AN OVERVIEW ON NOVEL TRENDS IN ORALLY MOUTH DISSOLVING TABLET


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ABSTRACT

Novel drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and bio-chemical parameters pertinent to their performance. Fast dissolving tablet (FDT) is one such type of an innovative and unique drug delivery system which is swiftly gaining much attention in the research field of rapid dissolving technology. The convenience of administration and improved patient compliance are important in the design of oral drug delivery system which remains the preferred route of drug delivery inspite of various disadvantages. One such problem can be solved in the novel drug delivery system by formulating “mouth dissolving tablets” (MDTs) which disintegrates or dissolves rapidly without water within few seconds in the mouth due to the action of superdisintegrant or maximizing pore structure in the formulation. Despite tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. Patient convenience and compliance oriented research have resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance, as one such example, with increased consumer choice, for the reason of rapid disintegration or dissolution and self-administration even without water or chewing and provides a quick onset of action. The aim of the review article is to give an overview on potential benefits offered by FDTs as an oral drug delivery system for various kinds of patients suffering from different diseases and disabilities. Desired characteristics and challenges for developing fast disintegrating drug delivery systems, quality control tests,
various techniques used in the preparation of fast disintegrating drug delivery systems like lyophilisation technologies, tablet molding method, sublimation techniques, spray drying techniques, mass extrusion technology, use of superdisintegrants and also reviews the patented technologies for fast disintegrating dosage forms and future prospects.

**KEYWORDS:** Fast dispersing tablet, patented technology, superdisintigrants, improved bioavailability, novel dosage forms, mouth dissolving tablet.

**INTRODUCTION**
Orally disintegrating systems have craved a popular position amongst the oral drug delivery systems due to the highest component of compliance they enjoy in patients especially the geriatrics and pediatrics. In addition, patients suffering from dysphagia, motion sickness, repeated emesis, uncooperative and mental disorders, bedridden or developmentally disabled patients. Patients with persistent nausea, who are travelling, or who have little or no access to water are also good candidates for FDDTs. To fulfil these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Fast Disintegrating Tablets (FDTs).

Fast disintegrating/dissolving tablets (FDT) are single unit solid unit dosage forms that disintegrate or dissolve rapidly (in few seconds) in mouth without the need of water or chewing. These dosage forms show good stability, ease of manufacturing and ease of handling by patient. The drug is immediately released from dosage form and is readily available for absorption, improving its onset of action and its bioavailability in some cases (soluble drugs), to some extent it is also possible to achieve absorption of some drugs across the oral mucosa directly into the systemic circulation, avoiding first pass metabolism & its subsequent side effects. The product can be taken any way and any time. It does not require liquid to swallow. It is ready for use in emergency situations.

The main criteria for fast disintegrating (dissolving) tablet is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 to 60 seconds, without need of water and should have pleasant mouth feel.

Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a compliance. Pharmaceutical technologists have put in their best efforts to develop a fast dissolving/ disintegrating drug delivery system (FDDTs).

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, or Effervescent Drug Absorption System. [8] In order to allow fast dissolving tablets to dissolve in the mouth, these are made of either very porous or soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging. To overcome this problem, a few companies made current robust forms of fast dissolving tablets such as Zydis (R.P. Scherer, Inc.), WOWTAB (Yamanouchi Pharma Technologies, Inc.), and OraSolv and DuraSolv (Cima Labs, Inc.), FlashDose (Fuisz Technologies, Ltd.), Flashtab (Prographarm Group), and OraQuick (KV Pharmaceutical Co., Inc.), Quick-Dis (Lavipharm Laboratories Inc.), NanoCrystal (Elan Corp).

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient’s tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. According to European Pharmacopoeia, the FDT should disperse/disintegrate in less than three minutes. The basic approach used in development of FDT is use of superdisintegrants like Cross linked carboxymethyl cellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolodone (Polyplasdone) etc., which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. 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.[9-13] The technologies used in developing FD tablets is maximizing pore structure of the tablet matrix are freeze-drying, Tablet Molding, Direct
Compression Method, spray drying and sublimation Technology, sugar based excipients etc.\cite{14}

**DESIRED PREREQUISITES FOR FAST DISSOLVING TABLETS**\cite{15}

- Ease of Administration to the patient who cannot swallow, such as the elderly, bedridden patients, and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid onset of action and an improved bioavailability.
- Have a pleasant mouth feel.
- Exhibit low sensitive to environmental conditions such as humidity and temperature.
- It should have sufficient hardness to withstand rigors during manufacturing processes and post manufacturing handling.
- Good accurate dosing compared to liquids.
- Should leave minimal or no residue in mouth after disintegration.
- Be compatible with taste masking excipients.
- Allow high capacity of drug loading.
- Rapid drug therapy intervention
- Broad applicability to several drugs and diseases.
- Be amenable and variable to existing processing and packaging machinery.
- The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- It should be cost effective.
- Be portable and without fragility concern.
- Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

