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Fast Dissolving Tablets: A New Venture in Drug Delivery

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ABSTRACT

Despite disadvantages, oral drug delivery remains the preferred route of drug delivery. Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. FDTs are intended and designed to disintegrate and dissolve in saliva and then easily swallowed without need of water, which is a major benefit over conventional dosage form. Fast dissolving tablets can be prepared by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, and sublimation. Some of the patented technologies with improved performance, patient compliance, and enhanced quality have emerged in the recent past. In 1986, the first lyophilized fast-dissolving technology Zydis was introduced by Cardinal formerly R. P. Scherer and after that there was a continuous growth in names, technologies & patented technology by different companies such as Wowtab technology, oraquick technology etc. Various excipients are employed in the formulation for example superdisintegrants such as crospovidone (CP), sodium starch glycolate (SSG), croscarmellose sodium and PVP as binder and many more. The review also covers the evaluation parameters including pre-compression and post compression parameters and packaging of FDTs. There are multiple fast-dissolving OTC and Rx products on the market worldwide, most of which have been launched in the past 3 to 4 years. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology. Thus, in near future, it is expected that this delivery system will get much importance as that of conventional delivery systems. This article provides a comprehensive review of various technologies.

Key Words: Oral delivery, fast dissolving tablet, drug delivery, Novel dosage forms.

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INTRODUCTION

Due to a society that is becoming increasingly aged, the development of an appropriate dosage form for the elderly is most desirable. Because the changes in various physiological functions associated with aging including difficulty in swallowing, current dosage forms, like tablets and capsules, are impractical [1] In accordance with the transition to an aging society and changes in the living environment, a demand has arisen for the development of drug dosage forms that can be readily handled and taken by the elderly, children, or patients whose intake of water is restricted [2]

One study showed that approximately 26% of 1576 patients do not take their prescribed medication as they encountered problems when swallowing conventional tablets. Often, the main complaints are the size, surface and taste of the tablets. An estimated 35% of the general population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy [3].

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and is also seen in swallowing conventional tablets and capsules, which results in high incidence of non-compliance and ineffective therapy. Recent advances in the novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one which will rapidly disintegrate or dissolve in the mouth without the need of water; fast dissolving tablets (FDT) [3, 4, 5]

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance[6]

Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets

that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people[7]

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar[5, 6].

The US Food and Drug Administration (FDA) centre for drug evaluation and research defines the FDT formulation in the "orange book as ''a solid dosage form containing medicinal substances which disintegrates/dissolves rapidly, usually within a matter of seconds, when placed upon the tongue''. The tablets disintegrate into smaller granules or melt in the mouth from a hard solid structure to a gel like structure, allowing easy swallowing by the patients. The disintegration time for those tablets varies from a few seconds to more than a minute[8, 9].

Oral fast dissolving tablets (FDTs) help overcome some of these problems: the rapid disintegration of the tablet into a solution (containing the drug) enables those who find difficulty in or experience discomfort when swallowing (dysphagia) and to have a more 'patient friendly' experience[10].

There are several synonyms in use of FDTs like orodispersible, orally disintegrating tablets, quick dissolving tablet, fast melt tablets, rapid disintegrating tablets and freeze dried wafers. These tablets releases the medicament in the mouth for absorption through local oromucosal tissue and through pre-gastric (Oral cavity, Pharynx, and oesophagus), gastric (stomach) and post-gastric (small and large intestine) segments of Gastro Intestinal Tract (GIT) [8].

Fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients [11].

Oral fast-dissolving dosage forms, also known as 'fast-melt', 'fast-disintegrating' or 'mouth-dissolving' dosage forms, are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form, be it a tablet (the most common form) or a capsule , into a solution or suspension in the mouth without the need for water [10]. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration. The solution containing

the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect [12].

Despite the growing popularity and success of FDTs over the past decade, many FDTs still face problems of low mechanical strength, high friability and poor disintegration times. The European Pharmacopoeia describes fast-disintegrating tablets or 'orodispersable' tablets as uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed, and as tablets which should disintegrate within 3 min[10].

Recently, European Pharmacopoeia has used the term ''Orodispersible tablet'' for tablets that disperses readily and within 3 min in mouth before swallowing[13].

FDTs improve drug dissolution as well as onset of clinical effect and the pregastric absorption of drugs, which avoids first pass hepatic metabolism to reduce the dose than those observed from conventional dosage forms and finally, increase the bioavailability of drugs [14, 15].

