



## FAST DISSOLVING TABLETS: AN OVERVIEW

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### ABSTRACT

Tablet is the most popular dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however the problem of swallowing is common fact which leads to poor patient compliance. To overcome this drawback, fast dissolving tablets (FDT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate in saliva within few seconds without chewing and additional water. According to European Pharmacopoeia, the FDT should disperse/disintegrate in less than three minutes. The basic approach used in development of FDT is the use of superdisintegrant like Cross linked carboxymethylcellulose (Croscarmellose), Primogel, Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets.

**Keywords:** Fast dissolving tablet, Superdisintegrant, Bioavailability.

### INTRODUCTION

The conventional dosage forms like tablet and capsule have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration, easy to manufacture and it can be deliver in accurate dose. One important drawback of such dosage form is the difficulty in swallowing. Therefore, tablet must be rapidly dissolve or disintegrate in the oral cavity.<sup>1, 2</sup> USFDA defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue." Fast dissolving tablets are also known as mouth-dissolving tablets, Oro-dispersible tablets, rapimelts, and porous tablets. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.<sup>3, 4</sup> Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form. The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute.

### ADVANTAGES OF FAST DISSOLVING TABLETS

- Improved patient's compliance
- No water needed
- No chewing needed
- Improved stability
- Suitable for controlled as well as fast release actives
- Cost- effective

### THE NEED FOR DEVELOPMENT OF FDTs

#### 1. Patient Factors

Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with a glass of water. These include the following: very elderly patients of depression who may not be able to swallow the solid dosage forms, a middle-aged patient undergoing radiation therapy for breast cancer, a schizophrenic patient who may try to hide a conventional tablet under his or her tongue, a patient with persistent nausea.

#### 2. Effectiveness Factor

Dispersion in saliva in oral cavity causes pre-gastric absorption of drug which dissolves. Any pre-gastric absorption avoids first pass hepatic metabolism which increase the bioavailability. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism.

#### 3. Manufacturing and Marketing Factors

As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation and extend patent protection. For examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy.<sup>5</sup>



**Table 1:** Ingredients and Technologies Used for Formulating FDT<sup>6</sup>

Drug	Ingredients Used	Technologies Used	Disintegration Time (Sec)
Rizatriptan Benzoate	Primoge, Ac-di-sol, Kollidon, Avicel PH102, Magnesium stearate, Sucralose.	Direct Compression	85
Granisetron HCl	Cyclodextrin, Magnesium stearate, Lactose, Mannitol.	Direct Compression	17
Amlodipine Besilate	Mannitol, Eudragit EPO.	Compression & then sublimation	15-38
Aceclofenac	SSG, Mannitol, MCC.	Direct compression	12 – 27
Modafinil	MCC, Lactose, Pre gelatinized starch	Wet Granulation	--
Fexofenadine	Mannitol, Crospovidone, Precipitated silica, sucralose.	Direct Compression	15-20
Topiramate	Mannitol, HP- $\beta$ -CD, PEG3350, Mannose.	Wet Granulation	--
Chlorpromazine HCl	Sodium starch glycolate, Croscarmellose, Pregelatinised starch.	Direct compression	Less than 60

### SELECTION OF FDT DRUG CANDIDATES

Several factors must be considered while selecting drug candidate for FDT:

- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.
- The drugs that produce toxic metabolites by first pass liver metabolism.
- Drugs having ability to diffuse into the epithelium of the upper GIT and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- Drugs with a short half-life and frequent dosing.
- Drugs which are having very bitter or unacceptable taste.
- Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.<sup>7-8</sup>

### PROMISING DRUGS TO BE INCORPORATED IN FAST DISSOLVING TABLETS

#### 1. Analgesics and Anti-inflammatory Agents

Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.

#### 2. Anthelmintics

Albendazole, Bephenium, Dichlorophen, Ivermectin, Mebendazole, Oxarnniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Thiabendazole.

#### 3. Anti-arrhythmic Agents

Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate.

#### 4. Anti-bacterial Agents

Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Doxycycline, Erythromycin, Ethionamide, Nitrofurantoin, Rifampicin, Sulphabenzamide, Sulphacetamide, Sulphafurazole, Sulphamethoxazole, Tetracycline, Trimethoprim.

#### 5. Anti-coagulants

Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

#### 6. Anti-depressants

Amoxapine, Ciclazindol, Mianserin, Nortriptyline, Trazodone, Trimipramine.

#### 7. Hypoglycemic agents

Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide, Tolbutamide.

#### 8. Anti-epileptics

Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid.

#### 9. Anti-fungal Agents

Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Terbinafine, Terconazole, Tioconazole, Undecenoic Acid.

