REVIEW ARTICLE

Fast Disintegrating Drug Delivery Systems: A Review with Special Emphasis on Fast Disintegrating Tablets

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Abstract
The development of pharmaceutical technology in past years has presented the development of alternative dosage forms for patients who may have difficulty in swallowing of conventional tablets. Fast disintegrating drug delivery systems (FDDDSs) are the system which disintegrate and release the active ingredient quickly and that do not require water to aid swallowing. Among the FDDDSs, the fast disintegrating tablets (FDTs) are the more acceptable form of drug delivery system because of its convenience of self-administration and compactness. In the conditions (pediatric and geriatric patients, difficulty in swallowing, uncooperative patients), where the traditional tablets and capsules administration is inconvenient, the fast dissolving/disintegrating tablets are perfect alternative. According to European Pharmacopoeia, the FDT disintegrate in less than three minutes. The basic approach used in development of FDT is the use of superdisintegrants which provide instantaneous disintegration and thereby releasing the drug in saliva. Taste of the drug is one of the most important parameters which should be taken in account for the development of FDTs. Oral administration of bitter drugs with an acceptable degree of palatability can be achieved by taste masking approach. This communication reviews the applications and technologies involved in formulation of FDDDSs specially focused on FDTs.
INTRODUCTION

Oral route is the most preferable route for drug delivery, despite of several disadvantages associated with it. A number of oral dosage forms have been developed over the past two decades to improve patient compliance, bioavailability and to reduce the adverse effects. In this era, fast dissolving/disintegrating drug delivery system (FDDDS) began to gaining popularity and acceptance since they can disintegrate/dissolve quickly in the oral cavity upon contact with saliva, resulting in solutions or suspensions form of the administered medicine. Apart from favorable anatomic and physiologic features of the oral cavity that allow modulation of drug permeation, high degree of vascularization, minimal enzymatic pool and bypass hepatic metabolism make the oral cavity an ideal site for drug delivery. The Zydis (Catalent Pharma Solutions, Somerset, NJ) based on lyophilization technology is the first approved FDDDS (Claritin Reditabs, Schering Plough, Kenilworth, NJ) in the United States in 1996. Advantages of fast disintegrating drug delivery systems over conventional dosage forms include rapid drug absorption, quick drug therapy, convenience of administration and patient acceptance especially for pediatric, geriatric, dysphagic, psychiatric patients and travelers. These systems combine the advantages of both liquid formulations and conventional tablet formulations. In addition, pharmaceutical companies have found an opportunity to extend the product life cycle and to differentiate their products by offering new dosage forms. These systems are more useful where immediate rapid peak plasma concentration is required to achieve a desired pharmacological response. Because of the drug dispersion in saliva, pre-gastric absorption can take place from the buccal, pharyngeal or gastric regions. Most of the drugs are bitter in taste so taste masking of such drugs is of critical importance in the development of an acceptable FDDDS.

TYPES OF FAST DISINTEGRATING DRUG DELIVERY SYSTEM

Fast disintegrating drug delivery systems are broadly classified into three categories.

1. Orally disintegrating films and wafers
2. Fast disintegrating capsules
3. Fast disintegrating tablets

Fast disintegrating tablets have gained more popularity compared to other fast disintegrating delivery systems as these utilize standard equipment, and materials and their production costs are low. Most of these tablets are characterized by good mechanical strength, although this can result in an increase in the disintegration time of the tablet.

Films and Wafers

These are thin elegant films of edible water-soluble polymers of various sizes and shapes. The films are manufactured by preparing a non-aqueous solution of water soluble polymer such as carboxy methylcellulose (CMC), hydroxyl ethylcellulose (HEC), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), sodium alginate, etc. The FDDDS comprises thin, printable, low moisture, non-tacky films that are convenient for dosing, suitable for easy packing, handling and application. The films may be flexible or brittle, opaque or transparent, but are designed to provide rapid disintegration without the need of water. The orally disintegrating films have the advantage of large specific surface area for disintegration. At the same time, rapid hydration rate facilitates an almost immediate softening of quick dissolving film in the oral cavity. The wet-tack and mucoadhesive properties of the system are designed to secure the film to the site of application. A major limitation of these formulations is low drug loading capacity and limited taste masking options.