**DRUG SELECTION CRITERIA**\cite{16}

The ideal characteristics of a drug for oral dispersible tablet include:

- Partially non ionized at the oral cavities pH
- Ability to permeate the oral mucosa.
- Small to moderate molecular weight
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Good stability in water and saliva.
Drugs which have lower bioavailability, are good candidates for FDT.

Short half-life and frequent dosing drugs are unsuitable for FDT.

Very bitter taste and odour drugs are unsuitable for ODT. Patients who concurrently take ant cholinergic medications may not be the best candidates for these drugs.

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

**THE NEED FOR DEVELOPMENT OF FDTS**[17]

**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:

- Patients who are unwilling to take solid preparation due to fear of choking.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A patient with persistent nausea, who may be journey, or has little or no access water.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.

**Effectiveness factor**

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric 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 pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of 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 pregastric segments of GIT.[18]

**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. Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved.

**QUALITY CONTROL TESTS FOR FAST DISINTEGRATING TABLETS**

- Appearance, size and shape
- Hardness and friability
- Tablet Thickness
- Wetting time
- Weight variation test
- Dissolution characteristics
- Water absorption ratio
- Disintegration time
- Content uniformity
- Stability testing of drug

**CHALLENGES IN FORMULATING FDTs[19]**

**Mechanical strength and disintegration time**

FDTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many FDTs are fragile and there are many 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.
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.

Hygroscopicity
Many orally disintegrating dosage forms cannot uphold physical integrity under normal conditions of temperature and humidity as they are hygroscopic. Hence forth, they need protection from humidity which demands a specialized product packaging.

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. FDTs should leave minimal or no residue in mouth after oral administration. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.

Amount of drug
The application of FDT 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 less than 400 mg for insoluble drugs and lower than 60 mg for soluble drugs. This parameter is especially challenging during formulating a fast-dissolving oral films or wafers.

Cost
The technology used for FDTs 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.

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.
DRUGS EXPLORED FOR FDTS\textsuperscript{[20]}

**Analgesics and Anti-Inflammatory Agents**
Aloxiprin, Auranofin, Azapropazone, Benoary-ate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim.

**Anthelmintics**
Albendazole, Bephenium Hydroxynapthoate, Cambendazole, Dichlorophen, Ivernectin, Mebendazole, Oxarnique, Oxfendazole, Praziquantel, Pyrantel Embonate, Thiabendazole.

**Anti-Arrhythmic Agents**
Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate.

**Anti-bacterial Agents**
Benethamine Penicillin, Cinoxacin, Ciprofloxacin HCl, Clarithromycin, Cloxacillin, Doxycycline, Erythromycin, Ethionamide, Imipenem, nalidixic acid, Nitrofurantoin, Rifampicin.

**Anti-coagulants**
Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

**Anti-depressants**
Amoxapine, Ciclazindol, Maprotiline HCl, Mianserin HCl, Trazodone HCl, Trimipramine Maleate.

**Anti-diabetics**
Glipizide, Tolazamide, Tolbutamide Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide.

**Anti-Epileptics**
Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine.

**Anti-fungal Agents**
Amphotericin, Butoconazole nitrate, Clotrimazole, Econazole nitrate, Fluconazole.

**Anti-gout Agents**
Allopurinol, Probencid, Sulphinpyrazone.
Anti-Hypertensive Agents
Amlodipine, Carvedilol, Benidipine, Darodipine, Diazoxide, Felodipine, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.

Anti-malarials
Amodiaquine, Chloroquine, Chlorproguanil HCl, Halofantrine HCl, Mefloquine HCl, Proguanil HCl, Pyrimethamine.

Anti-Muscarinic Agents
Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine, Oxyphencylcimine, Tropicamide.

Anti-Neoplastic Agents and Immunosuppressants
Aminoglutethimide, Amsacrine, Azathioprine, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone.

Anti Protozoal Agents
Benznidazole, Clioquinol, Decoquinate, Diodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nitrofurazone, Omidazole, Tinidazole.

Anti-Thyroid Agents
Carbimazole, Propylthiouracil.

Anxiolytic, Sedatives, Hypnotics and Neuroleptics

Cardiac Inotropic Agents
Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.
Corticosteroids
Beclomethasone, Budesonide, Desoxymethasone, Flunisolide, Prednisone, Methylprednisolone, Triamcinolone.