Moreover, drug candidates that undergo pre-gastric absorption when formulated as orally disintegrating tablets may show increased oral bioavailability. The key parameters that are to be considered in the process of formulating an orally disintegrating tablet are taste and the disintegration time. Both of these are related either directly or indirectly to the oral cavity. Of the total oral mucosa, 15% of it consists of specialized mucosa, which is present on the dorsum of the tongue. It is mainly involved in identifying the taste of the formulation. Saliva is mainly constituted by water (99.5% w/v) and the remaining 0.5% w/v is constituted by dissolved compounds. The principal components of saliva are inorganic electrolytes (0.2%w/v), gases (CO2, N2, and O2), nitrogen products, such as urea and ammonia, vitamin C, creatinine, and mucins. The accepted range of normal salivary flow is comprised from about 0.1 to 0.2 mL/min and reaches 7 mL/min upon stimulation [16].

Desired Criteria for Fast Dissolving Tablets[17, 18]

- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- It should have pleasant mouth feel.
- Should have an acceptable taste masking property.
- It should have sufficient hardness to withstand rigors during manufacturing processes and post manufacturing handling.
- It should allow high drug loading.
- Should leave minimal or no residue in mouth after disintegration.
- Should exhibit low sensitivity to environmental conditions (temperature and humidity).

- Should allow the manufacture of tablet using conventional processing and packaging equipments.
- It should be cost effective.

Advantages of Fast Dissolving Tablets[17, 19]

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients.
- Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- Good mouth feel property of Mouth dissolving drug delivery system helps to change the basic view of medication drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Beneficial in cases such as motion sickness (kinetosis), sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.

Limitations of Fast Dissolving Tablets[19, 20, 21]

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Patients who concurrently take anticholinergic medications may not be the best candidates for FDTs and patients with Sjogren's syndrome or dryness of mouth due to decreased saliva production may not be the good candidates for these tablet formulations.
- FDTs are hygroscopic in nature, so must be kept in dry place.
- FDTs require special packaging for proper stabilization and safety of stable product.

THE NEED FOR DEVELOPMENT OF FDTs [20, 22, 23, 24]

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes. The paediatrics and geriatric populations are the primary targets, as both the groups found it difficult to swallow conventional tablets.

Patient factors

Orally fast dissolving 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:

- Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- 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.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

Effectiveness factors:

- Increased bioavailability and faster onset of action are a major claim of these formulations. Because the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention and increased bioavailability of drugs are possible.
- The pre-gastric drug absorption avoids the first-pass metabolism and drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.
- 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.

Manufacturing and marketing factors:

- Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size.
- 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 under-treated patient populations.
- As examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy.

  Merck's Japanese subsidiary launched Lipola M (simvastatin FDT), a line extension of its blockbuster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004.
- Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient population.

CHALLENGES IN FORMULATING FDTs [15, 20, 23, 25]

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. Henceforth, 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.

SELECTION OF THE FDTs DRUG CANDIDATES [23, 26, 27]

Several factors must be considered when selecting drug candidates for delivery as FDT dosage forms:

- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form**.** e.g. selegiline, apomorphine, buspirone etc.
- The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT**.**
- Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.

- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs**.**
- Patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
- Drugs which are having short half-life and needs frequent dosing, which are very bitter or either having unacceptable taste whose taste masking cannot be achieved or which require controlled or sustained release are inappropriate for FDT formulation.

POTENTIAL CANDIDATE FOR FDTs [20, 24, 25, 28]

Analgesics and Anti-inflammatory Agents: Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim.

Anthelmintics: Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, 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, Probenecid, 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-migraine Agents: Dihydroergotamine Mesylate, Ergotamine Tartrate, MethysergideMaleate, Pizotifen Maleate, Sumatriptan Succinate.

Anti-neoplastic Agents and Immunosuppressants: Aminoglutethimide, Amsacrine,Azathioprine, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide.

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

Anti-parkinsonian Agents: Bromocriptine Mesylate, Lysuride Maleate.

Anxiolytic, Sedatives, Hypnotics and Neuroleptics: Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole.

TECHNOLOGIES USED FOR MANUFACTURING OF FDTs

The technologies used for manufacturing of FDTs broadly classified in two categories:

Non-Patented Technologies: Freeze drying, Tablet molding, Spray drying, Mass extrusion, Melt granulation, Cotton candy process, Sublimation, Phase transition process and Direct Compression.

