FAST DISSOLVING TABLETS: PREPARATION, CHARACTERIZATION AND EVALUATION: AN OVERVIEW

Md.Nehal Siddiqui*, Garima Garg, Pramod Kumar Sharma
Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Baghpat Bypass,Delhi Roorkee Highway, Meerut-250005, U.P.
***Email:** nehalmiet786@gmail.com

ABSTRACT

Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Recently researcher developed the fast dissolving tablet (FDT) with improved patient compliance and convenience. FDTs are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. FDTs overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in pediatric and geriatric patients. This review includes ideal properties, characteristics, challenges in formulation, suitability of drug candidates, various technologies developed for FDT, patented technologies, evaluation methods and various marketed products.

Keywords: Fast dissolving tablet, Oral route, Excipients, Oral dissolving tablet.

INTRODUCTION

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms.Tablet is still most popular conventional dosage forms existing today because of ease of self administration ,compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance[1]. Difficulties in swallowing of tablet and capsule are also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection[2]. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[2].

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."

Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients[3,4]. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form[5]. The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute[6-9].

The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking[10,11]. In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability, convenience and patient compliance. Some tablets are designed to dissolve in saliva within a few seconds, and so called true fast-dissolving tablets. Fast dissolving technology offers following advantages[11-16],

- Improved compliance/added convenience
- No water needed
- No chewing needed
- Better taste
- Improved stability
- Suitable for controlled as well as fast release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery
- Cost- effective.

SALIENT FEATURES OF FDTs

- does not require water for oral administration
- have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling
- allow high drug loading
- Insensitive to environmental conditions such as humidity and temperature
- Adaptable and amenable to existing processing and packaging machineries
- Cost effective.
- have a pleasant mouth feel[17]

THE NEED FOR DEVELOPMENT OF FDTs

Patient factors[18,19]: Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- patients who have difficulty in swallowing or chewing solid dosage forms
- patients incompliance due to fear of choking
- very elderly patients of depression who may not be able to swallow the solid dosage forms
- an eight-year old patient with allergies desires a more convenient dosage form than antihistamine syrup
- a middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker
- a schizophrenic patient 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 factor

Dispersion in saliva in oral cavity causes pre-gastric absorption of drug which dissolves. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass hepatic metabolism which increase the bioavailability. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

Manufacturing and marketing factors

As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and 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 ODT), a line extension of its block-buster, 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 in this way company's reputation can be improved.

CHARACTERISTICS:

FDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Traditional tablet formulations generally do not require taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overcome the bitter taste of the drug[20]. In fast dissolving/disintegrating tablets include sweeteners and flavors for taste-masking but many bitter drugs are not masked by taste masking agent. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of drug particles[21].

LIMITATIONS: [19]

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required during manufacturing process.
- The tablets may leave unpleasant taste and/or grittiness in oral cavity if not formulated properly.
- Drugs with larger doses are difficult to formulate into FDT e.g. rifampin (600 mg), ethambutol (1000mg) etc.

INGREDIENTS TO BE USED FOR FDTs

This includes both the active ingredient i.e. drug and the excipients. Excipients balance the properties of the actives in FDTs. The role of excipients is important in the formulation of fast-melting tablets. The temperature of the excipients should be preferably around 30–35^{0}C for faster melting properties.

Ingredients and Technologies Used for Formulating FDT: Ingredients and technologies used for formulating FDT are shown in table 1[19].