Diuretics
Acetazolamide, Amiloride, Bendrofluazide, Chlorthalidone, Ethacrynic Acid, Frusemide, Metolazone, Spironolactone, Triamterene.

Anti-Parkinsonian Agents
Bromocriptine Mesylate, Lysuride Maleate.

Gastro-Intestinal Agents
Bisacodyl, Cimetidine, Cisapride, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Ranitidine.

Histamine H1-Receptor Antagonists
Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, Flunarizine, Meclozine, Oxatomide, Terfenadine, Triprolidine.

Lipid Regulating Agents
Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.

Local Anaesthetics
Lidocaine

Neuro-Muscular Agents
Pyridostigmine.

Nitrates and Other Anti-Anginal Agents
Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

Nutritional Agents
Betacarotene, Vitamin A, Vitamin B2, Vitamin D, Vitamin E, Vitamin K.
Opioid Analgesics
Codeine, Dextropropoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine.

Proteins, Peptides and Recombinant Drugs
Insulin (Hexameric/Dimeric/Monomeric Forms), Glucagon, Growth Hormone (Somatotropin), Polypeptides or Their Derivatives, (Preferably With A Molecular Weight from 1000 To 300,000), Calcitonins And Synthetic Modifications Thereof, Enkephalins, Interferons (Especially Alpha-2 Inter Feron For Treatment Of Common Colds).

Sex Hormones
Clomiphene Citrate, Danazol, Ethinyloestradiol, Medroxyprogesterone Acetate, Mestranol, Methyltestosterone, Norethisterone, Norgestrel, Oestradiol, Conjugated Oestrogens, Progesterone, Stanozolol, Stiboestrol, Testosterone, Tibolone.

Stimulants
Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mharmaizolin, pemoline.

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 flavourings.

Table 2: Name and weight percentage of various excipient

<table>
<thead>
<tr>
<th>Name of the Excipients</th>
<th>Percentage used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superdisintegrants</td>
<td>1-15%</td>
</tr>
<tr>
<td>Binder</td>
<td>5-10%</td>
</tr>
<tr>
<td>Antistatic agent</td>
<td>0-10%</td>
</tr>
<tr>
<td>Diluents</td>
<td>0-85%</td>
</tr>
</tbody>
</table>

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, mechanical strength and they are more effective intragranularly.
Figure 1: Flowchart depicting the disintegration and delivery mechanism of an ODT following oral administration.

This superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Table 3: List of superdisintegrants

<table>
<thead>
<tr>
<th>Superdisintegrants</th>
<th>Example</th>
<th>Mechanism of Action</th>
<th>Special comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosscarmellose®</td>
<td>Crosslinked cellulose</td>
<td>-Swells 4-8 folds in &lt; 10 seconds.</td>
<td>-Swells in two dimensions.</td>
</tr>
<tr>
<td>Ac-Di-Sol®</td>
<td></td>
<td>-Swelling and Wicking both.</td>
<td>-Direct compression or granulation</td>
</tr>
<tr>
<td>Nymce ZSX®</td>
<td></td>
<td></td>
<td>-Starch free</td>
</tr>
<tr>
<td>Primellose® Solutab®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivasol® L-HPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>Crosslinked PVP</td>
<td>-Swells very little And returns to original size after compression but act by capillary action</td>
<td>-Water insoluble and spongy in nature so get porous tablet</td>
</tr>
<tr>
<td>Crosspovidon M®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollidon®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyplasdone®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Crosslinked Starch</td>
<td>Swells 7-12 folds in &lt; 30 seconds</td>
<td>-Swells in three dimensions. and high level serve as sustain release matrix.</td>
</tr>
<tr>
<td>Explotab®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primogel®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alginic acid NF Satialgine®</td>
<td>Crosslinked Alginic acid</td>
<td>-Rapid swelling in aqueous medium or wicking action</td>
<td>-Promote disintegration in both dry or wet granulation.</td>
</tr>
<tr>
<td>Soy polysaccharides</td>
<td>Natural super disintegrant</td>
<td>-</td>
<td>-Does not contain any starch or sugar. Used in nutritional products.</td>
</tr>
<tr>
<td>Emcosoy®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indion 414,</td>
<td>Ion exchange resins</td>
<td>It has a high water uptake capacity</td>
<td>-rapid disintegration without</td>
</tr>
<tr>
<td>Amberlite IPR 88</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Kyron 314

Polacrilin Potassium
- Rapid swelling in aqueous medium
Used as a Tablet disintegrant and a taste masking agent.

