12 folds in <30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
<b>Alginic acid NF</b> <b>Satialgine®</b>	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
<b>Soy polysaccharides</b> <b>Emcosoy®</b>	Natural super disintegrant	-----	-Does not contain any starch or sugar. Used in nutritional products.
<b>Calcium silicate</b>		-Wicking action	-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 valsartan 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 croscarmellose.

#### 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<sup>39</sup>.

#### 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</sup>.

#### 9. Nanonization

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 ZYDIS® 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 "dome-shaped" 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

contain a non-directly compressible filler and a lubricant. They may or may not contain effervescence, and the drug need not be taste masked.<sup>46</sup> DuraSolv tablets are compressed at higher hardness compared to OraSolv that allows for packaging in bottles or push through blisters.

**Advantage:** low cost of goods, standard manufacturing technology, standard packaging format and materials, and low development costs and risks.

**Disadvantage:** slightly longer disintegration time.

**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.

**Advantage:** compared to other freeze dried dosage forms include absence of preservatives.

**4. Flashtab:** Flashtab tablet matrix consists of a swellable agent (modified starch or microcrystalline cellulose) and a super disintegrant (croscopolone 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 "CEFORM™ 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 <sup>53</sup>.

**10. Nanocrystal technology<sup>54</sup>:** 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/advatab<sup>55</sup> :** 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 <sup>56- 59</sup>:**

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:

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

Therefore

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

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
1	<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,

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

Where,  $D_b$  = Bulk Density.

Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm<sup>3</sup>. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

$$D_b = M/V_b$$

Where,

$D_b$  = Bulk Density

$M$  = Weight of sample in gm

$V_b$  = 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 a

bulk density apparatus). It is expressed in g/ml and is given by

$$D_t = M / V_t$$

Where, M is the mass of powder

$V_t$  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,

$$V = V_b - V_t$$

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

$V_t$  = 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

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

Porosity is frequently expressed in percentage and is given as

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

#### 6) Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by

$$D_t - D_b$$

$$I = \frac{D_t - D_b}{D_t} \times 100$$

$$D_t$$

Where,  $D_t$  is the tapped density of the powder and  $D_b$  is the bulk density of the powder.

If the bed of particles is more compressible the blend will be less flowable.

#### 7) 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:

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where,  $D_t$  is the tapped density.

$D_b$  is the bulk density.

Hausner's ratio  $< 1.25$  – Good flow = 20% compressibility index

$1.25$  – Poor flow = 33% compressibility index

8) Identification of drug sample: It was confirmed by melting point determination and also by FT-IR spectral analysis.

#### 9) Drug excipient Compatibility study:

Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

### 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	$\pm 10$
More than 80 mg but less than 250 mg	$\pm 7.5$
250 mg or more	$\pm 5$

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

Friability Attempts for decreasing the disintegration time increase the friability of ODTs than the conventional tablets. Dosage forms like Zydys 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 determined 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 <sup>64</sup>:

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 <sup>65</sup>:

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 <sup>63</sup>:

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 -to-date 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.

**Table 4:** List Of Marketed Fast Dissolving Tablets <sup>16, 66</sup>

S. No.	Trade Name	Active Drug	Manufacturer
1.	Falden fast melt	Piroxicam	Pfizer Inc., NY, USA
2.	Claritin redi Tab	Loratadine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merk and Co., NJ, USA
4.	Zyprexa	Olanzapine	Eli Lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merk and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7.	Zomig-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
8.	Zephar TM	Selegiline	Amarin Corp., London, UK
9.	Tampra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
10.	Fabrectol	Paracetamol	Prographam, Chateaufort, France

Patients may be surprised when tablets begin to dissolve in the mouth. They might expect a faster onset of therapeutic action. Counseling of patient about this dosage form can avoid any confusion or misunderstanding in taking FDT. As with all dosage form technologies, some patient populations are better served by their use than others. Patient information that needed to provide includes:

- While counseling pharmacist must told to the patient about the differences' between FDT and effervescence.
- Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation. Decreased volume of saliva may slow the rate of dissolution/disintegration and decrease the bioavailability of the product.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- Patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.
- About need to handle carefully because some of FDT developed may not have sufficient mechanical strength?