Many techniques are used for the manufacture of orally disintegrating films. Some of them include hot-melt extrusion, solid-dispersion extrusion, rolling and solvent casting technique. These techniques are used either alone or in combination to manufacture orally disintegrating films. The flexibility and strength of the film should be selected properly to facilitate automatic rewinding, die cutting and packing during manufacturing. The flexibility and strength are determined based on the tensile strength, elongation, Young’s modulus, blending length and tear resistance of the film. Examples of marketed oral fast disintegrating film are Betamethasone (APR Applied Pharma Research SA), Caffeine (FlatMints), Caffeine
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(Lavipharm Laboratories, Inc.), Dextromethorphan (APR Applied Pharma Research SA), Doxazosin (Labtec GmbH), Folic acid/B-12 (Watson), Loratadine (Lavipharm Laboratories, Inc.) and Loratadine (MonoSolRx, LLC).

XGel® film Technology was developed by BioProgress for the development of fast disintegration/dissolution film using water soluble polymers. XGel film potentially enhances the product stability. This product is derived from a non-animal source, so it is acceptable for vegetarians. The film can be coloured, layered or taste masked.

Rapidfilm®, a thin film, was developed by LabTec GmbH. The film is manufactured by laminating process. The rapid dissolution in saliva was ensured using water soluble polymers. Complete disintegration of the film occurs within 20 sec. Rapidfilm consists of a drug, water soluble polymers, softener and filler. Flavoring and sweetening agents are used to mask the unpleasant taste of drug. Rapidfilm is packed in boxes or in credit-card shaped RapidCard®.

Soluleaves technology is used to develop fast dissolving films. These films release the active ingredients when come in contact with the saliva. Soluleaves are designed in such a way that they adhere to the oral mucosa and allow the drug to release within 15 min.

Roh et al. compared pharmacokinetic parameters of an orally disintegrating film with a film coated tablet containing sildenafil in healthy Korean subjects. The results suggested that the pharmacokinetics of the orally disintegrating film of sildenafil did not differ significantly from those of the conventional film coated tablet formulations. The formulations were well tolerated with no serious adverse effects.

Preis et al. developed taste masked orodispersible films containing dimenhydrinate using cyclodextrin and maltodextrin as solubilizing and complexing agents. The films were evaluated by X-ray diffraction, scanning electron microscopy and polarized light microscopy. Two commercially available electronic taste sensing systems were used to evaluate the taste masking property. The results of X-ray-diffraction and polarized light microscopy study showed no recrystallization of dimenhydrinate. In vitro taste assessments revealed taste-masking effects of formulation.

Rapidly dissolving film of cetirizine hydrochloride using pullulan as a film forming agent was developed by Mishra and Amin. The films were formulated using solvent casting method. The films were investigated for the effect of type of casting surface and plasticizer on film separation and taste masking properties. Sweeteners, flavours and citric acid were used for taste masking. The in vitro and in vivo disintegration times were found to be 20 and 30 sec, respectively. The films exhibited satisfactory thickness, tensile strength, elongation and elastic modulus. Surface morphology suggested even distribution of drug in the film and uniformity of the film.

**Fast Disintegrating Capsules**

Fast disintegrating capsules for administration in the oral cavity are prepared either by perforation or by vacuum-drying of conventional capsules. When compared to other fast disintegrating dosage forms such as lyophilized sponges or tablets, capsules have various advantages. Particularly, high drug-loading capacity and absence of compression during manufacture are of importance. A US patent was granted in September 2004 for the development of fast disintegrating capsules using foamburst technology. In this technology, gas is blown into the film during development, resulting in a film with a honeycombed structure. The voids in the film may be empty, gas-filled or filled with other materials. The light honeycombed structure results in capsules that dissolve rapidly in the oral cavity.