Gellan Gum
Anionic polysaccharide of linear tetrasaccharide
- Promote disintegration in both dry or wet granulation

L-HPC
L-HPC Low hydroxyl propyl cellulose
It has a high water uptake capacity

Smecta
Their layered leaves like structure consist of aluminium and octahydral layers sandwiched between two tetrahydral silica layers.
- It has high affinity for water makes it good disintegrant

<table>
<thead>
<tr>
<th>Mechanism of action of superdisintegrants</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Porosity and capillary action (Wicking)</td>
</tr>
</tbody>
</table>
| Capillary action is always the first step in tablet disintegration. Suitable aqueous medium into which tablet is placed, penetrates into the tablet and replaces the air adsorbed on the particles there by weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. Unlike swelling, which is mainly a measure of volume expansion with accompanying force generation, water wicking is not necessarily accompanied by a volume increase. The ability of a system to draw water can be summarized by Washburn’s equation:  

\[ L^2 = (\gamma \cos \theta/2\eta) \times rt \]

The Washburn equation is too simplistic to apply to a dynamic tablet-disintegration process, but it does show that any change in the surface tension (\(\gamma\)), pore size (r), solid-liquid contact angle (\(\theta\)) or liquid viscosity (\(\eta\)) could change the water wicking efficiency. L is the length of water penetration in the capillary and t is the time. |  
| b) Swelling |  
| Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is to penetrate in the tablet and disintegration is again slows down. |
c) **Due to disintegrating particle/particle repulsive forces**

Another mechanism of disintegrating attempts to explain the swelling of tablet made with “non swellable” disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

d) **Due to deformation : (Elastic recovery)**

Most materials, which undergo a plastic deformation during compression, try to return to their initial shape as soon as possible (stored potential energy). In the tablet matrix, there is no means to recover the former shape. But as soon as water penetrates into the tablet matrix and the forces, which keep the particles together, are diminished, those particles have the ability to expand back.

e) **Due to release of gases**

Carbon dioxide gets released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

f) **Because of heat of wetting (air expansion)**

When disintegrants with exothermic properties gets wetted localized stress is generated due to capillary air expansion, which helps in disintegration of the tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

g) **Deformation recovery**

Deformation recovery theory implies that the shape of disintegrant particles is distorted during compression and the particles return to their precompression shape upon wetting, thereby causing the tablet to break apart. Such a phenomenon may be an important aspect of
the mechanism of action of disintegrants such as Crosspovidone and starch that exhibit little or no swelling.

h) By enzymatic reaction
Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

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 stearylfumarate, 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.
Other Excipients

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 mouth feel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.
Type 2 saccharides (maltose and maltitol) exhibit high mouldability and low dissolution rate.

Flavours
Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil thyme oil, oil of bitter almonds. Flavoring agents include, vanilla, citrus oils, fruit essences

Sweeteners
Aspartame

Fillers
Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

Surface active agents
Sodiumdodecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.

Lubircants
Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethyleneglycol, liquid paraffin, magnesium lauryl sulfate, colloidal silicon dioxide

VARIOUS TECHNIQUES FOR “FDTs” PREPARATION
Many techniques are used for the preparation of fast disintegrating tablets which are shown in table 4.[22]
Table 4: Different techniques with method and characteristics of prepared fast disintegrating tablets

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Techniques</th>
<th>Method and their characteristics of prepared FDTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disintegrants addition</td>
<td>The basic principle involved in formulating Fast-dissolving tablets by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel. Similar to conventional tablets with higher percentage of disintegrants, lower hardness and higher percentage of friability.</td>
</tr>
<tr>
<td>2</td>
<td>Tablet Molding</td>
<td>In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.</td>
</tr>
<tr>
<td>3</td>
<td>Spray-Drying</td>
<td>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 dissolution. Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.</td>
</tr>
<tr>
<td>4</td>
<td>Freeze drying or Lyophilization</td>
<td>Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that 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. The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.</td>
</tr>
<tr>
<td>5</td>
<td>Sublimation</td>
<td>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. Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.</td>
</tr>
<tr>
<td></td>
<td>Process</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>6</td>
<td>Compaction a) Melt granulation</td>
<td>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. It melts in the mouth and solubilizes rapidly leaving no residue. Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol.</td>
</tr>
<tr>
<td>7</td>
<td>Nanonization</td>
<td>Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).</td>
</tr>
<tr>
<td>8</td>
<td>Direct compression</td>
<td>Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. It is most cost effective tablet manufacturing technique.</td>
</tr>
<tr>
<td>9</td>
<td>Mass-Extrusion</td>
<td>This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.</td>
</tr>
<tr>
<td>10</td>
<td>Cotton Candy Processs</td>
<td>Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDTs. It can accommodate high doses of drug and offers improved mechanical strength.</td>
</tr>
<tr>
<td>11</td>
<td>Three Dimensional Printing (3DP)</td>
<td>The 3DP method provides zero order drug delivery, patterned diffusion radiant drug release by micro structure diffusion barrier technique, cyclic drug release and another drug release profiles. The technique is often referred to as solid free form fabrication or computer automated manufacturing or layered manufacturing.</td>
</tr>
</tbody>
</table>
12 Fast Dissolving Films

