FAST DISSOLVING TABLETS: A PROMISING APPROACH FOR DRUG DELIVERY

Abstract

Aim of novel drug delivery system is to enhance safety and efficacy of drugmolecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast dissolving tablets. Now-a-days fast disintegrating tablets (FDTs) gaining significance with wide variety of drugs serving many purposes. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds (less than 60 seconds) without chewing and additional water. The basic approach used in development of FDTs is the use of superdisintegrants and the elimination of bitterness. FDTs reduces the disadvantages of conventional dosage form especiallydysphasia (difficulty in swallowing) in pediatric and geriatric patients. These oral dosage forms have many benefits such as self medication, increased compliance, ease of manufacturing and noninvasive.

This review presents description of fast dissolving tablets including need for development, challenges in formulation, suitability of drug candidates, composition, various technologies involved, advantages, disadvantages, and evaluation parameters.

Keywords-: Fast dissolving tablet, superdisintegrants, and disintegration.

Introduction

The conventional dosage forms (tablets and capsules) have wide range of acceptance up to 50-60 % of the total dosage forms[1]. Tablet is most popular dosage form of existing forms because of ease of self administration, compact in nature, easy to manufactureand it can be delivered in accurate dose[2].

There is one drawback associated with tablets and that is difficulty in swallowing and chewing in some patients particularly in geriatric and pediatric patients. This problem can be avoided by means of fast dissolving tablets. One such problem can be solved in the novel drug delivery system by formulating "mouth dissolving tablets" which disintegrates or dissolves rapidly without water within few seconds in themouth due to the action of superdisintegrant or maximizing pore structure in the formulation[3].

Fast dissolving tablets are defined as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". Fast dissolving tablets are especially designed for dysphagia, geriatric, pediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations. Fast dissolving tablets are also referred as quick disintegrating tablets, mouth dissolving tablets, oral rapid disintegratingtablets, rapid dissolving tablets, porous tablets and rapid melt tablets[4].

The basic approach used in development of FDT is the use of superdisintegrants like ac-di-sol, sodium starch glycol ate, kollidon, crospovidone, croscarmellose sodium, l-hydroxypropyl cellulose, in a concentration of 1.5 to 7.5%. Superdisintegrants provide instantaneous disintegration of tablet, thereby releasing the drug in saliva and absorbed through oral mucosa thus drug enters directly into systemic circulation which in turn provides rapid onset of action.

The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement ofbioavailability. Elimination of bitter taste of drug is an important criterion in the development of mouth dissolving tablets[5].

Advantages[6, 7, 8]

1. Rapid dissolution and absorption of drug.
2. Avoidance of first pass metabolism.
3. No need of water to swallow thedosage form.
4. Ease of administration to patients who have difficulty to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients.
5. Convenience of administration and accurate dosing as compared to liquid formulations.
6. Bioavailability of hydrophobic and insoluble drugs gets increased due to quicker disintegration and dissolution.
7. Avoidance of risk of choking and suffocation during oraladministration.
8. New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Disadvantages[9, 10]

1. They are fragile and brittle.
2. FDTs are required to be kept in dry surrounding because of their hygroscopic nature.
3. It needs special packaging for protection duringstorage and transportation.
4. The tablets usually have insufficient mechanical strength. Hence, careful handling is required during manufacturing process.
5. The tablets may leave unpleasant taste and/or grittiness in oral cavity if not formulated properly.
6. Drugs with larger doses are difficult to formulate.

Criteria for fast dissolving tablets[11]