Table 1: Ingredients and Technologies Used for Formulating FDT

Drug(s)	Ingredients Used	Technologies used	Disintegration time (sec)
Rizatriptan benzoate	Primogel, Ac-di-sol, Kollidon, Avicel PH102, Orocell, Talc, Aerosil and Magnesium stearate, Aspartame and Sucralose.	Direct compression	85
Capecitabie	Crospovidone, HPMC, Mannitol, MCC.	Direct compression	50
Granisetron HCl	Cyclodextrin, CCS, Magnesium stearate, Lactose, Mannitol.	Direct compression	17.1
Amlodipine Besilate	Avicel PH 101 or 301, Mannitol, Eudragit EPO.	Direct compression followed by sublimation	15-37.8
Aceclofenac	SSG, Mannitol, MCC.	Direct compression technique	12.2 - 27.5
Modafinil	CCS , MCC, Lactose, Pre- gelatinized starch.	Wet granulation	--
Resperidone	Mannitol, Aspartame, PEG 400 &4000, MCC (Ph 200), Gelucire 44/14.	Spray drying and compression	Below 30
Clarithromycin or Cefixime	Carrageenan NF, Tricalcium phosphate, Avicel PH 105, LS HPC, Sucrose stearate.	Extrusion spheronization	Less than 60
Famotidine	Mannitol, PVP K30, Dextran, Sucralose, Sugar, Lactose.	Freeze drying	2-6
Epinephrine bitartrate	Avicel PH-301,Crospovidone, Mannitol, LS HPC(LH11), Magnesium stearate.	Direct Compression	Less than 10
Diclofenac, Acetylsalicylic Acid	Mannitol, Sodium CMC, Citric acid in ethanol, EC, Aspartame.	Molding, decompression	--
ADH	CCS, Sodium bicarbonate, Lactose.	Granulation	--
Ibuprofen Indomethacin Naproxen Diclofenac	Crospovidone, SSG, Mannitol, MCC, Xanthan gum, Silica, Magnesium stearate, Na saccharine, Talc.	Direct Compression	8-15
Ondansetron	SSG, Polacrillin potassium, MCC, Colloidal SiO_2, Aspartame, Talc.	Direct Compression	10-15sec
Fexofenadine	Mannitol, Crospovidone, Precipitated silica, Magnesium stearate, sucralose.	Direct Compression	15-20 sec
Ascorbic acid, Cimetidine	Erythritol, D-mannitol, MCC, Corn starch, Pregelatinized starch.	Molding, direct Compression	31-37
Topiramate	Mannitol, CCS, Hydroxypropyl-β-cyclodextrin, PEG3350, Mannose, SiO_2, Lactose.	Wet Granulation	--
Sildenafil	Crosspovidone, Aspartame, Mannitol.	Freeze drying	< 30
Olanzapine Donepezil	MCC, Mannitol, Sodium stearyl fumerate, Polacrilin potassium, Aspartame, Strawberry flavor.	Direct compression	< 30
Chlorpromazine HCl	Sodium starch glycolate, Crospovidone, Croscarmellose, L-HPC,Pregelatinised starch.	Direct compression	Less than 60

HPMC- Hydroxypropylmethylcellulose # MCC- Microcrystalline cellulose

CCS –Crosscarmillose sodium # SSG- Sodium Starch Glycolate

PEG- Polyethylene glycol # LS HPC-Low-substituted hydroxylpropylcellulose

PVP-Polyvinylpyrollidone # EC- Ethylcellulose

CHALLENGES IN FORMULATING FDTs:

Palatability: Most orally disintegrating drug delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance[13, 22].

Mechanical strength: In order to allow FDTs to disintegrate in the mouth, they are made with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may increase the cost. Only few technologies such as Wowtab® by Yamanouchi Shaklee and Durasolv® by CIMA labs can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles[23,24].

Hygroscopicity: Several FDTs are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging[19].

Amount of drug: For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs[1].

Aqueous solubility: Water-soluble drugs form eutectic mixtu.res, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process[25].

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[26].

SELECTION OF FDT DRUG CANDIDATES:

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[27,28]. 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[29].
- Drugs with a short half-life and frequent dosing.
- Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
- Pharmaceutical Companies have formulated FDT for various categories of drugs such as neuroleptics, cardiovascular agents, analgesics, antiallergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction[20].

EVALUATION:

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

Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation[30]. Weight variation specification as per I.P. is shown in table 2.

Table 2: weight variation and accepted % deviation

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

Hardness: The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Monsanto tablet hardness tester). It is expressed in kg or pound[31].

Friability: To achieve % friability within limits (0.1-0.9%) for an FDT is a challenge for a formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Friability of each batch was measure in "Electro lab friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min or total 100 revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation[32].

$$F = \frac{(W_{initial} - W_{final})}{W_{initial}} \times 100$$

Mechanical Strength: Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters for the determination of mechanical strength.

Crushing Strength or Tablet Tensile strength: It is the force required to break a tablet by compression in the radial direction, it is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet was measured by using Pfizer hardness testers. It is calculated by an average of three observations. Tensile strength for crushing (T) is calculated using equation

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

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet respectively[33].

Measurement of Tablet Porosity: The mercury penetration porosimeter can be used to measure the tablet porosity. The tablet porosity (ε) can be calculated by using following equation,

$$\varepsilon = 1 - m / (\rho_t V)$$

Where ρ_t is the true density, and m and V are the weight and volume of the tablet, respectively[29].