A non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), 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, dissolution in 5 sec, instant drug delivery.

PATENTED TECHNOLOGIES FOR FAST DISINTEGRATING TABLETS

Zydis technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginites are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycines prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.\(^{[23]}\)

Pharmaburst technology

Pharmaburst™ is a “Quick Dissolve” delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch faces mouldability saccharine are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldablilty saccharides.\(^{[24]}\)

Advatab technology

Advatab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is
distinct from other ODT technologies as it can be combined with Eurand’s complimentary particle technologies like its world leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

**Orasolv technology**

Orasolv technology has been developed by "CIMA" labs. This technology involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet equipment’s are used for preparation of tablets. Less force of compaction is used for manufacturing to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system.

**Flash Dose technology**

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets. Flash dose tablets consist of self binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

**Durasolv technology**

DuraSolv is Cima”s second-generation fast-dissolving/ disintegrating tablet formulation. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tableting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.\[25\]

**Wow tab technology**

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water “. The active ingredients may constitute up to 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldability saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs.\[26\]
Sheaform Technology

The technology is based on the preparation of floss that is also known as “Shearform Matrix”, which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide aciform flow properties and this facilitate blending the recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet.[27]

Quick-Dis Technology

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick- Dis™, is Lavipharm”s proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit dose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within 30 seconds and 95% within 1 minute.[28]

OraQuick

KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable,
meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives. This technology evaluates parameters such as: Rate of absorption and dissolution, pleasant mouth feel, taste, physical strength, bioavailability, and stability. [29]

**Frosta technology**

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet. [30]

**Lyoc tech**

This is patented technology of Laboratories L. Lafon, Maisons Alfort, France. It utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations. [31]

**Dispersible Tablet Technology**

Lek in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methanesulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and...
cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.\textsuperscript{[32]}

**Nanocrystal technology**

For fast disintegrating tablets, Elan's proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nanocrystal technology. Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into FDT dosage forms because manufacturing losses are negligible.\textsuperscript{[33]}

**Advantol 200**

Specially formulated for nutraceutical applications Advantol 200 is a directly compressible excipient system offering "Soft-Melt" functionality and it requires no special manufacturing equipment or tooling. To make robust “softmelt” tablets it requires standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions.

**Mechanism of Super disintegrants**

Generally there are four major mechanisms for tablets disintegration as follows:

1. **Swelling:** Superdisintegrants which act by this mechanism work on the fundamental of “swell” and “burst” When the Super-Disintegrant comes in contact with the water/saliva, the aqueous phase extras more adhesive force upon the superdisintegrant as compared to other excipients and drug resulting in swelling and trust or breaking apart of the tablet. Most of the Superdisintegrants follow this mechanism. Of them, the widely used are starch and its modifications. Given below is the list of the natural as well as the synthetic Superdisintegrants having swelling mechanism.
Table 5

<table>
<thead>
<tr>
<th>Synthetic Superdisintegrants</th>
<th>Natural Superdisintegrants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>Pectin</td>
</tr>
<tr>
<td>Modified Starch</td>
<td>Agar</td>
</tr>
<tr>
<td>Cross-linked PVP</td>
<td>Veegum</td>
</tr>
<tr>
<td>Cross-linked sodium CMC</td>
<td>Bentonite</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>Ion exchange Resin (Indion 414)</td>
</tr>
<tr>
<td>StaRX1500(Pregelatinized Starch)</td>
<td></td>
</tr>
</tbody>
</table>

2. Porosity and Capillary Action (Wicking)

This mechanism suggests that primarily all the particles of the tablet are surface wetted in the given aqueous media. Water then penetrates into the core of the tablet, reducing the inter-particle bond thus aiding in breaking of the tablet. Thus it is termed as capillary action or wicking as slowly, the wetting rises in the tablet with ultimate result of breakage of tablet. Here the porosity of the tablet is of the utmost importance as it is the fundamental requirement for easy and quick wetting/water uptake. The more porous the material the greater the rate of wetting and disintegration time is less.