Patented Technologies:

Zydis technology, Orasolv technology, Durasolv technology, Wowtab technology, Dispersible tablet technology, Flashtab technology, Oraquick technology, Lyoc technology, Nanocrystal technology, Frosta technology, Pharmabrust technology.

Non-patented Technologies:

Lyophilization or Freeze-Drying:

A process in which water is sublimated from the product after freezing is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. A typical procedure involved in the manufacturing of FDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the

freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze- drying technique has demonstrated improved absorption and increase in bioavailability [11, 29, 30].

Tablet Molding:

Tablets prepared by this method are solid dispersions. The drug can exist as discrete particles or micro particles in the matrix. Molded tablets are less compact than compressed tablets, with a porous structure that facilitates rapid disintegration and easy dissolution. Molded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But molded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength [8, 30].

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as compression moulding). Then the solvent can be removed by air-drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen [31]. The heat moulding 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. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated [32].

Spray Drying:

This technology produces highly porous and fine powders as the processing solvent is evaporated during the process. In this method to prepare FDTs hydrolyzed and nonhydrolyzed gelatine were used as supporting matrix, mannitol as bulking agent and sodium starch glycolate or crosscarmellose sodium as superdisintegrant. Disintegration and dissolution were further increased by adding acidic substances like citric acid or alkali substance like sodium bicarbonate. This formulation technique gives porous powder and disintegration time < 20 sec [33]

Mass Extrusion:

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 cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste [22].

Melt Granulation:

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water soluble drugs, such as griseofulvin This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilizes rapidly leaving no residues [34].

Cotton Candy Process:

Another technology for manufacturing fast dissolving tablets is the cotton candy process, also known as candy floss process, which involves centrifugation to produce a floss-like crystalline structure. In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shear foam process. The matrix is cured and milled to make flowable, compactible, and highly soluble filler. Because of the formation of the formation of porous three-dimensional structures with the active ingredients encased in the pores, the resulting surface area is high. Therefore, dispersion and dissolution occur quickly when the product is placed in the mouth. This technology is patented as FlashDose® by Fuisz Technology (Chantilly, Virgina, U.S.A.) [35].

Sublimation Process:

The key to rapid disintegration of FDT is the preparation of a porous structure in the tablet matrix. To generate such a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, menthol, camphor, naphthalene, urea, urethane or phthalic anhydride could be compressed along with other excipients into a tablet. The volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique are reported to usually disintegrate in 10- 20 sec. Even solvents like cyclohexane, benzene could be used as pore forming agents. Koizumi et al. (1997) applied the sublimation technique to prepare highly porous compressed tablets that were rapidly soluble

in saliva. Mannitol and camphor were used, respectively, as tablets matrix and subliming material. Camphor was vaporized by subliming in vacuum at 80°C for 30 min to develop pores in the tablets. Gohel et al. (2004) used camphor along with Crospovidone to prepare fast disintegrating tablets of nimesulide [36].

Phase Transition Process:

Kuno et. al., investigated processes for the disintegration of FDTs by phase transition of sugar alcohols using erythritol (m. pt. 122°C), xylitol (m.pt. 93-95°C), trehalose (97°C), and mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol [33, 37].

Direct Compression Method:

Direct compression is the easiest way to manufacture tablets and, therefore, FDTs. The great advantage of direct compression is the low manufacturing cost. It uses conventional equipment, commonly available excipients, and a limited number process steps. Moreover, high doses can be accommodated in FDTs, the final weight of which can easily exceed that of other production methods. The direct-compression tablet's disintegration and solubilization are based on the single or combined action of disintegrants, water-soluble excipient and effervescent agents. The disintegration time is, in general, satisfactory, although the disintegrating efficacy is strongly affected (and limited) by tablet size and hardness. Large, hard tablets can have a disintegration time greater than that usually required for FDTs. As a consequence, products with optimal disintegration properties often have a medium–small size (weight) and/or a low physical resistance (high friability and low hardness). Breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of the blister alveolus all result from insufficient physical resistance [38]. Direct compression is viewed as the technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs [36]. This technique can now be applied to preparation of FDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants: In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of

disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar Based Excipients: This is another approach to manufacture FDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose,mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. 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 maltilol) exhibit high mouldability and low dissolution rate [32].

Table 1 shows some the superdisintegrants used in preparation of fast dissolving tablets.