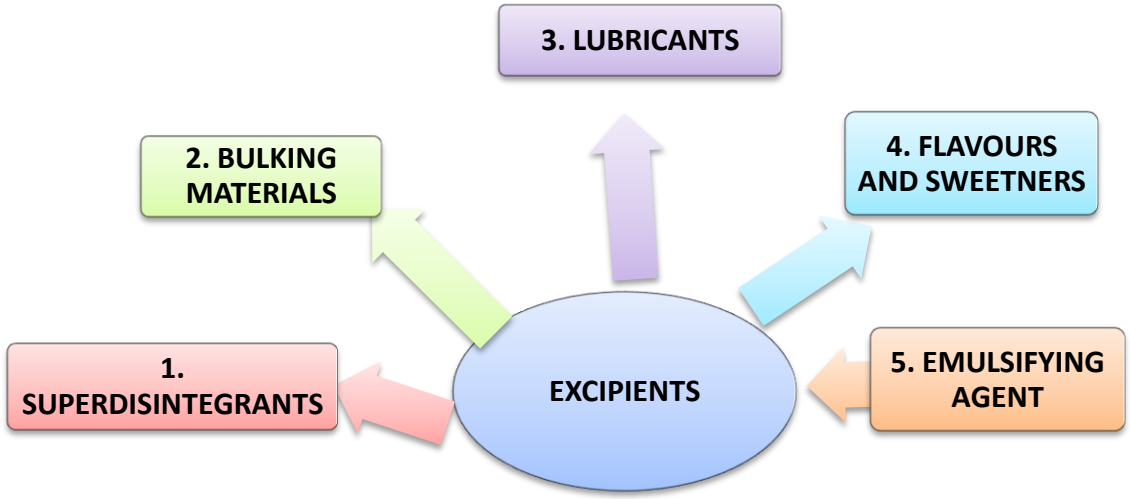
1. Free from bitter taste.
2. Dose lower than 20 mg.
3. Small to moderate molecularweight.
4. Good solubility in water and saliva.
5. Partially nonionized at the oral cavity's pH.
6. Ability to permeate oral mucosal tissue.

Criteria for the selectin of drug[12, 13]

The ideal characteristics of a drug for fast dissolving tablets include:

1. Drug should have ability to permeate the oral mucosa.
2. At least partially non ionized at the oral cavity pH.
3. Have the ability to diffuse into theepithelium of the upper GIT.
4. Short half life and frequent dosing drugs are unsuitable for fast dissolving tablets.
5. Drug should have good stability in saliva and water.
6. Drugs have very bitter or unacceptable taste and odor is unsuitable for orodispersible tablets (ODT).

Excipients used in fast dissolving tablets



Ingredients of fast dissolving tablets

Table 1: Ingredients of fast dissolving tablets

Serial no.	Name of excipients	Role of excipient	Example
1.	Superdisintegrants	To promote moisture penetration and disintegration/dispersion of the matrix of dosage form in dissolutionfluids. These are generally used in a low concentration (1-10%)[14].	Croscarmellose sodium (Ac-Di-Sol), Crosspovidone, sodium starch glycolate (SSG).
2.	Bulking materials	Contributes functions of a diluent, filler and cost reducer. These agents improve the textural characteristics which further enhance the disintegration.	Mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate.
3.	Lubricants	Remove grittiness and assist in the drug transportmechanism from the mouth down into the stomach[15].	Talc, waxes and oils,PEG,stearic acid and derivatives, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin.
4.	Flavours and Sweetners	Makes more palatable and pleasing products for patients, mask bitterness and disagreeable tastes of some active ingredients. Both natural and synthetic flavors aree used.	Flavours- Peppermint flavour, clove oil, anise oil, eucalyptus oil. Sweetners-Sugar, dextrose and fructose, aspartame, sodium saccharin, sugar alcohols and sucralose.

5.	Emulsifying agent	They aid in rapid disintegration and drug release withoutchewing, swallowing or drinking water. They also stabilizes the immiscible blends and enhances bioavailability[16].	Alkyl sulfates, propylene glycol esters, lecithin, sucrose esters.

Criteria for the selection of super disintegrants[17]

1. Produce rapid disintegration, when tablet comes in contact withsaliva in the mouth/oral cavity.
2. Be compactable enough to produce less friable tablets.
3. Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.
4. Have good flow, since it improves the flow characteristics of total blend.

Mechanism of super-disintegrants[18, 19]

The four major mechanisms for tablet disintegration are as following-:

1. Swelling- When tablet comes in contact with water thenswelling occurs and thus adhesiveness of other ingredients of the tablet is lost, causing the tablet disintegration.

2. Porosity and Capillary Action (Wicking) -Due to the porous nature of the tablet, the liquid is drawn (wicking action) into the tablet through capillary action, thus the inter-particulate bonds get ruptured causing disintegration of tablet.