3. Particle/Particle Repulsive Forces

Guyot-Hermann has proposed a particle repulsion theory. This theory states the swelling via tablet made of “nonswellable” disintegrants. This works on the principle of electric repulsive force of particles. It is mandatory for the tablet to come in contact with water thus generating repulsive force, making particles repel each other and thus the tablet disintegrates. This mechanism uses the biological enzymes as disintegrants. Binder which are easily broken by salivary enzymes are used in the tablet. Upon the contact with the saliva these binders are catalyzed thus disintegrating the tablet. This mechanism also couples the swelling and burst phenomenon where the binder swells and bursts to release drug as granules. Examples: Binder Starch metabolised by Amylase; Sucrose by Invertase; Gums by Hemicellulose; Alginate by Carragenase.

4. Deformation

Starch grains are generally thought to be “elastic” in nature that is grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed permanently and are said to be “energy rich” with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in “energy rich” starch grains than it is for starch grains that have not been deformed under pressure.
Evaluation Parameters

It is important to evaluate the formulated drugs in order to determine the quality of the tablet.

Given below are the fundamental evaluation parameters.

**Table 6: Evaluation parameters of FDT**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Variation</td>
<td>Weight Variation tests are carried out according to either USP, IP, BP.</td>
</tr>
<tr>
<td>Hardness</td>
<td>Hardness of the tablet should be lesser than conventional tablet falling in the range of 3-4kg/cm²²</td>
</tr>
<tr>
<td>Friability</td>
<td>Friability should be within the range of 0.1-0.9%.</td>
</tr>
<tr>
<td>Mechanical Strength</td>
<td>Should possess adequate mechanical strength to absorb the transportation shock and avoid breakage of tablet</td>
</tr>
<tr>
<td>Tablet Porosity</td>
<td>Tablet porosity is conducted (as per ICH guideline)</td>
</tr>
<tr>
<td>Disintegration Studies</td>
<td>The time period at which the tablet starts to disintegrate in given aqueous media is determined</td>
</tr>
<tr>
<td>Dissolution Studies</td>
<td>Dissolution Studies carried out according to USP, IP, BP.</td>
</tr>
<tr>
<td>In-vitro Dispersion time</td>
<td>At optimum and fixed pH and temperature, time taken for dispersion of tablet in media is determined</td>
</tr>
<tr>
<td>Wetting time and water absorption</td>
<td>Use of simulated saliva to check the wetting time of tablet as well as water absorption</td>
</tr>
<tr>
<td>Stability Studies</td>
<td>Stability studies (including Accelerated Stability studies) are conducted according to the ICH guidelines</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>Content uniformity according to either USP, IP, BP.</td>
</tr>
</tbody>
</table>

Challenges of Fast Dissolving Tablet’s

Despite the advantages of this formulation, it faces number parameters that come across as a challenge. These are listed below

**Table 7: Challenges faced while preparing FDT**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palatability</td>
<td>Drug should be made palatable to the patient, for easy administration, and should be sweet in nature. This is a challenge as most drugs are bitter in taste.</td>
</tr>
<tr>
<td>Mechanical Strength</td>
<td>The tablet should have optimum mechanical strength, along its excipients added, should not break easily, nor be friable. This is a challenge as the drug should rapidly disintegrate in oral cavity and yet have good mechanical strength</td>
</tr>
<tr>
<td>Hygroscopicity</td>
<td>This formulation is hygroscopic in nature as it should dissolve/ disintegrate when it comes in contact with water. Thus the vital mechanism of the formulation is a challenge and a limiting step</td>
</tr>
<tr>
<td>Aqueous Solubility</td>
<td>Aqueous solubility becomes a major issue if the drug is hydrophobic in nature or highly Lipophilic, thus it won’t dissolve/disintegrate in mouth leading to grittiness and residue in mouth.</td>
</tr>
<tr>
<td>Drug Concentration</td>
<td>Only potent drugs or drugs having a narrow therapeutic index, can be made into FDT’s. These tablets are small in size utilizing minimum excipients and</td>
</tr>
</tbody>
</table>
Table Size

Oral dissolving tablets should have an optimum tablet size of 7-9mm, and should not exceed it.

List of Patented technologies based branded Products

The list of patented technologies and their brand products are given in table 8.