Table 1: Super-Disintegrants used in FDTs [39, 40]

Super Disintegrants	Nature	Properties	Mechanism	Trade Names
Crospovidone	Crosslinked homopolymer of N-vinyl-2-pyrrolidone	Particle size 100 µm, Insoluble in water	Both Swelling and Wicking	Kollidon, Polyplasdone
Croscarmellose Sodium	Crosslinked form of sodium CMC	Particle size 200 mesh, insoluble in water	Swelling	Ac-di-sol, NYMEE 25X, NYMCEL
Sodium Starch Glycolate	Crosslinked low substituted carboxy methyl ether of polyglycopyranose	Particle size 140 mesh, insoluble in organic solvents	Water uptake followed by rapid swelling	Explotab Primojel
Acrylic acid derivatives	Poly (acrylic acid) super porous hydrogel	Particle size 106 µm	Wicking action	
Effervescent mixture	Citric acid, tartatic acid, sodium bicarbonate	Crystalline nature	Effervescence	
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water	Swelling	
NS-300	Carboxy methyl cellulose	Particle size 106 µm	Wicking type	
ECG-505	Calcium salt of CMC	Particle size 106 µm	Swelling type	
L-HPC	Low hydroxyl propyl cellulose	Particle size 106 µm	Both swelling and wicking type	

Patented Technologies:

Some of the important patented technologies for preparation of FDTs and the list of patented technologies and their products are given in Table 3.

Table 2: Some of the important patented technologies for preparation of FDTs [22, 23, 41]

S.No	Technique	Novelty	Advantages	Disadvantages
1.	Zydis	First to market, Freeze Dried	Quick dissolution, Self-preserving and increased bioavailability	Expensive process, poor stability at higher temperature and humidity
2.	Orasolv	Unique taste-masking, lightly compressed	Taste-masking is twofold, quick dissolution	Low mechanical strength
3.	Durasolv	Compressed dosage form, Proprietary taste masking	Higher mechanical strength than Orasolv, Good rigidity	Inappropriate with larger dose
4.	Flashdose	Unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy	High surface area for dissolution	High temperature required to melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity
5.	Flashtab	Compressed dosage form containing drug as microcrystal	Only conventional tabletting Technology	------
6.	Wowtab	Combination of low mouldability and high mouldability saccharides. SMOOTHMELT action gives superior mouth feel	Adequate dissolution rate and hardness	No significant change in bioavailability
7.	Oraquick	Uses patented taste masking technology	Faster and efficient production	------
8.	Ziplet	Incorporation of water insoluble inorganic excipients for excellent physical performance	Good mechanical strength, satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg)	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution

Table 3: List of patented technologies and their products [23, 27, 34, 41, 42]

S.No	Technology	Process Involved	Patent Owner	Drugs Used (Brand Name)	Drug Release
1.	Zydis	Lyophillization	R.P. Scherer Inc.	Loratidine (Claritin Reditab and Dimetapp quick dissolve)	Dissolves in 2-10 sec.
2.	Quicksolv	Lyophillization	Jansen Pharmaceuticals	Cisapride monohydrate (Propulsid Quicksolv)	------
3.	Flashtab	Lyophillization	Ethypharm	Ibuprofen (Nurofen Flashtab)	Dissolves within 1 min.
4.	Lyoc	Multiparticulate Compressed tablets	Farmlyoc	Phloroglucinol Hydrate (Spasfon Lyoc)	------
5.	Orasolv	Compressed tablets	Cima Labs Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Rapimelt	Disintegrates in 5-45 sec.
6.	Durasolv	Molding	Cima Labs Inc.	Hyoscyamine Sulphate (NuLev),	Disintegrates in 5-45 sec.

7.	Rapitab	Compressed tablets	Schwarz Pharma	------	------
8.	Wowtab	Multiparticulate Compressed tablets	Yamanouchi PharmaTechnologies, Inc.	Famotidine (Gaster D)	Disintegrates in 5-45 sec.
9.	Fast Melt	Molding	Elan Corp.	------	------
10.	Ziplets	Molding	Eurand	Ibuprofen (Cibalgina Due Fast)	------
11.	Flashdose	Cotton-candy process	Fuisz Technology Ltd.	Tramadol Hcl (Relivia Flash dose)	Dissolves within 1 min.
12.	Oraquick	Micromask Taste masking	KV Pharm. Co, Inc.	Hyoscyamine sulphate ODT	------
13.	Advatab	Microcaps and diffuscap CR Technology	Eurand International	Advatab Cetrizine, Advatab Paracetamol	Disintegrates in less thab 30 sec.
14.	Fuisz	Sugar based matrix known as floss	Fuisz pharmaceutical Ltd.	Diphenydramine & Pseudoephedrine	-------

EXCIEPIENTS USED TO PREPARE FDTs [21, 43]

Superdisintegrants:

Crospovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pre-gelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good Flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

Flavours:

Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptos oil thyme oil, oil of bitter almonds. Flavoring agnets include, vanilla, citus oils, fruit essences.