#### 10. Anti-gout Agents

Allopurinol, Probenecid, Sulphinpyrazone.

#### 11. Anti-hypertensive Agents

Amlodipine, Carvedilol, Benidipine, Darodipine, Diltiazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Niacardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.



**12. Anti-malarials**

Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine.

**13. Anti-migraine Agents**

Dihydroergotamine, Ergotamine, Methysergide, Pizotifen, Sumatriptan.

**14. Anti-neoplastic Agents and Immunosuppressants**

Aminoglutethimide, Chlorambucil, Cyclosporin, Estramustine, Etoposide, Melphalan, 5-MP, Methotrexate, Mitomycin, Mitotane, Procarbazine, Tamoxifen.

**15. Anti-Protozoal Agents**

Clioquinol, Diloxanide, Dinitolamide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole.

**16. Anti-thyroid Agents**

Carbimazole, Propylthiouracil.

**17.  $\beta$ -blockers**

Acebutolol, Atenolol, Labetalol, Metoprolol, Oxprenolol, Pindolol, Propranolol.

**18. Corticosteroids**

Beclomethasone, Betamethasone, Budesonide, Cortisone, Desoxymethasone, Dexamethasone, Fludrocortisone, Flunisolide, Flucortolone, Fluticasone Propionate, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone.

**19. Diuretics**

Acetazolamide, Amiloride, Bendroflumazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid, Furosemide, Metolazone, Spironolactone, Triamterene.

**20. Anti-parkinsonian Agents**

Bromocriptine Mesylate, Lysuride Maleate.

**21. Gastro-intestinal Agents**

Bisacodyl, Cimetidine, Cisapride, Diphenoxylate, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Ranitidine.

**22. Lipid regulating Agents**

Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.

**23. Nitrates and Other Anti-anginal Agents**

Amyl Nitrate, Glycerol Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

**24. Oral Vaccines**

Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, Measles, Lyme Disease.<sup>10-12</sup>

**VARIOUS TECHNIQUES FOR FDT PREPARATION**

Many techniques are used for the preparation of fast dissolving tablets.

**1. Disintegrant Addition**

This technique involves the addition of superdisintegrants in optimum concentration to achieve rapid disintegration. For example, Crosspovidone (3%w/w) and crosscarmellose (5%w/w) used in prochlorperazine maleate formulation. FDT prepared by this technique are similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.

**Table 2:** List of Superdisintegrants

Superdisintegrants	Example
Crosscarmellose (Ac-Di-Sol)	Crosslinked Cellulose
Crosspovidone M (Kollidon)	Crosslinked PVP
Sodium starch glycolate (Primogel)	Crosslinked Starch
Soy polysaccharides (Emcosoy)	Natural super Disintegrant
Alginic acid NF (Satialgine)	Crosslinked alginic acid

**2. Freeze drying or Lyophilization**

In lyophilization, the drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. The tablets are highly porous having high specific surface area which dissolves rapidly and shows improved absorption and bioavailability.

**3. Moulding**

Water-soluble ingredients with a hydro-alcoholic solvent are used and are molded into tablets under pressure lower than that used in conventional tablet compression. Molded tablets are very less compact than compressed tablet that enhances disintegration and finally absorption increased.

**4. Sublimation**

In sublimation, inert solid ingredients that volatilize rapidly like camphor ammonium carbonate, hexamethylenetetramine was added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure that increases the dissolution.

**5. Mass Extrusion**

This technique involves the softening of active blend by using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of these softened mass through the extruder or syringe to get a cylindrical shape into even segments to form tablets. The dried product



can be used to coat granules of bitter tasting drugs and there by masking their bitter taste.

## 6. Direct Compression

In this technique conventional equipment and the most commonly available excipients and a limited number of processing steps are involved. It is most cost effective tablet manufacturing technique.

## 7. Compaction

### A) Melt Granulation

Tablets are prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. Tablets prepared by this method melt in the mouth and solubilizes rapidly leaving no residue.

### B) phase-transition process

Tablets in phase transition process are prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol.

## 8. Nanonization

Nanonization involves size reduction of drug to nanosize by milling the drug using wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. This is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process.

## 9. Fast Dissolving Films

Firstly, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, CMC, HPMC, hydroxyl ethyl cellulose, PVP or sodium alginate), drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. The thin films size less than 2x2 inches that dissolved in 5 sec, instant drug delivery and flavored for bitter drugs.<sup>13-14</sup>

## PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS<sup>15-17</sup>

### Zydis Technology

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a

special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

### Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

### Orasolv Technology

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

### Flash Dose Technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

### Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high

mouldability saccharide and compressed into tablet.

### Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion spheronisation. All the processing utilized conventional tableting technology.