**Fast Disintegrating Tablets (FDTs)**

Fast disintegrating tablets are the most common dosage form in fast disintegrating drug delivery system. These tablets have been given various names such as mouth dissolving, fast melting, fast dissolving, orodisperse, melt-in-mouth, fast disintegrating tablets. According to European Pharmacopoeia, the orodisperse tablets are those which disperse rapidly before swallowing, when placed in buccal cavity.
Fast disintegrating tablets are characterized by high porosity, low density, and low hardness. When administered, an *in-situ* suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed. Recently, the orally disintegrating tablet terminology has been approved by the Nomenclature and Labeling Committee of USP. The US-FDA (Food and Drug Administration) has defined FDT as a solid dosage form containing drug, which disintegrates rapidly when placed upon the tongue. The US FDA has specifically defined two main criteria to be fulfilled by the FDTs in its publication ‘Guidance for Industry: Orally disintegrating tablets’:23

1. Orally disintegrating tablets should have an *in vitro* disintegration time of approximately 30 sec or less.
2. The weight of orally disintegrating tablet should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factors into the acceptability of an orally disintegrating tablet for both patients and regulators.

The FDA guidance defines the upper limits of the orally disintegrating tablet category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an orally disintegrating tablet.

**Challenges in the Development of FDTs**

Formulation and manufacturing of FDTs is a great challenge for the formulation scientist, as they pose a number of problems in the manufacturing and quality control. For the formulation of a successful FDT, the formulation scientist should fulfill all the criteria given below:24

- The FDTs should disintegrate rapidly
- They should have sufficient mechanical strength
- FDT should have an acceptable size. Increase in tablet size should be avoided
- The FDTs should not leave any residue in mouth
- The FDTs should protect the drug from moisture
- The mechanical and disintegration properties of the FDTs should not be altered by the drug properties
- The developed FDTs should be compatible with the existing taste masking technologies
- The FDTs should allow good package design

**Advantages of Fast Disintegrating Tablets**

The FDTs show the following advantages, in comparison to the oral formulations:25

1. They provide high drug loading and good chemical stability as compared to liquids.
2. They are unit dosage forms, and hence, do not need measuring the dose, which is an essential drawback in the case of liquids.
3. They are suitable during travelling or other such situations where water may not be available.
4. They have a pleasing mouth feel, odor and taste along with sufficient strength to withstand manufacture, packaging, storage and handling.
5. The onset of action is rapid from FDTs, due to fast dissolution of drug.
6. FDTs are convenient to manufacture with existing processing machinery used in conventional tablets.

Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance, which in turn decides the commercial success of the product. To improve the palatability of a pharmaceutical product, many techniques have been developed, which have not only improved the taste of the product, but also the stability and performance of the product. Taste masking is of critical importance in the formulation of an acceptable FDT. Conventional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until it passes the oral cavity. The current methods of taste masking in FDTs include sweeteners and flavors. However, these are not sufficient means for taste masking of many bitter drugs. The primary method of taste masking includes adsorption onto or complexation with carriers and spray coating of drug particles.
Components of FDTs
Important components used in the formulation of FDTs should allow quick release of the drug, resulting in faster disintegration and dissolution. The main excipients used are super-disintegrants, sugar based excipients and taste masking agents. Excipients balance the properties of the active drug thus the chemistry of these excipients should be studied to prevent interaction with the active drug. The role of excipients is important in the formulation of FDTs because these when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. The excipients with good aqueous solubility will facilitate disintegration/dissolution. Saccharides such as mannitol, sucrose, lactose, glucose, and xylitol are used frequently in formulating FDTs. Mannitol is one of the most commonly used excipient for the development of FDTs because of its water solubility. It also produces a unique cooling sensation in the mouth and has a pleasant taste. Sucrose can act as a dry binder in the amorphous state by undergoing a phase transition, and also as a liquid binder during wet granulation.

Disintegration of FDTs
To ensure fast disintegration of tablet, water must quickly ingress into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Maximizing the porous structure of the tablet matrix and incorporating appropriate disintegrating agent or highly water soluble excipients in the tablet formulation are the basic approaches used in the current FDTs technologies. Basically, the major function of a disintegrant is to oppose the efficacy of the binder and the physical forces that act under compression to form the tablet. The disintegration and dissolving times may be further influenced by varying the formulation composition.