#### 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.

#### REFERENCES

1. Valleri M, Mura P, Maestrelli F, Cirri M, Ballerini R (2004). Development and evaluation of glyburide fast dissolving tablets using solid dispersion technique. *Drug Dev Ind Pharm* 30(5): 525-534.

2. Fu Y, Yang S, Jeong SH, Kimura S, Park K (2004). Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. *Crit Rev Ther Drug Carrier Syst* 21: 433–76.
3. Ghosh TK, Pfister WR (2005). Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceuticals perspective; In: Drug delivery to the oral cavity: Molecules to market. New York, CRC Press 337-356.
4. Dobetti L (2001). Fast melting tablets: Developments and technologies. *Pharm Technol Drug Deliv Suppl* 44-50.
5. Deepak K (2004). Orally disintegrating tablets. *Tablets Capsule* 7: 30-35.
6. Brown D (2001). Orally disintegrating tablets: Taste over speed. *Drug Deliv Technol* 3: 58-61.
7. Robin h. Bogner, r.ph. ph.d., associate professormeghan f. Wilkosz, pharm.d. (cand.)University of connecticutschool of pharmacy,storrs, ct,fast dissolving tablets,us pharmacist,13/09/2002
8. Parakh SR, Gothoskar AV (2003). A review of mouth dissolving tablet technologies. *Pharm Tech* 27: 92-98.
9. Shu T (2002). Studies of rapidly disintegrating tablets in oral cavity using coground mixture of mannitol with crospovidone. *Chem Pharm Bull* 50: 193-198.
10. Chang RK, Guo X, Burnside BA, Cough RA (2000). Fast dissolving tablets. *Pharm Tech* 24: 52-58.
11. Reddy L.H., Ghosh B., Rajneesh (2002) Fast dissolving drug delivery systems: a review of the literature. *Indian J. Pharm. Sci.* 64(4): 331-336.
12. Bradoo R (2001). Fast Dissolving Drug Delivery Systems. *J. Am. Med. Asso.* 4: 27-31.
13. Bandari S, Mittapalli RK, Gannu R, Rao YM (2008). Orodispersible tablets: An overview. *Asian J Pharm* 2(1): 2-11.
14. O'Connor R, Schwartz J: "Extrusion and spherionization technology. In Pharmaceutical Pelletization Technology", Marcel Dekker Inc., New York 1989; 37: 187.
15. Agarwal V, Kothari BH, Moe DV, Khankari RK. Drug delivery: Fast-dissolve systems. In: Swarbrick J, Encyclopedia of pharmaceutical technology. New York, USA: Informa Healthcare Inc. 2006; 1104 –1114.
16. Fini A, Valentina B, Gian CC, Celestino R, Carlos A, Fonseca de M (2008). Fast dispersible/slow releasing ibuprofen tablets. *Eur. J. Pharm. Biopharm.* 69: 335–341.
17. Masters K. Spray Drying Fundamentals: Process stages and Layouts. In: Spray Drying Handbook. USA: Longman Scientific and Technical, New York, 5th ed. 1991: 23–64.
18. Hughes L (2005). Selecting the right ion exchange resin. *Pharma Quality* 1: 54–56.
19. Jeong SH, Park K (2008). Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. *Int. J. Pharm.* 353: 195–204.
20. Prasad N, Straus D, Reichart G (1999). Cyclodextrin flavor delivery systems. US Patent 6,287,603.
21. Venkatesh DP, Geetha Rao CG (2008). Formulation of taste masked orodispersible tablets of ambroxol hydrochloride. *Asian J. Pharm.* 2: 261-264.
22. Ohwaworhu F., Adelakun T (2004). Phosphoric acidmediated depolymerization and decrystallization of  $\alpha$ -Cellulose obtained from Corn Cob: Preparation of Low Crystallinity Cellulose and some Physicochemical Properties. *Tropical J. Pharm. Res.* 4(2): 509-516.
23. Venkateswarlu B.S, Chandira B.S , Talele A , Debjit B, Chiranjib (2010). Formulation and evaluation of fast dissolving tablets of Carvidilol. *The Pharma Research (T. Ph. Res.)* 3: 203-220
24. Virely P, Yarwood R (1990). Zydis – a novel, fast dissolving dosage form. *Manuf. Chem.* 36 37.
25. Seager H (1998). Drug delivery product and the Zydis fast-dissolving dosage form. *J. Pharm. Pharmacol* 50: 375-382.
26. Shoukri R.A , Ahmed I.S , Shamma R.N (2009). In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets. *European Journal of Pharmaceutics and Biopharmaceutics* 73: 162–171
27. Bhoyar P.K , Baheti J.R, Naranje P.A, Bhandarkar S, Muraleedharan R, Deotale B.M (2012). Formulation design and optimization of taste masked rapid disintegrating tablets using freeze drying method. *World J of Pharmaceutical Research* 1(2): 340-352
28. Mishra DN, Bimodal M, Singh SK, Vijaya Kumar SG (2006) Spray dried excipient base: a novel technique for the

