ABSTRACT

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry. Fast disintegrating tablets (FDTs) are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water. Fast disintegrating tablets (FDTs) aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, to achieve better patient compliance. Fast disintegrating tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an opportunity for product life extension in the many elderly persons which have difficulty in taking conventional oral dosage form (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. The current article is focused on ideal requirements, need for development of FDTs, challenges in formulation, suitability of drug candidates, superdisintegrants employed, various technologies developed for FDTs, patented technologies like Wowtab, Durasolv, Orasolv, Flashtab, Zydis, Frosta technology, Sheaform, Ceaform technology, Nanocrystal technology which have gained importance in international market, evaluation methods and various marketed products.

KEYWORDS: Fast disintegrating tablets (FDTs), Superdisintegrants, Enhanced bioavailability, Patient’s compliance, Patented technology, Evaluation.
1. INTRODUCTION

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation, and is moving rapidly.\[1\] Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance.\[2\] The most popular dosage forms are being conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is „Dysphagia” or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy.\[3\] Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance.\[4\] In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form.\[5\] Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a fast dissolving/ disintegrating drug delivery system (FDDTs).\[6\] The Center for Drug Evaluation and Research(CDER), US FDA defined Fast-dissolving/disintegrating tablets (FDDTs) are “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. Recently European Pharmacopoeia also adopted the term “Oro Dispersible Tablet” defined as „„uncovered tablet for buccal cavity, where it disperses before ingestion”.\[7\] Fast disintegrating tablets (FDT) are also known as „ „fast dissolving”, „mouth dissolving”, „rapid-dissolve”, „quick disintegrating”, „orally disintegrating”, „rapimelt”, „fast melts”, „orodispersible”, „melt-in-mouth”, „quick dissolving”, „porous tablets”, „EFVDAS” or „Effervescent Drug Absorption System”.\[8\] Fast disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. When Faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach.
In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (crosscarmelllose), sodium starch glycolate (primogel, explotab), cross linked polyvinylpyrollidone (crospovidone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug 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 subjected to first pass metabolism is reduced as compared to standard tablet.[9] The target populations for these new fast-dissolving/disintegrating dosage forms have generally been 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 for FDDTs.[10] Pharmaceutical marketing is another reason for the increase in available orally /disintegrating products. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and undertreated patient populations.[11]

Biopharmaceutical Consideration[12]

When new drug delivery system put on, it is must that to consider Biopharmaceutical factor like metabolism and excretion.

Pharmacokinetics

Study has done on absorption, distribution, metabolism and excretion in this consideration. Drug attains therapeutic level after absorption and therefore elicits pharmacological effect, so both rate and extend of absorption is important. There is delay in disintegration and therefore dissolution in conventional dosage form while FDTs is rapidly disintegrates in oral cavity and dissolution is rapid. Due to disintegration of FDTs in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. There are many factors on which drug distribution depends like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of
distribution of water-soluble drugs and increased volume of distribution (Vd) of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamics: Drug receptor interaction impaired in elderly as well as in young adult due to undue development of organ. Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin. Decreased sensitivity of the CVS to β-adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes’ cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient.

Requirements of fast disintegrating tablets

The tablets should

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds. Allow high drug loading.
- Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

Advantages of fast disintegrating tablets

- FDTs offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:
Accurate dosing: Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

Enhanced bioavailability: Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.

Rapid action: Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

Patient compliance: No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.

Ease of administration: Convenient to administer specially for geriatric, pediatric, mentally disabled and bedridden patients who have difficulty in swallowing.

Obstruction free: No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance. Enhanced palatability: Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.

Simple packaging: No specific packaging required. It can be packaged in push through blisters.

Business avenue: Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

Cost effective: Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

The need for development of fast disintegrating tablets

The need for non-invasive delivery systems persists due to patient’s poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management. 2.1. Patient factors Fast disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:
Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.

Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.

Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.

Patients with persistent nausea for a long period of time are unable to swallow.

Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.

Mentally challenged patients, bedridden patients and psychiatric patients.

**Effectiveness factor**

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

**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, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and undertreated patient populations.

**Challenges in formulation of fast disintegrating tablets**

Mechanical strength and disintegration time: It is obvious that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential. FDTs are formulated to obtain disintegration time usually less mechanical strength is a prime challenge.[19]
Taste masking
As most drugs are unpalatable, rapid disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient’s oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.[17,20]

Aqueous solubility
Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.[21,22]

Hygroscopicity
Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.[23]

Amount of drug
The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.[24]

Size of tablet
It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.[25]

Mouth feel
FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.[19]
Sensitivity to environmental conditions

FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water.\[^{19}\]

**Drug candidates suitable for fast disintegrating tablets (FDTs)\[^{26}\]**

Several factors must be considered while selecting an appropriate drug candidate for development of orally fast disintegrating dosage forms.

Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.

Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.

- Patients with Sjogren’s syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
- Drugs with a short half-life and frequent dosing. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g. selegiline, apomorphine, buspirone etc.
- The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.
- Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.