The FDT breaks down into smaller particles and then produces a homogeneous suspension or solution due to following mechanisms:

- Capillary action
- High swellability of disintegrants
- Capillary action and high swellability
- Chemical reaction (Release of gases)

Formulation and Manufacturing Technologies for FDTs
The performance of FDTs depends on the technologies used in their manufacturing. A number of basic formulation technologies have been employed for the formulation of FDTs, viz., freeze drying, spray drying, sublimation and cotton candy process. These technologies require specialized equipment and processes. The other technologies include compression, lyophilization, molding and mass-extrusion. All these technologies can be broadly classified into two categories, namely, those employing cold processes (non-heating) and those employing hot processes (heating).

Cold Process Technologies
Compression
The compression method is most popular and easiest way to manufacture FDTs, because of easy implementation, cost-effectiveness, use of conventional excipients and equipment. The basic need of compression method is the availability of super-disintegrants, water soluble excipients, effervescent agents and sugar based excipients. A direct-compression FDT formulation usually contains diluent, disintegrant, lubricant, flow-aid, flavor, sweetener, and color. FDTs can be manufactured by either granulation or physical mixing (using directly compressible excipients) techniques. Most effective super disintegrants for FDTs include modified cellulose, crosspovidone, microcrystalline cellulose, cross-linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone, sodium starch glycolate and partially substituted hydroxypropyl cellulose. These excipients absorb water due to the capillary action, swell and break the tablets. The optimum disintegration time can be achieved by means of critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to disintegrant concentration and above this, the disintegration time remains approximately constant or even may increase.
Sharma et al. developed taste masked fast disintegrating tablets of promethazine HCl via solid dispersion technique using Eudragit E100. The drug release studies were carried out in phosphate buffer (pH 6.2). The formulations were evaluated for in vivo taste determination. The tablet with drug polymer ratio of 1:4 did not give any taste of drug and shows minimum release in phosphate buffer (pH 6.2). The effect of crosspovidone and crosscarmellose was evaluated to find out effect of both the polymers on in vitro and in vivo disintegration time. Crosspovidone 20% w/w gave the minimum disintegration time. The tablets of the final formulation containing 38.16% mannitol and 9.14% of microcrystalline cellulose showed the minimum disintegration time of 23 sec. The taste evaluation of the tablets in comparison to quinine sulfate in human volunteers revealed a considerable taste masking.

Mizumoto et al. prepared fast disintegrating tablets using mannitol as a low compressible saccharide and maltose as a high compressible saccharide. The amorphous maltose present on the surface of mannitol particles absorbs moisture during the conditioning process (25°C and 70% RH) and recrystallized. When crystallization of maltose occurs, the particles adhere to each other, resulting in increased tablet hardness. The tablet hardness and disintegration time were found to be 4.0–5.8 kg cm$^{-2}$ and 10 to 15 s, respectively. The communication recommended lactose, sucrose, glucose, mannitol, erythritol and xylitol as low compressible saccharides and maltose, sorbitol, trehalose and maltitol as high compressibility saccharides.

Shimizu et al. developed fast disintegrating tablet containing enteric-coated microgranules of lansoprazole. The effects of enteric layer and compression on dissolution behavior were examined. The effect of methacrylic acid, ethyl acrylate methyl methacrylate and triethyl citrate on the dissolution in the acid and buffer stage was evaluated. The absorption properties of fast disintegrating tablet and lansoprazole capsules were compared in Beagle dogs. The absorption profiles of fast disintegrating tablets ($\text{AUC}_{0-8h} = 2.55 \pm 0.75$ mg h/mL) were similar to those of capsules ($\text{AUC}_{0-8h} = 2.55 \pm 0.95$ mg h/mL).

**Lyophylization**

Lyophylization allow drying of heat sensitive drugs and biological at low temperature conditions that allow removal of water by sublimation. Freeze drying or lyophylization process normally consists of following steps:

- The drug is dissolved/ dispersed in an aqueous solution of mannitol, gelatin, starch or hydrophilic gum and the resultant mixture is poured onto the blister film.
- Freezing the products at $-40^\circ\text{C}$ to $-50^\circ\text{C}$ by passing through a specially designed cryogenic freezing unit so that the water in the product becomes ice.
- Then under the reduced pressure, sublimating the ice directly into water vapor.
- Drawing off the water vapors.