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Technology</th>
<th>Process involved</th>
<th>Patent owner</th>
<th>Drugs Used (Brand name)</th>
<th>Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zydis</td>
<td>Lyophilization</td>
<td>R.P.Scherer Inc.</td>
<td>Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)</td>
<td>Dissolves in 2-10 sec.</td>
</tr>
<tr>
<td>2</td>
<td>Quicksolv</td>
<td>Lyophilization</td>
<td>Jansen Pharmaceutical</td>
<td>Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-tab)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Flashtab</td>
<td>Lyophilization</td>
<td>Ethypharm</td>
<td>Ibuprofen (Nurofen Flashtab)</td>
<td>Dissolves within 1 min.</td>
</tr>
<tr>
<td>4</td>
<td>Lyoc</td>
<td>Multiparticulate Compressed tablets</td>
<td>Farmlyoc</td>
<td>Phloroglucinol Hydrate (Spasfon Lyoc)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Rapitab</td>
<td>Compressed Tablets</td>
<td>Schwarz Pharma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Wow tab</td>
<td>Compressed Molded Tablets</td>
<td>Yamanouchi Pharma Technologies, Inc.</td>
<td>Famotidine (Gaster D)</td>
<td>Disintegrates in 5-45 sec.</td>
</tr>
<tr>
<td>7</td>
<td>Durasolv</td>
<td>Molding</td>
<td>Cima Labs Inc.</td>
<td>Hyoscyamine Sulfate (NuLev), Zolmitriptan (ZMT)</td>
<td>Disintegrates in 5-45 sec.</td>
</tr>
<tr>
<td>8</td>
<td>Flashdose</td>
<td>Cotton candy process</td>
<td>Fuisz Technology Ltd</td>
<td>Tramadol HCl (Relivia Flash dose)</td>
<td>Dissolves within 1 min.</td>
</tr>
<tr>
<td>9</td>
<td>Oraquick</td>
<td>Micromask taste Masking</td>
<td>Micromask taste Masking</td>
<td>Hyoscyamine Sulfate ODT</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Advatab</td>
<td>Microcaps &amp; diffuscap CR Technology</td>
<td>Eurand International</td>
<td>AdvaTab cetirizine, AdvaTab Paracetamol</td>
<td>Disintegrates in less than 30 sec.</td>
</tr>
<tr>
<td>11</td>
<td>Pharmabrust</td>
<td>Direct compression of powder mixture</td>
<td>SPI Pharma</td>
<td>-</td>
<td>Disintegrates in less than 30 sec.</td>
</tr>
<tr>
<td>12</td>
<td>Fast melt</td>
<td>Molding</td>
<td>Elan Corp</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Zipllets</td>
<td>Molding</td>
<td>Eurand</td>
<td>Ibuprofen (Cibalgina Due Fast)</td>
<td>Disintegrates in less than 30 sec.</td>
</tr>
<tr>
<td>14</td>
<td>Orasolv</td>
<td>Compressed Tablets</td>
<td>Cima Labs Inc</td>
<td>Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt)</td>
<td>Disintegrates in 5-45 sec.</td>
</tr>
</tbody>
</table>
PACKAGING OF FDTs\textsuperscript{[35]}

Packing is one of the important aspects in manufacturing FDTs. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a great extent. The products obtained by lyophilization process including various technologies such as Zydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For the above reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome shaped blister, which prevents vertical movement of tablet with in the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv, Wow tab, Pharmaburst oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles.