**Drugs to be promising in corporate in fast disintegrating tablets (FDTs)\[^{27, 28}\]**

Table 1: List of Drug to be incorporate in FDTs

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics and Anti-inflammatory Agents</td>
<td>Aloixiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen, Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin,</td>
</tr>
<tr>
<td>Category</td>
<td>Examples</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Anti-bacterial Agents</td>
<td>Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.</td>
</tr>
<tr>
<td></td>
<td>Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixic Acid, Nitrofurantoin, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxine, Sulphamerazine, Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Tetracycline, Trimethoprim</td>
</tr>
<tr>
<td>Anti-Migraine Agents</td>
<td>Dihydroergotamine Mesylate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate</td>
</tr>
<tr>
<td>Anti-Muscarinic Agents:</td>
<td>Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine, Oxyphencylcimine, Tropicamide</td>
</tr>
<tr>
<td>Local Anaesthetics:</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Neuro-Muscular Agents:</td>
<td>Pyridostigmine</td>
</tr>
</tbody>
</table>

**Excipients commonly used for FDTs preparation**

Excipients used in FDTs contain at least one superdisintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavorings.

**Superdisintegrants**

In recent years, several newer agents have been developed known as “Superdisintegrants”. A “Superdisintegrants” is an excipient, which is added to tablet or capsule blend to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The use of superdisintegrants is the basic approach in the development of fast disintegrating tablets (FDTs). Superdisintegrants plays a major role in the dissolution and disintegration of the tablets. It is essential to choose an optimum
concentration of superdisintegrants so as to ensure rapid disintegration and high dissolution rates of tablets.\(^{[30]}\)

Superdisintegrants provide rapid disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.\(^{[31-33]}\) The optimum concentration of the superdisintegrant can be selected according to the critical concentration of the disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, where as above this concentration the disintegration time remains almost constant or even increases.\(^{[34]}\)

**List of super disintegrants\(^{[9]}\)**

<table>
<thead>
<tr>
<th>Superdisintegrants</th>
<th>Example</th>
<th>Mechanism of Action</th>
<th>Special comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC</td>
<td>Crosslinked cellulose</td>
<td>Swells 4-8 folds in &lt; 10 seconds. -Swelling and Wicking both.</td>
<td>-Swells in two dimensions. -Direct compression or granulation -Starch free</td>
</tr>
<tr>
<td>Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®</td>
<td>Crosslinked PVP</td>
<td>Swells very little And returns to original size after compression but act by capillary action</td>
<td>get porous tablet</td>
</tr>
<tr>
<td>Sodium starch glycolate Explotab® Primogel®</td>
<td>Crosslinked starch</td>
<td>-Swells 7-12 folds in &lt; 30 seconds</td>
<td>serve as sustain release matrix</td>
</tr>
<tr>
<td>Calcium silicate</td>
<td></td>
<td>-Wicking Action</td>
<td>Highly porous, Optimum concentration is b/w 20-40%</td>
</tr>
</tbody>
</table>

**Binders**

The choice of a binder is critical in a fast- dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredient. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. Main role of Binders is to keep the composition of these fast-melting tablets together during the compression stage. Binders commonly used are cellulosic
polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers it will be advantageous to select ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures, and the most commonly acrylic polymer used are the ammonio-methacrylate copolymer (Eudragit. RL and RS), polyacrylate (Eudragit NE), and polymethacrylate (Eudragit E). The temperature of the excipient should be preferably around 30–35ºC for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

**Antistatic agent and diluents**

The most common antistatic agents used are colloidal silica (Aerosil), precipitated silica (Sylod.FP244), micronized or non-micronized talc, maltodextrins, beta-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearyl fumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. Commonly used Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols and preferably mannitol.

**Various techniques for “fdts” preparation**

Many techniques are used for the preparation of fast disintegrating tablets which are shown in table 4.\[16, 21, 30, 37, 38\]

Different techniques with method and characteristics of prepared fast disintegrating tablets

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Techniques</th>
<th>Method and characteristics of prepared FDTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disintegrant addition</td>
<td>The basic principle involved in formulating Fast disintegrating tablets by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel. Sodium starch glycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants. Characteristics.</td>
</tr>
<tr>
<td>2</td>
<td>Freeze Drying or Lyophilization</td>
<td>Lyophilization Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that</td>
</tr>
</tbody>
</table>
allow removal of water by sublimation. 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. Characteristics: The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.

Sublimation

Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethylenetetramine) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. Characteristics: Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.

Spray-Drying

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.

Evaluation of fast disintegrating tablets

Tablets from all the formulation were subjected to following quality control test\cite{54,55}

General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.


**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. Ten tablets were taken and their thickness was recorded using micrometer.

**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.

**Friability (F)**

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre-weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions.

**Wetting Time**

Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured.

**Water absorption Ratio**

A piece of tissue paper folded twice was placed in a small Petridish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed.

**REFERENCES**