Once the ice is sublimated, the products are freeze-dried.

Freeze-drying allows immediate dissolution of the dosage form because of high porosity, and enhances drug stability of moisture-sensitive drug substances; while, a porous structure is associated with low physical strength and high friability, thus special packaging is required. The lyophylization results in preparations which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Along with the poorly stable and fragile product other major disadvantages of this technology are that it is a relatively expensive and time consuming process.

Corveleyn and Remon reported the effect of various formulation and process variables on the characteristics of orally disintegrating tablets containing hydrochlorothiazide developed by lyophylization technique. Gelatin, hydroxyethylcellulose, maltodextrin, and xanthan gum were used to prepare tablets. The concentration of maltodextrin was found to affect the disintegration time, mechanical strength and pore size of the tablets. The hardness of tablets was increased proportionally with the increase in maltodextrin concentration. The mechanical strength of the tablets was also dependent on the xanthan gum concentration. The disintegration time of the tablet containing hydroxyethylcellulose was much shorter compared to those containing xanthan gum as a binder at the same concentration. Addition of
polyethylene glycol (PEG) 6000 (1%, m/V) resulted in an increase in drug release from the tablets within 10 min.

**Spray Drying**

In this technique, the processing solvent is evaporated rapidly by spray drying, which makes the product highly porous and thus can be used in manufacturing FDTs. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets.34

**Hot Process Technologies**

**Molding**

The preparation of FDTs using molding technology (solid dispersion) employs water-soluble ingredients so that the tablet dissolves completely and rapidly. Molding process is of two types, namely solvent method and heat method. The solvent method involves moistening powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. Tablets manufactured by this method are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated.

Laitinen et al.35 prepared solid dispersion to evaluate the dissolution behavior of perphenazine using 0.1 mol/l HCl solution. Various ratios of PEG 8000 and PVP K30 were used as carriers. It was observed that the dissolution rate of perphenazine was improved at all drug/polymer ratios compared to crystalline or micronized perphenazine. DSC and FTIR results showed that perphenazine dihydrochloride salt was formed and hydrogen bond formation occurred between perphenazine and the polymers.

Modi and Tayade36 used molding method to prepare oral disintegrating tablets of valdecoxib. Valdecoxib was kneaded with polyvinyl pyrrolidone (PVP K-30) and compressed into tablets. Release behavior of the developed tablet was compared with the commercial product. A phase solubility method was used to evaluate the effect of water soluble polymers on aqueous solubility of the drug. The study concluded that the molding technique improved release behavior of valdecoxib.

**Sublimation**

Camphor, ammonium bicarbonate, naphthalene, urea, and urethanes are inert solid ingredients, which volatilize readily. These ingredients are granulated with other excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, generating a porous structure, which leads to the rapid dissolution of the tablet. Cyclohexane and benzene can also use for the generation the porosity in the matrix.

Suresh et al. developed salbutamol sulphate oral disintegrating tablets using a volatile substance like camphor/ammonium bicarbonate. Study results showed that the physicochemical properties of tablets were within the official limits and disintegration time was 5-40 s.37

Comoglu et al.,38 examined the analgesic effect to relieve headache between the commercial tablets and fast disintegrating tablets of diclofenac potassium. The tebelets were developed by direct compression method using a sublimation approach against placebo. The in vivo study demonstrated that 50 mg diclofenac potassium, as a single dose of fast disintegrating tablets or commercial tablets, was effective in relieving the pain with more superior compared to placebo tablets.

Patel and Patel39 prepared oral disintegrating tablets of etoricoxib using sublimation technique. Granules containing drug, aspartame, sublimating agent (camphor/ammonium bicarbonate), crospovidone and
mannitol were prepared by the wet granulation method. Menthol was sublimed by exposing granules to the vacuum resulting in porous granules. The porous granules were subjected to compression. It was observed that the dissolution profile of etoricoxib was improved by sublimation technique.