**Table 3:** Patented technology and their products

Technology	Process involved	Drug used
Zydis	Lyophilization	Loratidine
Quickslov	Lyophilization	Cisapride, Risperidone
Flashtab	Lyophilization	Ibuprofen
Orasolv	Compressed Tablet	Paracetamol, Zolmitriptan
Wow Tab	Compressed Moulded Tablet	Famotidine
Flashdose	Cotton-candy Process	Tramadol HCL
Oraquick	Micromask Taste Masking	Hyoscamine Sulphate

**EVALUATION**<sup>19-23</sup>

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

**1. Weight Variation**

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.

**Table 4:** weight variation and accepted % deviation

Average Weight of Tablet	% Deviation
80 mg or less	10.0
More than 80 mg but less than 250 mg	7.5
250 mg or more	5.0

**2. Hardness**

The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers. It is expressed in kg or pound.

**3. Friability**

To achieve % friability within limits (0.1-0.9%) for an FDT is a challenge for a formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Friability of each batch was measure in "Electro lab friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation.

**4. Mechanical Strength**

Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters for the determination of mechanical strength. Crushing Strength or Tablet Tensile strength is the force required to break a tablet by compression in the radial direction. It is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet was measured by using Pfizer hardness testers. It is calculated by an average of three observations. Tensile strength for crushing (T) is calculated using the equation,

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

Where, F is the crushing load,

d and t denote the diameter and thickness of the tablet respectively.

**5. Measurement of Tablet Porosity**

The mercury penetration porosimeter can be used to measure the tablet porosity. The tablet porosity ( $\epsilon$ ) can be calculated by using following equation,

$$\epsilon = 1 - m / (\rho t V)$$

Where  $\rho t$  is the true density,

m and V are the weight and volume of the tablet, respectively.

**6. Wetting Time and Water Absorption Ratio**

Wetting time of dosage form is related with the contact angle. Lower wetting time implies a quicker disintegration of the tablet. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully placed in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted. The water absorption ratio, R can be the determined according to the following equation;

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

$W_b$ ; The weight of the tablet before keeping in the petridish,

$W_a$ ; The wetted tablet from the petridish is taken and reweighed.

**7. Moisture Uptake Studies**

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

**8. In-vitro Dispersion Time**

Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C. Time required for complete dispersion of a tablet was measured.

**9. Disintegration Test**

The time for disintegration of FDTs is generally less than 1 min and actual disintegration time that patient can experience ranges from 5 to 30s. The disintegration test



for FDT should mimic disintegration in mouth within saliva.

### 10. Disintegration in Oral Cavity

The time required for complete disintegration of tablets in mouth was obtained from six healthy volunteers, who were given tablets from the optimum formulation.

### 11. Dissolution Test

The dissolution methods for FDT are practically identical to conventional tablet when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of FDT in the same way as their ordinary tablet counterparts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 25-75 rpm is commonly used. Since the dissolution of FDTs is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile.

### 12. Clinical Studies

*In vivo* studies show the actual action of FDT in the oral-esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. The investigation using gamma-scintigraphy showed that the dissolution and buccal clearance of fast disintegrating dosage forms was rapid. The esophageal transit time and stomach emptying time were comparable to those of traditional dosage forms i.e. tablets, capsules, or liquid forms.

### 13. Stability Study (Temperature Dependent)

The fast dissolving tablets stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i)  $40 \pm 1^\circ\text{C}$

(ii)  $50 \pm 1^\circ\text{C}$

(iii)  $37 \pm 1^\circ\text{C}$  and RH  $75\% \pm 5\%$

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization such as visual defects, Hardness, Friability, Disintegrations, and Dissolution etc. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at  $25^\circ\text{C}$ .

### CONCLUSION

The concept of Fast Dissolving tablet is evolved to overcome some of the problems that existed in conventional solid dosage form (tablet and capsule) i.e. difficulty in swallowing in pediatric and geriatric patients who constitute a large proportion of world's population. Psychiatric patients, victim of stroke and patient who are suffering from gastric irritation refuses to swallow the

solid unit dose. In such patients drug can be easily administered by using FDT. It also leads to improve efficacy, bioavailability, rapid onset of action, better patient compliance due to its quick absorption from mouth to GIT as the saliva passes. As a drug entity nears the end of its patent life, pharmaceutical manufacturer need a new and improved dosage form for the given drug entity. A new dosage form must allow a manufacturer to extend market exclusivity. In this regard, FDT is the best suitable dosage form for the manufacturers. In future FDT may be most acceptable and prescribed dosage form due to its quick action (within minute). Their characteristic advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in today's scenario of hectic life.

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