formulation of orally disintegrating tablets. *Chem Pharm Bull* 54(1): 99-102.

29. Masareddy R, Kokate A, Shah V (2011). Development of orodispersible tizanidine HCl tablets using spray dried coprocessed excipient bases. *Indian J Pharm Sci* 73:392-6

30. Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M (1997). New method of preparing high-porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. *Int. J of Pharm.* 152(1): 127-31

31. Kumar R., Patil M.B., Patil S.R., Paschpura M.S (2009). Development & characterization of melt-in-tablets of Haloperidol by sublimation technique. *Int. J. of Pharmacy & P'ceutical Sci.* 1(1): 65-73.

32. Shukla D, Chakraborty S, Singh S, Mishra B (2009). Mouth Dissolving Tablets I: An Overview of Formulation Technology. *Sci Pharm.* 77: 309–26.

33. Bhaskaran S, Narmada GV (2002). Rapid dissolving tablets a novel dosage form. *Indian Pharmacist* 1: 9–12.

34. Mansing G. Patil, Suhas M. Kakade and Sandhya G. Pathade (2011). Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique. *Journal of Applied Pharmaceutical Science* 01(06): 178-181

35. Bhowmik D, Chiranjib B, Pankaj K, Chandira RM (2009). Fast Dissolving Tablet: An Overview. *Journal of Chemical and Pharmaceutical Research* 1(1): 163-177.

36. Avani RG, Sanjay BP, Krutika KS (2008). Formulation and evaluation of oro dispersible tablets of ondansetron hydrochloride by direct compression. *Int J Pharm Nanotech.* 1(1):106-111.

37. Shailesh Sharma, Gupta GD. (2008). Formulation and characterization of fast-dissolving tablet of promethazine theoclate. *Asian J Pharm.* 2(1): 70-72.

38. Jain CP, Naruka PS (2009). Formulation and evaluation of fast dissolving tablets of valsartan. *Int. J. Pharm. & Pharm Sci.* 1(1): 219-26

39. Kuno Y, Kojima M, Ando S, Nakagami H (2005). Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. *Journal of Controlled Release* 105(1, suppl 2): 16-22.

40. Chiver TE, Minn O(2003) Process for making candy floss. US patent 730057.

41. Elan Corporation, plc.Orally Disintegrating Tablets (ODT) -Nanomelt™. <http://www.elan.com> / EDT / nanocrystal 5 technology/orally\_disintegrating\_tablet.asp

42. DeRoche CC. Consumer preference for orally disintegrating tablets over conventional forms of medication: Evolving methodology for medication intake in dysphagia. Lecture presented at the 12<sup>th</sup> Annual Meeting of the Dysphagia Research Society, San Francisco, CA, 2-4 Oct., 2003, *Dysphagia*, 20 (1): 77- 86,(2005).

43. Kearney P, Wong SK(1997) Method for Making Freeze Dried Drug Dosage Forms. US Patent 5,631,023.

44. Wehling F, Schuehle, S, Madamala N(1993) Effervescent Dosage Form with Microparticles. US Patent 5,178,878.

45. Katzner L, Jones B, Khattar J, Kosewick J(2000) Blister Package and Packaged Tablet. US Patent 6,155,423.

46. Khankari R, Hontz J, Chastain S, Katzner L(2000) Rapidly Dissolving Robust Dosage Form. US Patent 6,024,981.

47. Laboratoire Lafon.(1985) Galenic Form for Oral Administration and its Method of Preparation by Lyophilization of an Oil-in-Water Emulsion. European Patent 0,159,237.