3. Deformation-The superdisintegrants get deformed during tabletcompression and upon contact with water they regain their normal structure which causes an increase in size of deformed particles resulting in the breaking of tablet.

4. Due to repulsive forces-Another mechanism of disintegration attempts the swelling of tablet made with'nonswellable' disintegrants. Nonswelling particle also cause disintegration of tablets. Generation of electric repulsive forces between particles promotes the disintegration of tablet and water is required for it.

Conventional techniques used in the preparation of fast dissolving tablets

The various techniques used for the preparation offast dissolving tablets are-:

1. Direct Compression[20]-

It is considered as the best method to prepare orallydisintegrating dosage forms. The general scheme of direct compression is as follows:

Milling→ Sieving → Mixing → Compression

It is one of the most popular and convenient techniques for the preparation of FDTs. Here the FDTs are punched at significantly lower forces (4–10 kN) than the conventional tablets.

2. Sublimation/ effervescent-

Rapid disintegration of fast dissolving tablets is due to the presence of a porous structure in tablet matrix. Hence to generate porous matrix, volatile ingredientsare used then removed by sublimation, leaving behind a porous matrix, were compressed along with other excipients into a tablet.

3. Mass extrusion-

It involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a

cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets.

4. Tablet molding-

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followedby compression at low pressures in molded plates to form a wetted mass. The solvent is then removed by air-drying.

5. **Lyophillization / Freeze drying-**

This technique creates an amorphous porous structure that can dissolve rapidly. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is 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. Thenthe frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying[21].

6. Melt granulation-

It is a process by which powders are efficiently agglomerated by a meltable binder which can be a molten liquid, a solid or a solid that melts during the process. It is used to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. Thisapproach is used to prepare FDTs with sufficient mechanical integrity.

7. Nanonization –

A Nanomelt technology 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.

8. Cotton candy process - This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. In this process matrix of polysaccharides are formed by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with activeingredients and excipients after re-crystallization and subsequently compressed to FDT[22].

9. Three-dimensional printing (3DP) –

It is a rapid prototyping technology, which involves constructing specific layers that uses powder processing and liquid binding materials.

Important patented technologies for fast dissolving tablets

1. Zydis Technology

This is the patented technology of Catalent Pharma solutions. Zydis formulation is a unique freeze dried tablet in whichdrug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossyamorphous structure, which imparts strength. Blister packs are used for Zydis products to protect the formulation from moisture present in the environment[23].

2. Durasolv Technology

Durasolv is the patented technology of CIMA labs. Tablets produced by this technology have much higher mechanical strength and the production is a faster and effective. The tablets made by this technology consist of drug, filler and a lubricant. Tablets areprepared by using conventional tabletting equipment and have good rigidity. These can be packaged into

conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amount of active ingredients[24].

3. Ziplets Technology

This technology is patented by Passano con Barnago, Italy. It can be used with water insoluble compounds as both bulk actives and as coated microparticles. These tablets are with improved mechanical strength and optimal disintegration time at low compression force. In fact, tablets composed primarily of water-soluble components often tend to dissolve rather thandisintegrate, resulting in a much longer disintegration time[24].

4. Flash Dose Technology

Flash dose technology has been patented by fuisz. Flash dose tablets consist of self-binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets preparedusing flash dose technology is the first commercial product launched by Biovail Corporation[25].

5. Flash Tab Technology

Prographarm laboratories have patented the Flash tab technology. Active ingredient is used in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation andextrusion spheronisation. All the processing utilized conventional tabletting technology[25].

6. Novel Hole Technology

It is developed to minimize the disintegration time and maximize the patient compliance. Tablets formulated by this technique usually disintegrate in 10–20 s.In this technology, highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. These volatile materials are then removed bysublimation creating a highly porous matrix. Absolute surface area of the tablet increases due to hole formation. The main mechanism involved in whole technology is sublimation.

7. Oraquick Technology

The Oraquick fastdissolving/ disintegrating tablet formulation utilizes a patented taste masking technology. There is no utilization of solvents to mask taste, thus leads to faster and more efficient production. Since there is lower heat of production thanalternative fast dissolving/ disintegrating technologies, so it is appropriate for heat sensitive drugs. Oraquick claims quick dissolution in a matter of seconds, with good taste masking[24].