Wetting time and water absorption ratio: Wetting time of dosage form is related to with the contact angle. Lower wetting time implies a quicker disintegration of the tablet.

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

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

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

W_a; The wetted tablet from the petridish is taken and reweighed[34].

Moisture uptake studies:

Moisture uptake studies for FDT should be conducted to assess the stability of the dosage form. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37^0C for 24h. The tablets were weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to check the moisture uptake by the other excipients. Tablets were weighed and the percentage increase in the weight was recorded.

In-vitro dispersion time: Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37+0.5°c. Time required for complete dispersion of a tablet was measured.

Disintegration test: The time for disintegration of FDTs is generally less than 1 min and actual disintegration time that patient can experience ranges from 5 to 30s. The disintegration test for FDT should mimic disintegration in mouth within saliva[35].

Modified disintegration test: A petridish (10cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

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

Dissolution test: The dissolution methods for FDT are practically identical to conventional tablet when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of FDT in the same way as their ordinary tablet counterparts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 25-75 rpm is commonly used. Since the dissolution of FDTs is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets (≥1gram) may produce a mound in the dissolution vessel which can be prevented by using higher paddle speeds[36].

Clinical studies: *In vivo* studies show the actual action of FDT in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. The investigation using gamma-scintigraphy showed that the dissolution and buccal clearance of fast disintegrating dosage forms was rapid[37]. The esophageal transit time and stomach emptying time were comparable to those of traditional dosage forms i.e. tablets, capsules, or liquid forms[38].

Stability study (Temperature dependent): The fast dissolving tablets stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 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 such as visual defects, Hardness, Friability, Disintegrations, and Dissolution etc. The data obtained is fitted into first order equations to determine the kinetics of degradation.

Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

VARIOUS TECHNIQUES FOR "FDT" PREPARATION: Many techniques are used for the preparation of fast dissolving tablets which are shown in table 3: [2, 13, 39-41]

Table 3: Different techniques with method and characteristics of prepared fast dissolving table

Techniques	Method and characteristics of prepared FDT
1-Disintegrant addition	-involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For e.g. MCC and sodium starch glycolate are used in formulation of efavirenz,Crystalline cellulose(AvicelPH-102)and low substituted HPEC used in oxybutinin and pirenzepine formulation. Crosspovidone used in galanthamine HBr. Crosspovidone (3%w/w) and crosscarmellose Na (5%w/w) used in prochlorperazine maleate formulation. **Characteristics:** similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friabilty.
2- Freeze Drying or Lyophilization	-the drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. Finally the blisters are packaged and shipped. **Characteristics:** The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.
3- Moulding	-water-soluble ingredients with a hydro-alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression. **Characteristics:** Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased.
4- Sublimation	- inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethylenetetramine) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. **Characteristics:** porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.
5-Spray-Drying	-by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution. **Characteristics:** prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.
6-Mass-Extrusion	-involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. **Characteristics:** The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.
7- Direct Compression	- conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. **Characteristics:** It is most cost effective tablet manufacturing technique.
8-Cotton candy process	- involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT. **Characteristics:** It can accommodate high doses of drug and offers improved mechanical strength.
9- Compaction; a) Melt granulation	- prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. **Characteristics:** It melts in the mouth and solubilizes rapidly leaving no residue.
b) Phase-transition process	- prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. **Characteristics:** The compatibility increased and so sufficient hardness gained by the formulation.
10-Nanonization	- involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. **Characteristics:** It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).
11- Fast Dissolving Films	-a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. **Characteristics:** The thin films size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste.

PATENTED TECHNOLOGIES: [42-46]

Rapid-dissolving characteristic of FDTs is generally attributed to fast penetration of water into tablet matrix resulting in its fast disintegration. Several technologies have been developed on the basis of formulation aspects and different processes and patented by several pharmaceutical companies. Table 4 of patented technology is given below;

List of Patented technologies based branded Products: The list of patented technologies and their brand products are given in table 5.