48. Pebley WS, Jager NE, Thompson SJ(1994) Rapidly Disintegrating Tablets. US Patent 5,298,261.

49. Robinson J, McGinity J(2002) Effervescent Granules and Method for Their Preparation. US Patent 6,488,961.

50. Mizumoto T, Masuda Y, Fukui M.(1996) Intrabuccally Dissolving Compressed Moldings and Production Process Thereof. US Patent 5,576,014.

51. Mohan SC, Margret CR (2011). Recent advances in orodispersible tablets: A Review. *International Journal of Drug Discovery and Herbal Research* (2): 78-83.

52. Jeong SH, Fu Y, Park K (2005) Frosta\_: a new technology for making fast-melting tablets. *Expert Opinion on Drug Delivery* 2(6): 1107–1116.

53. Yourong Fu, Yang S, Jeong S H, Kimura S, Park K (2004). Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies. *Critical Reviews™ in Therapeutic Drug Carrier Systems* 21(6): 433–475.

54. Kaushik D, Dureja H, Saini TR (2004). Orally disintegrating tablets: An overview of melt-in mouth tablet technologies and techniques. *Tablets Capsules* 2: 30-6.
55. Dobetti L. (Eurand International), Fast Disintegrating tablets, PCT Patent WO 99/44580-A1; 1999.
56. Yoshio K, Masazumi K, Shuichi A, Hiroaki N (2005). Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. *J. Control. Release* 105(1-2): 16-22.
57. Mishra DN, Bimodal M, Singh SK, Vijaya Kumar SG (2006). Spray dried excipient base: a novel technique for the formulation of orally disintegrating tablets. *Chem Pharm Bull* 54 (1): 99-102.
58. Rasheed SH, Arief M, Gajavalli SR, Vani PS, Rao KS, Kumar S, Rao T, Hussain SS (2011). A Comparison of different superdisintegrants in designing of fast dissolving tablets of salbutamol sulphate. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2(2): 155-163.
59. Mukesh, Ratnaparkhi P, Mohant GP, Upadhyay L (2009). Fast Dissolving Tablet. *Journal of Pharmacy Research* 2(1): 5-12.
60. Basawaraj S Patil, Upendra Kulkarni, Parik Bhavik, Srinivas R Soodam, Prakash G Korwar , Formulation and evaluation of mouth dissolving tablets of nimesulide by new coprocessed technique *Research Journal of Pharmaceutical, Biological and Chemical Sciences* ISSN: 0975-8585, 587-592.
61. Lachman L, Liberman H, Kanig J, "The theory and practice of industrial pharmacy", Varghese Publishing House, Mumbai, 3rd Edn, 1987: 297
62. Daharwal S, Jangde R, Saraf S, Saraf S (2008). Taste masking method for bitter drug and tasteless dispersible tablet: an overview. *Famvita.Net Journal* oct.: 1-3.
63. Morita Y, Tsushima Y, Yasui M, Termoz R, Ajioka J, Takayama K (2002) Evaluation of the disintegration time of rapidly disintegrating tablets via a novel method utilizing a CCD camera. *Chem. Pharm. Bull* 50 (9): 1181 - 1186.
64. United States Pharmacopoeia USP25 NF20. The Official Compendia of Standards. First annual Asian edn., Rockville, MD:United States Pharmacopoeial Convention Inc. 2002.
65. Mohammad yaheya, mohammad ismail (2009). drug-food interactions and role of pharmacist. *Asian Journal of Pharmaceutical and Clinical Research* 2 (4).
66. Sammour OA, Hammad MA, Megrab NA(2006). Formulation and Optimization of Mouth Dissolve Tablets Containing Rofecoxib Solid Dispersion. *AAPS PharmSciTech*. 7(2): 162-69.
67. GBI Research's report. Oral Drug Delivery Market-- Controlled and Sustained Release to be major Revenue Generators. November 2010.