**Cotton Candy Process**

Cotton candy process is also known as ‘candyfloss’ process and forms the basis of FlashDose technology. FlashDose is prepared using Shearform™ technology (patented by Fuisz Technology Ltd.) in association with Ceform TT™ technology. In candyfloss or shearform technology, the matrix is formed from saccharide or polysaccharide processed into amorphous floss by simultaneous action of flash melting at temperature between 180-266°F and centrifugal force. Thermolabile drugs can be incorporated by replacing sucrose with polymaltodextrins and polydextrose in the floss formulation. The matrix is then cured or partially recrystallized to produce good flow properties and compressibility. The candyfloss can be milled and blended with active ingredients and other excipients and subsequently compressed into tablets. However, the high processing temperature limits the use of this technology to thermostable compounds only. Shearform™ is a process of making microspheres as an alternative method of taste masking. The product is highly porous and offers a pleasant mouth feel due to fast solubilization of sugars.40

**Mass-Extrusion**

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using a heated blade to form tablets. The dried cylinder can also be used for taste masking of bitter drugs.

Rapamune was launched by Wyeth as the first product containing sirolimus NanoCrystals. The coated Rapamune tablets are more convenient and show a 27% increased bioavailability compared to the Rapamune® solution.41

**Patented Formulation Technologies**

Some patented formulation technologies, based on different mechanism, used to formulate the fast disintegrating tablets are described in Table 1. Each dosage form varies regarding its mechanical strength, stability, mouth feel, taste, rate of dissolution in saliva, swallow-ability, rate of absorption from the saliva solution and overall bioavailability. Currently, different products based on four fast-dissolving/disintegrating technologies are available the U.S. market: Zydis (R.P. Scherer Inc.), WOWTAB (Yamanouchi Pharma Technologies Inc.), and OraSolv and DuraSolv (Gima Labs Inc.). Products based on three others technologies are available outside the U.S. market FlashDose (Fuisz Technologies Ltd.), Flashtab (Prographarm Group), and OraQuick (KV Pharmaceutical Co. Inc.). However, Biovail Corp. filed an NDA for FDA approval for a FlashDose version of fluoxetine.43

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<th>Patented technology</th>
<th>Basic technology</th>
<th>Company</th>
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<td>Microcaps abd Direct compressed tablets</td>
<td>Eurand</td>
<td>AdvaTab Cetrizine, AdvaTab Paracetamol</td>
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<td>Effervescent system</td>
<td>Elan Corporation</td>
<td>Effervescent ibuprofen, acetaminophen,cimetidine, naproxen, and acetaminophen and codeine combination product</td>
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<td>Bioval (Fuisz Technology Ltd. (now Valeant))</td>
<td>Fluoxetine, Nurofen&lt;sup&gt;®&lt;/sup&gt; Meltlets Ibufrofen, Paroxetine, Ralivia FlashDose, Zolpidem</td>
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Using the concept of Gregory et al, Scherer has patented the Zydis technology. It was the first marketed new technology based fast disintegrating tablet. With more than 20 products launched in 50 countries, it is considered as the best orally disintegrating tablet (ODT) technology.

A lightweight and fragile Zydis tablet is produced by lyophilizing or freeze-drying the drug in a gelatin matrix and dispensed in a special blister pack. The Zydis product is dissolved in the oral cavity within 2 to 3 sec and no water is required. This formulation is considered to act as self-preserving because of the low water concentration in the freeze-dried product, which prevents microbial growth. Because of dispersion of drug in saliva, pre-gastric absorption can take place from buccal, pharyngeal and gastric regions, thereby increasing the oral bioavailability of drugs in comparison to the traditional tablets.

In Zydis technology, the amount of incorporated soluble drug should be less than 60 mg. The particle size of insoluble drugs should be in the range of 50-200 mm to prevent sedimentation during processing. Freeze-drying is a relatively expensive manufacturing process. Zydis formulation has poor stability at higher temperatures and humidity as it readily absorbs water and can undergo degradation. Utilizing a unique lyophilization process, Zydis® is produced via four-steps: 6,44,45

- **Step 1 – Mixing:** The liquid solution or suspension containing drug is formulated using polymeric structure (gelatin) and a saccharide (mannitol) in water. Mannitol crystallizes during freezing, thereby providing an elegant appearance and rigidity. Mannitol solubilizes readily and improves taste and mouth feel.
- **Step 2 – Filling and Freezing:** The above liquid containing drug is precisely filled into pre-formed blisters and passed through a specially designed cryogenic freezing process cooled with liquid nitrogen to control the size of ice crystals.
- **Step 3 – Lyophilization:** The above frozen units are then transferred to freeze dryers for the lyophilization process.
- **Step 4 – Sealing:** The blister containing dried Zydis® units are then sealed via a heat-seal process to protect the product from varying environmental conditions and ensure product stability.