Table 4: Important patented technologies for preparation of FDTs

S. No.	Technique	Advantages	Disadvantages
1.	Zydis	Quick dissolution, Self-preserving and increased bioavailability.	Expensive process, poor stability at higher temperature and humidity.
2.	Orasolv	Taste-masking is twofold, quick dissolution.	Low mechanical strength.
3.	Durasolv	Higher mechanical strength than Orasolv, Good rigidity.	Inappropriate with larger dose.
4.	Flashdose	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	Only conventional tabletting technology	--
6.	Wow tab	Adequate dissolution rate and hardness.	No significant change in bioavailability.
7.	Oraquick	Faster and efficient production, appropriate for heat-sensitive drugs.	--
8.	Ziplet	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 5: For patented technology and their brand products

S. No.	Technology	Process involved	Patent owner	Drugs Used (Brand name)
1.	Zydis	Lyophilization	R.P.Scherer Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
2.	Quicksolv	Lyophilization	Jansen Pharmaceutical	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-tab)
3.	Flashtab	Lyophilization	Ethypharm	Ibuprofen (Nurofen Flashtab)
4.	Lyoc	Multiparticulate Compressed tablets	Farmlyoc	Phloroglucinol Hydrate (Spasfon Lyoc)
5.	Orasolv	Compressed Tablets	Cima Labs Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt)
6.	Durasolv	Molding	Cima Labs Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)
7.	RapiTab	Compressed Tablets	Schwarz Pharma	--
8.	Wow tab	Compressed Molded Tablets	Yamanouchi Pharma Technologies, Inc.	Famotidine (Gaster D)
9.	Fast melt	Molding	Élan Corp.	--
10.	Ziplets	Molding	Eurand	Ibuprofen (Cibalgina Due Fast)
11.	Flashdose	Cotton-candy process	Fuisz Technology Ltd.	Tramadol HCl (Relivia Flash dose)
12.	Oraquick	Micromask taste Masking	KV Pharm. Co., Inc.	Hyoscyamine Sulfate ODT
13.	Advatab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetrizine, AdvaTab Paracetamol

FDTs WITH PATENTED TASTE MASKING TECHNOLOGY:

- CIMA Labs' taste masking technique involving coating of drug with dissolution retarding excipient[47].
- Microcaps process involving microencapsulation by coacervation phase separation technique[48,49]

Solutab technology involving coating of drug with sustained release agent followed by coating with enteric polymer and finally with mannitol and mixing of drug with cyclodextrins[50] are some of the tastes masking approaches.

MARKETED PRODUCTS: The commercialized products of FDT which are available in market are given in table 6.

Table 6: Marketed products

Brand name	Drug	Pharmaceutical company
Benadryl Fastmelt	Diphenhydramine	Pfizer
Benadryl Fast melt	Diphenhydramine	Warner Lambert
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Domray MD	Domperidone	Ray Remedies
Dolib MD	Rofecoxib	Panacea
Feldene melt	Piroxicam	Pfizer
Febrectol	Paracetamol	Prographarm
Imodium Instant melts	Loperamide Hcl	Janssen
Kemstro	Baclofen	Schwarz Pharma
Klonopin Wafers	Clonaxepam	Roche
Maxalt-MLT	Rizatriptan Benzoate	Merck
Mosid MT	Mosapride	Torrent
Nulev	Hyoscyamine sulfate	Schwarz Pharma
Nimulid MD	Nimusulide	Panacea
Orthoref MD	Rofecoxib	Biochem
Olanex Instab	Olanzepine	Ranbaxy
Pepcid ODT	Famotidine	Merck
Rofaday MT	Rofecoxib	Lupin
Torrox MT	Rofecoxib	Torrent
Valus	Valdecoxib	Glenmark
Zotacet MD	Cetrizine Hcl	Zota Pharma
Zyprexa	Olanzapine	Eli lilly
Zofran ODT	Ondansetron	GSK
Zomig ZMT and Rapimelt	Zolmitriptan	Astra Zeneca
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-Delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-Delhi, India

FDTS UNDER DEVELOPMENT: The fast dissolving tablets which are under development are Reglan ODT, Metoclopramide Zydis, Citalopram ODT, Tramadol ODT.

CONCLUSION

FDT concept evolved to overcome some of the problems that existed in conventional solid dosage form i.e. difficulty in swallowing of tablet in pediatric and geriatric patients who constitute a large proportion of world's population. FDT may lead to improve efficacy, bioavailability, rapid onset of action, better patient compliance due to its quick absorption from mouth to GIT as the saliva passes. Fast dissolving tablet acts like solid dosage form when outside the body and solution when administered. In future FDT may be most acceptable and prescribed dosage form due to its quick action (within minute). Their characteristic advantages such as

administration without water, anywhere, anytime lead to their increased patient compliance in today's scenario of hectic life. Considering the many benefits of FDTs, a number of formulations are prepared in FDT forms by most of the pharmaceutical companies. Because of increased patient demand, popularity of these dosage forms will surely expand in future.