Sweeteners:

Aspartame, Sugars derivatives.

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:

Sodiumdoecylsulfate,sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.

Binder:

Polyvinylpyrrolidone(PVP), Polyvinylalcohl(PVA), Hydroxypropyl methylcellulose(HPMC).

Colour:

Sunset yellow, Amaranth etc.

Lubricants:

Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

EVALUATION OF ADJUVANTS

Precompression Parameters:

Prior to compression into tablets, the blend was evaluated for properties such as:

Angle of Repose (θ):

The frictional forces in case of loose powder are measured by the angle of repose. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by funnel method.

Angle of Repose was calculated using the formula:

$\tan \theta = 2h/d$

$\tan \theta = h/r$

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

Where, θ = Angle of repose

H = height of the pile (cms)

r = radius of heap (plane surface occupied by the powder) [44, 45]

Table 4 shows the angle of repose and their flow characteristics.

Table 4: Angle of repose as an indication of powder flow properties

S.No.	Angle of Repose(°)	Type of Flow
1.	<20	Excellent
2.	20-30	Good
3.	30-40	Passable
4.	>40	Very Poor

Bulk Density (D_b):

It is the ratio of total mass of powder (M) to the bulk volume (V_b). Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is".

Bulk density (expressed in gm/ml) was calculated according to formula mentioned below:

$D_b = M/V_b$

Where, M = Mass of the Powder

V_b= Bulk volume of the powder [46, 47].

Tapped Density (D_t):

It is the ratio of total mass of powder to the taped volume of powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 seconds interval. The tapping was continued until no further change in volume was noted.

Tapped density (expressed in gm/ml) was calculated according to formula mentioned below:

$D_t = M/V_t$

Where,

M = Mass of the Powder

V_t = Tapped volume of the powder [46, 48].

Carr's Index (Carr's Consolidation Index):

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

% compressibility (I) = [Tapped density – Bulk density/ Tapped density] x 100 [45].Table 5 shows the relationship between % compressibility and Flowability.

Table 5: Relationship between % compressibility and Flowability

S. No.	% Compressibility	Flowability
1.	5-12	Excellent
2.	12-16	Good
3.	18-21	Fair passable
4.	23-35	Poor
5.	33-38	Very Poor
6.	<40	Very Very Poor

Hausner Ratio:

It is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner ratio= Tapped density/ Bulk density

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25) [45].

Porosity:

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by:

€= Vb - Vp/ Vp =1- Vp/ Vb

Porosity is frequently expressed in percentage and is given as:

% € = (1 - Vp/ Vb) X 100 [28].

EVALUATION OF FAST DISSOLVING TABLETS

Tablets from all the formulation were subjected to following quality control test.

General Appearance:

The general appearance of a tablet, its visual identity and overall elegance is essential for consumer acceptance. It indicates tablet size, shape, colour, presence or absence of an odour, surface texture, physical flaws, consistency and legibility of any identification markings [40].

Size and shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled [40].

Tablet Thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer [49] Thickness of the tablet is measured by using vernier callipers. It is expressed in mm [50].

Uniformity of weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity [49, 51] Table 6 shows the average weight of the tablets and their % deviation.

Table 6: Average weight of the tablets and their % deviation

S. No.	Average Weight of Tablets (mg)	Maximum percentage difference Allowed
1.	130 or less	±10
2.	130-324	±7.5
3.	More than 324	±5

Tablet hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester or Pfizer hardness tester. It is expressed in Kg/cm^2. [45, 49].

Friability:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that

rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula:

% Friability = $[(W_1-W_2)100]/W_1$

Where,

W_1= Weight of tablet before test (Initial Weight)

W_2 = Weight of tablet after test (Final Weight)

Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%) [52].

Wetting Time:

Five circular tissue papers were placed in a Petri dish of 10-cm diameter. 10 ml of water containing 0.5% eosin, a water-soluble dye, was added to the Petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the Petri dish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in a replicate of six. Wetting time was recorded using a stopwatch [53].