LIST OF MARKETED COMMERCIALIZED PRODUCTS OF FDTS WHICH ARE AVAILABLE IN MARKET ARE GIVEN IN TABLE 9.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active drug</th>
<th>Manufacturer Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acivir DT</td>
<td>Acyclovir</td>
<td>Cipla</td>
</tr>
<tr>
<td>Alavert</td>
<td>Loratadine</td>
<td>Wyeth, U.S</td>
</tr>
<tr>
<td>Allegra ODT</td>
<td>Fexofenadine</td>
<td>Sanofi Aventis, France</td>
</tr>
<tr>
<td>Cibalginadue FAST</td>
<td>Ibuprofen</td>
<td>Novartis Consumer Health</td>
</tr>
<tr>
<td>Clonazepam ODT</td>
<td>Clonazepam</td>
<td>Par Pharmaceutical, U.S</td>
</tr>
<tr>
<td>Domray MD</td>
<td>Domperidone</td>
<td>Ray Remedies</td>
</tr>
<tr>
<td>Feldene melt</td>
<td>Piroxicam</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Dolib MD</td>
<td>Rofecoxib</td>
<td>Panacea</td>
</tr>
<tr>
<td>Febrectol</td>
<td>Paracetamol</td>
<td>Prographarm</td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Olanzepine</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>Imodium lingual</td>
<td>Imodium</td>
<td>R.P.Scherer Corp., U.S.A</td>
</tr>
<tr>
<td>Insure-MD</td>
<td>Nimesulide</td>
<td>SuzenPharma, Hyderabad India</td>
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<tr>
<td>Mirtazapine ODT</td>
<td>Mirtazapine</td>
<td>Teva Pharmaceuticals</td>
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<tr>
<td>Mosip-MT</td>
<td>Mosapride citrate</td>
<td>Torrent Pharmaceuticals, Ahmedabad, India</td>
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<td>Pepcidin Rapitab</td>
<td>Pepcid</td>
<td>Merck &amp; Co., U.S.A</td>
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<td>Calritin Reditabs</td>
<td>Calritin</td>
<td>Schering Plough, U.S.A</td>
</tr>
<tr>
<td>Romilast</td>
<td>Montelukast</td>
<td>Ranbaxy lab. Ltd. New-delhi, India</td>
</tr>
<tr>
<td>Benadryl Fastmelt</td>
<td>Diphenhydramine</td>
<td>Warner Lambert, NY, USA</td>
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<tr>
<td>S.NO.</td>
<td>Product</td>
<td>Manufactured by</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Dextromethorphan HBr (cough suppressant), MonoSolRx</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Donepezil rapid dissolving films, Ondansatron rapid dissolving films</td>
<td>Labtec Pharma</td>
</tr>
<tr>
<td>3</td>
<td>Little Colds Sore Throat Strips Pectin (from vitamin C)</td>
<td>Prestige Brands</td>
</tr>
<tr>
<td>4</td>
<td>Chloraspetic Relief Strips Benzocaine; menthol</td>
<td>Prestige Brands</td>
</tr>
<tr>
<td>5</td>
<td>Life-saving rotavirus vaccine to infants Johns</td>
<td>Hopkins undergraduate biomedical engineering students</td>
</tr>
<tr>
<td>6</td>
<td>Listerine Pocket Paks Breath Freshening Strips</td>
<td>Pfizer’s Warner-Lambert consumer</td>
</tr>
<tr>
<td>7</td>
<td>Methylcobalamin fast dissolving films, Diphenhydramine HCl fast</td>
<td>Hughes medical corporation</td>
</tr>
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<td></td>
<td>dissolving films, Dextromethorphan fast dissolving films, Folic Acid</td>
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<td>1mg fast dissolving films, Caffeine fast dissolving films</td>
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<td>8</td>
<td>Altoid Cinnamon Strips, Boots Vitamin C Strips, Cool Shock Peppermint</td>
<td>Dow Chemical Company</td>
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<td></td>
<td>Strips, Benzocaine Films, Caffeine</td>
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<tr>
<td>9</td>
<td>Energy Strips - Caffeine 20mg, Acetyl Salicylic Acid (Asa), Ondanset</td>
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<tr>
<td></td>
<td>ron Hcl, Dexamethasone, Nitroglycerine, Risperidone Vitamin B12,</td>
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<tr>
<td></td>
<td>Melatonin, Folic Acid, Biotin Benzocaine, Diphenhydramine Hcl,</td>
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<td>Dextromethorphan</td>
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**TABLE 10: LIST OF MARKETED FAST DISSOLVING FILMS**[^36]

**FUTURE PROSPECTIVE FOR MDTS**

Now there are various products available commercially in market which is produced by fast dissolving tablet technologies. Still there is wide area for research on this technology. Some of the challenges like formulating a drug of bitter taste and moisture absorbing nature create problems for formulation scientist. When the dose of drug is large it causes problem of increased disintegration time. The two points to be considered in case of MDTs are shortening the disintegration time at the same time keeping other parameters like friability, taste, and mouth feel and tablet strength within the accepted range. Using taste masking...
agents and super disintegrating without significant increase in the weight and volume of final dosage forms. Also there is a scope to develop better packaging system to make MDTs more stable during handling.

CONCLUSION
Fast disintegrating tablets technology gained more popularity in last decade. It emerged as a New Drug Delivery system for treating various patients and diseases. FDT offers advantages of both solid and liquid oral dosage forms. This system allows easy self administration without the need of water to swallow. Fast disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. It has provided new area for research and development both for industries and academics. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market. The primary attractive factor of MDT is quick disintegration in oral cavity without the aid of water, along with sufficient mechanical strength. This feature makes this formulation a highly recommendable choice for geriatric and pediatric patients. FDT in the near future is expected to grow at a great and rapid pace, owing to the advancement in the scientific research and discovery of new excipients, resulting in a future-ready, combative arena of pharmaceutical drug delivery systems.

REFERENCES