REFERENCES

1. Habib W, Khankari R, Hontz J, Fast-dissolving drug delivery systems, critical review in therapeutics, Drug Carrier Systems, 17(1), 2000, 61-72.
2. Seager H, Drug delivery products and Zydis fast dissolving dosage form, J. Pharm. Phamacol. 50, 1998, 375-382.
3. Kuchekar BS, Atul, Badhan C, Mahajan H S, Mouth dissolving tablets: A novel drug delivery system, Pharma Times, 35, 2003, 7-9.
4. Allen LV and Wang B., Particulate support matrix for making a rapidly dissolving tablet, 1997, US Patent 5595761.
5. Pebley WS, Jager, NE, Thompson SJ, Rapidly disintegrating tablets, US Patent No.5, 298,261, 1994.
6. Liang AC and Chen LH, Fast-dissolving intraoral drug delivery systems, Expert Opin.Ther. Patents, 2001, 11(6).
7. Morita Y, Tsusima Y, Yasui M, Termoz R, Ajioka J and Takayama K, Evaluation of Disintegration Time of Rapidly Disintegrating Tablets via a Novel Method Utilizing a CCD Camera, Chem. Pharm. Bull., 50(9), 2002, 1181-1186.
8. Schiermeir S and Schmidt PC.: Fast dispersible ibuprofen tablets, Eur. J. Pharm Sci. 15, 2002, 295-305,
9. Siewert M, Dressman J, Brown C, and Shah V, FIP/AAPS Guidelines for Dissolution/In Vitro Release Testing of Novel/Special Dosage Forms, Dissolution Technologies, February 2003.
10. Fu Y, Yang S, Jeong SH, Kimura S, Park K, Orally fast disintegrating tablets: development, technologies, taste-masking and clinical studies, Crit. Rev. Ther. Drug Carr. Syst., 21 (6), 2004, 433–475.
11. Bogner RH, Wilkosz MF, Fast-dissolving tablets: new dosage convenience for patients, U.S. Pharm. 27 (2002) 34–43.
12. Reddy LH, Ghose B and Rajneesh, Indian J. Pharm. Sci., 64(4),2002, 331- 336.
13. Kuchekar BS and Arumugam V, Indian J. Pharm. Edu., 35, 2001, 150.
14. Bhaskaran S, and Narmada GV, Indian Pharmacist, 1(2), 2002, 9-12.
15. Indurwade NH, Rajyaguru T H and Nakhat PD, Indian Drugs, 39(8), 2002, 405-09.
16. Devrajan, PV and Gore SP, Express Pharma Pulse, 7(1), 2000, Nov. 23,16.
17. Kuchekar BS and Arumugam V, Indian J. Pharm. Edu., 35, 2001, 150.
18. Slowson M, Slowson S, What to do when patients cannot swallow their medications. Pharm Times, 51, 1985, 90-96.
19. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. Pharm Tech, 2000; 24(6):52-58.
20. Bonger RH, Wilkosz MF, Fast dissolving Tablet. Accessed 2008.
21. Anon, Flavors and Flavoring, Int J Pharm Compounding; 1:1997, 90-92.
22. Goel H, Rai P, Rana V, Tiwary AK, Orally Disintegrating Systems: Innovations in Formulation and Technology, Recent Patents on Drug Delivery & Formulation, 2, 2008, 258-274.
23. Brown D, Orally disintegrating tablets: Taste over speed. Drug Deliv Tech, 3(6): 2001; 58-61.
24. Aurora J, Pathak V. Oral disintegrating technologies: Oral disintegrating dosage forms: An overview. Drug Deliv Technol, 5(3): 2005,50-54.
25. Ghosh TK, Chatterjee DJ., Pfister WR, Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceutical perspective.In: Ghosh TK and Pfister WR (Eds). Drug Delivery to the Oral Cavity: Molecules to Market. NY, USA: CRC Press, 2005, pp 337-356.
26. Sugihara M, Hidaka M, Saitou A. Discriminatory features of dosage form and package. Jpn J Hosp Pharm, 12: 1986, 322-328.
27. Pfister WR, Ghosh TK. Intraoral delivery systems: An overview, current status and future trends. In: Pfister WR, Ghosh TK (Eds). Drug delivery to the oral cavity: Molecules to Market. CRC Press, NY, USA, 2005, 1-40.
28. Ostrander K. Advances in fast dispersing technologies-zydis. Paper presented at the Annual Meeting of the AAPS, Salt Lake City, UT, 29 Oct., 2003.
29. Lies MC, Atherton AD, Copping NM., Freeze dried dosage forms and methods for preparing same. US Patent 5,188,825 (1993).
30. Indian Pharmacopoeia, Vol-2, The Controller of Publication Delhi, 1996, p-735.
31. Lachman L, Liberman H, Kanig J, The theory and practice of industrial pharmacy, 3rd edn., Varghese Publishing House, Mumbai, 1987, 297.