Water Absorption Ratio:

A small piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed. Water absorption ratio, R was determined by using following formula given:

$R= 100 \times Wa-W_b / W_b$

W_b is the weight of tablet before water absorption

W_a is the weight of tablet after water absorption [54, 55].

Moisture uptake studies:

Moisture uptake studies for FDTs should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37°C for 24 h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded [55, 56].

In-vivo Disintegration test:

The test was carried out on 6 tablets using the apparatus specified in I.P 1996 distilled water at 37ºc±2ºc was used as a disintegration media and the time in seconds is taken for complete disintegration of the tablet with no particulate matter remaining in the apparatus was measured in seconds [39, 40].

In-vitro dispersion time:

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of sorenson's buffer pH 6.8. Three tablets from each formulation was randomly selected and in-vitro dispersion time was performed [40, 48].

Dissolution test:

The development of dissolution method for FDT is comparable to approach taken for conventional tablets and is practically identical when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1NHcl, pH 4.5 and pH 6.8 buffers should be used for evaluation of FDT. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets, where a paddle speed of 50 rpm is commonly used. The USP 1 (basket) apparatus may have certain applications for FDT but used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile [40, 57].

Stability Study (Temperature Dependent):

The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C

(ii) 50 ± 1°C

(iii) 37 ±1 ° C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegration, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C [43].

PACKAGING OF FDTs [39]

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 wit 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 pushthrough blisters or in bottles.

FUTURE PROSPECTS

Although the FDT area has passed its infancy, as shown by a large number of commercial products on the market there are still many aspects to improve in the FDT formulations. Despite advances in the FDT technologies, formulation of hydrophobic drugs is still a challenge, especially when the amount of drug is high. The low dose drugs, such as Loratadine with 10 mg dose, pose little problem, but as the dose increases, the formulation sacrifices its fast disintegrating property. A new technology is being developed to incorporate higher doses of hydrophobic drugs without affecting the fast disintegrating property.

The disintegration times of most FDTs on the market are acceptable—i.e., less than 60 seconds—but certainly there is a room for improvement. Because the disintegration time is related to other formulation variables, a balance has to be maintained between shortening the disintegration time and other tablet properties. The tablet hardness, friability, and stability can be further improved to such a level that multi-tablet packaging in conventional bottles becomes a norm.

The future of FDTs lies in the development of FDTs with controlled release properties. If one FDT can deliver drugs with short half-lives for 12–24 hours, it would be a quantum improvement in the FDT technology. The added convenience and compliance of such formulations would be enormous. The future of FDTs also lies in the development of effective taste-masking properties. The use of coating poorly tasting drugs is commonly used, but it increases the total volume of the final formulation. There may be no magic solution to this, but more effective use of existing taste masking technologies is expected to alleviate the problems associated with taste masking.

In addition, the ability to formulate drugs in large doses will bring another important technological advancement. In general, the FDT formulations require large amounts of excipients, and having large doses of drug will only make the final formulation too big to handle. An FDT formulation that would require fewer excipients than the drug itself would be a breakthrough. While the problems to be solved are not easy, the history suggests that it is just a matter of time before they are solved.

A number of companies are having their own brands of fast dissolving tablets. The availability of various technologies and the multiple advantages of fast dissolving tablets will surely increase its popularity in the near future. In future, a day may come where these fast dissolving tablets due to their remarkable advantages may replace 50 to 60% of the conventional products.

CONCLUSION

Fast dissolving tablets have potential advantages over conventional solid oral dosage form because this drug delivery system helps to overcome some of the problems associated with conventional solid dosage form. i.e. difficulty in swallowing of tablet in paediatric and geriatric patients. This drug delivery is one of the great inventions of all the novel drug delivery systems. They have improved patient compliance, convenience, bioavailability, rapid onset of action. However, common people are not much aware of this delivery system. Therefore, pharmacists are responsible to spread the knowledge regarding this system. This dosage form should be handled carefully since they do not have sufficient mechanical strength. Patients who suffer from dryness of mouth should not be prescribed with FDTs, since minimum volume of saliva is necessary for it to disintegrate/dissolution. This dosage form is very much suitable for paediatric patients who having no primary teeth and for geriatric patients who have lost their teeth permanently. Thus, in near future, it is expected that this delivery system will get much importance as that of conventional delivery systems.

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