**Lyoc Technology**
Lyoc, a patented technology of Farmlyoc, is a porous and solid galenic form based on lyophilization of an oil-in-water emulsion placed in the blister alveolus. It is manufactured by freezing a paste like emulsion containing drug as bulk or as coated microparticles. Lyoc disintegrates rapidly but possesses poor mechanical strength due to porous nature. 47,48
Orasolv Technology
Orasolv was Cima’s (a subsidiary of Cephalon, Frazer, PA) first fast-dissolving/dispersing dosage form. The OraSolv technology disperses in the saliva with the aid of a low effervescent. The tablet matrix prepared using this technology dissolves in less than one min, leaving coated drug powder. The taste masking associated with the Orasolv formulation is two-fold. This technology is frequently used to develop over-the-counter formulations. The OraSolv tablets have the appearance of traditional compressed tablets. However, the OraSolv tablets are lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. The major disadvantage of the OraSolv formulations is its mechanical strength. For that reason, Cima developed a special packaging system for Orasolv (patented packaging technology PakSolv, Cima Labs). An advantage that goes along with the low degree of compaction of Orasolv is that the particle coating used for taste masking is not compromised by fracture during processing. Lyophilization and high degrees of compression, as utilized in Orasolv’s primary competitors, may disrupt such a taste masking approach. The OraSolv technology is utilized in six marketed products. These formulations can accommodate more than 1.0 g of single or multiple drug(s). Their disintegration time is less than 40 sec. The OraSolv formulations are hygroscopic in nature due to the presence of effervescent agent, and hence, aluminum blisters are used to protect the drug from moisture.

Durasolv Technology
Durasolv is Cima’s second-generation fast-dissolving/disintegrating tablet formulation. A Durasolv tablet has much higher mechanical strength than Orasolv tablet due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tableting equipment and have good rigidity (friability less than that 2%). The Durasolv product is produced in a faster and more cost-effective manner. Due to the good mechanical strength, Durasolv can be packaged in traditional blister packaging, pouches or vials. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter-tasting drug to a patient’s taste buds. Therefore, the Durasolv technology is best suited for formulations including relatively small doses of active compound. The Durasolv formulations are also hygroscopic in nature due to the presence of the effervescent agent and use aluminum blisters to protect the drug from moisture.

Quicksov
Quicksov, a patented technology of Janseen Pharmaceutica, is a porous solid form based on lyophylization technology obtained by freezing an aqueous solution/dispersion of the drug followed by drying using excess of alcohol (solvent extraction). Quicksov disintegrates very rapidly. This technology can be used only for those drugs that are insoluble in the extraction solvent. The drug used in this technology should have low aqueous solubility and fine particle size.

FlashDose Technology
Fuisz Technologies has three oral drug delivery systems related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, Soft Chew and EZ Chew technologies paved the way for Fuisz’s most recent development, FlashDose. The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This system consists of fibers of molten saccharides (dextrose, lactose or sucrose) or polysacharrides. The drug is blended with floss fibers and other excipients and compressed into tablets. The process is carried out at elevated temperature and humidity to ensure complete conversion of amorphous sugar fibers to crystalline material. Biovail’s (Mississauga, Canada) Flashdose system is based on sugar-floss system. This procedure has been patented by Fuisz and is known as Shearform. The final product has a high surface area for dissolution and disperses/dissolves quickly once placed onto the tongue. FlashDose tablets consist of self-binding shearform matrix termed as ‘floss’. Shearform matrices are prepared by flash heat processing and are of two types:

- Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.
- Dual floss consists of a first shearform carrier material (termed base floss, contains a carrier and at least one sugar alcohol generally sorbitol), and a second shearform binder matrix ('binder floss' contains a carrier and xylitol).

Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as Ceform and serves as an alternative method of taste masking.

Frostab®
Frostab® is a fast melting tablet, patented by Akina, Inc. The tablet compressed form highly plastic granules obtained by combining the porous plastic material, the water penetration enhancing agent, binder and drug. It dissolves rapidly in the mouth while possessing good hardness with low brittleness.

Wowtab Technology
The WowTab fast-dissolving/disintegrating tablet formulation is available in the Japanese market for a number of years and recently introduced into the U.S. market. WowTab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given ‘WithOut Water’. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property) by fluidized bed granulation method to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the Wowtab formulation is a more stable to the environment than the Zydis or OraSolv. It can be packed in conventional bottle or blisters. The Wowtab claims to offer superior mouth feel due to the patented Smoothmelt action. The Wowtab product dissolves quickly within 15 sec.

FlashTab technology
Prographarm laboratories have patented the FlashTab technology. This technology involves the preparation of rapidly disintegrating tablet by direct compression method. In this technology two different types of disintegrants are used: a disintegrant having high swelling force (e.g., modified cellulose), and a disintegrant having low swelling force (e.g., starch). Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the steps utilize the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one min.

Pharmaburst™
Pharmaburst™ is a co-processed excipient system patented by SPI Pharma Inc (New Castle, DE). Pharmaburst™ allows FDDDSs production with standard tablet press and tooling with high robustness, low friability and fast disintegration. This technology allows the product packaging in blisters or bottles using standard packaging equipment. Thus this technology reduces the manufacturing cost of the product.

Ora-Quick Technology
The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceuticals claims its microsphere technology, known as Micro mask, 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 it appropriate for heat-sensitive drugs. KV Pharmaceuticals also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable and achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution, with good taste masking. There are no products using
the OraQuick technology currently on the market, but KV Pharmaceutical has products in development stage such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

**Quick-Dis Technology**
Lavipharm Laboratories Inc (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system. The novel intraoral drug delivery system, Quick-Dis™, is Lavipharm's 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, time at which the film begins to break, 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 sec for Quick-Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by Quick-Dis™ is 50% and 95% released within 30 sec and 1 min, respectively.62,63,64

**Ziplet technology**
Ziplet technology patented of Eurand is based on molding of water insoluble drugs with the formulation excipients. This technology uses the addition of a water insoluble inorganic excipient with disintegrants. The water insoluble inorganic excipients enhance disintegration characteristics of tablets in comparison to water soluble sugars.65

**NanoCrystal Technology**
NanoCrystal technology, patented by Elan's for the development of fast dissolving tablets, can enable formulation to improve the product performance. NanoCrystal technology decreasing particle size and increases the surface area leads to an increase in dissolution rate. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm, which are produced by milling the drug substance using a proprietary wet milling technique.66 NanoCrystal fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet.
- Product differentiation based upon a combination of proprietary and patent-protected technology elements.
- Cost-effective manufacturing processes that utilize conventional unit operations.
- Wide range of doses per unit (up to 200 mg).
- Use of conventional, compendial inactive components.

The products are developed by combining NanoCrystal colloidal dispersions of drug with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and then lyophilized. This approach is especially attractive when working with highly potent or hazardous materials as it avoids various manufacturing operations, like granulation, blending, and tableting, that generate large quantities of powder dust and cause higher risk of exposure. This approach is also enables small quantity of drugs to be converted into fast dissolving tablets because manufacturing loss is negligible.

**CONCLUSION**
The development of orally disintegrating tablets is aimed to increase the performance of dosage form by decreasing the disintegration time and increasing the patient compliance by masking the unacceptable taste of drug. These systems are in general suitable for children and unconscious patients where the administration of conventional tablets is not possible. There are about 100 drugs that have been developed and marketed as fast disintegrating dosage forms using various technologies. Lyophylization is one of the best approaches used to develop such system for moisture sensitive drugs. The tablets formulated by direct compression have good mechanical strength and by considering this benefit a majority of oral fast dissolving systems are formulated as fast disintegrating tablet.
DECLARATION OF INTEREST
It is hereby declared that this paper does not have any conflict of interest.

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