32. Khan S, Kataria P, Nakhat P, Yeole P, Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating tablets. AAPS Pharm.Sci.Tech.; 8(2), 2007, 46.

33. Bi YX, Sunada H, Yonezawa Y, Danjo K, Evaluation of rapidly disintegrating tablets prepared by a direct compression method, Drug Dev Ind Pharm.; 25: 1999, 571-581. doi: 10.1081/DDC-100102211

34. Morita Y, Tsushima Y, Yasui M, Termoz R, Ajioka J, Takayama K. Evaluation of the disintegration time of rapidly disintegrating tablets via a novel method utilizing a CCD camera. Chem. Pharm. Bull., 50(9), 2002, 1181-1186.

35. United States Pharmacopoeia USP25 NF20, The Official Compendia of Standards, First annual Asian edn.,Rockville,MD: United States Pharmacopoeial Convention Inc. 2002.

36. Wilson CG, Washington N, Peach J, Murray GR, Kennerley J. The behaviour of a Fast dissolving dosage form (Expidet) followed by gamma-scintigraphy. Int J Pharm 40(1–2): 1987, 119–123.

37. Wilson CG, Washington N, Norman S, Greaves JL, Peach JM, Pugh K. A gamma scintigraphic study to compare oesophageal clearance of "Expidet" formulations, tablets and capsules in supine volunteers. Int J Pharm 46(3): 1988; 241–246.

38. Washington N, Wilson CG, Greaves JL, Norman S, Peach JM, Pugh K. A gamma scintigraphic study of gastric coating by Expidet, tablet and liquid formulations. Int JPharm; 57(1), 1989, 17–22.

39. Makino T, Yamada M and Kikuta J, Fast dissolving tablet and its production, 1993, European Patent, 0553777 A2

40. Bess WS, Kulkarni N, Ambike SH, Ramsay MP., Fast dissolving orally consumable solid film containing a taste masking agent and pharmaceutically active agent at weight ratio of 1:3 to 3:1, US Patent 7067116, 2006 Jun 27.

41. Meyers GL, Battist GE, Fuisz RC, Process and apparatus for making rapidly dissolving dosage units and product Thereform.PCT Patent WC 95/34293 A1; 1995.

42. Modi A, Tayade P, Enhancement of dissolution profile by solid dispersion (kneading) technique, AAPS Pharm. Sci. Tech., 18;7(3) ,2006, 68.

43. Reig AR, Plazas F, Galvan CJ, Heras NJ, Artes FM, Gabarron HE, Acceptance survey of a fast dissolving tablet pharmaceutical formulation in allergic patients. Satisfaction and expectancies,Allergol. Immunopathol. (Madr.), 34(3), 2006, 107-12

44. Ahmed IS, Nafadi MM, Fatahalla FA, Formulation of a fast-dissolving ketoprofen tablet using freeze-drying in blisters technique, Drug Dev. Ind.Pharm., 32(4), 2006,437-42

45. Cirri M, Valleri M, Mura P, Maestrelli F, Ballerini R, Development of fast dissolving tablets of flurbiprofen cyclodextrin complexes, Drug Dev. Ind. Pharm., 31(7), 2005,697-707.

46. Takagi H, Kajiyama A, Yanagisawa M, Rapidly disintegrable pharmaceutical composition, U.S.Patent 6,899,899. 2005,

47. Alkira TG, Sanftleben RA, Schuehle SS. Taste masking microparticles for oral dosage forms. US Patent 5,607,697. 1997.

48. Friend DR, Ng S, Sarabis RE, Weber TP, Geoffroy JM, Taste-masked microcapsule compositions and method of manufacture. US Patent 6,139,865. 2000.

49. Geoffroy JM, Friend DR, Ng S, Weber TP, Sarabis RE, Taste-masked microcapsule compositions and methods of manufacture, WO Patent 014179. 1998.

50. Stroppolo F, Ciccarello F, Milani R, Bellorini L. Oral pharmaceutical compositions containing cyclodextrins as taste masking agent. WO Patent 0,241,920. 2002.

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