8. Quicksolv Technology

This technology is patented by Janssen Pharmaceutica, Beese,Belgium. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Product formed by thistechnology has uniform porosity and adequate strength for handling. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction)[23].

9. Lyoc Technology

Lyoc technology is patented by pharmalyoc. It utilizes a freeze drying process but it differs from Zydis in that the product is frozen on the freeze dryer shelves. Oil in wateremulsion is prepared and placed directly into blister cavities followed by freeze-drying. Nonhomogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

10. Pharmabrust Technology

Pharmaburst technology is being patented by SPI pharma. Tablet prepared by this technique dissolve within 30-40 seconds. The tablet manufactured by this process involves a dryblend of a drug, flavors, and lubricant then followed by compression into tablets[26].

11. Frosta technology:

Akina patents this technology. Plastic granules are prepared and compressed at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet[27].

12. Nanocrystal Technology

This is patented by Elan, King of Prussia. It includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is moreadvantageous for highly potent and hazardous[26].

13. Wowtab

Wowtab technology was developed by Yamanouchi Pharma Technologies. "Wow" means without water. The active ingredients may constitute up to 50% w/w of the tablet. Saccharides of both low and high moldability are used to prepare the granules. Moldability is the capacity of a compound to be compressed. Highly Moldable substance has high compressibility and thus slow dissolution. The combination of high and low moldability is used to produce tablets of adequate hardness and a rapidly melting strongtablet. Wowtab product dissolves quicklyin 15 seconds or less[28].

Table 2: Commercially available Patented Fast dissolving Technologies

Patented Technology	Patent Holder	Technology Basis	Active Ingredients	Available Products
Advatab	Eurand International, Dayton OH	Direct compression	Cetrizine	AdvaTab Cetrizine
Durasolv	Cima Labs Inc,	Direct compression	Zolmitriptane	Zolmig®ZMT
Flashtab	Prographarm laboratories	Direct compression	Ibuprofen	Nurofen®Flash Tab
Flash Dose	Biovail(Fuisz Technology, Ltd)	Cotton Candy Process	Tramadol HCl	Relivia Flashdose®
Lyoc	Farmayoc	Freeze-drying	Phloroglucinol hydrate	Spasfon lyoc
Orasolv	Cima Labs Inc,	Direct compression	Mirtazapine	Remeron®SolTab
Oraquick	KV Pharm.Co.Inc.	Micromask taste masking	Hyoscyamine sulfate	Hyoscyamine sulphate ODT
QuickSolv	Janssen pharmaceutics	Freeze-drying	Cisapride monohydrate	Propulsid Quicksolv
Wowtab	Yamanouchi Pharma Tech,Inc	Direct compression	Famotidine	Gaster D
Zydus	R.P.Scherer,Inc [Cardinal Health]	Freeze-drying	Loratidine	Claritin®Reditab

Ziplets	Eurand International, Dayton OH	Direct compression	Ibuprofen	Cibalginadue Fast

Preformulation studies of blends

1. Bulk density[29]

Bulk density can be determined by pouring blend into a graduated measuring cylinder using a funnel and weigh.The bulk density can be calculated using the formula-:

Bulk density= (Weight of the powder)/(Bulk volume)

2. Tapped density[29]-

Same measuring cylinder should be set for the determination of tapped density that was used for the determination of bulk volume. Set measuring cylinder to 300 taps per minute and operate for 500 taps. The tapped density is calculated by the following formula-:

Tapped density= (Weight of the powder)/(Tapped volume)

3. Angle of repose (θ)[29] –

It is an indication of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The powder mixture is allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose is then calculated by measuring the height and radius of the heap of powder formed. It is calculated by the following formula-

$\tan \theta = h/r$

Where, θ = angle of repose,

h =height in cm,

r = radius in cm.

4. Carr's Index[30]

A simplex way of measurement of the free flow of powder. Carr's index measures the propensity of powder to be compressed and the flow ability of powder. Carr's index can be calculated from the bulk and tapped density by using following formula-

Carr's index=((Tapped density-Bulk density))/(Tapped density) X 100

5. Hausner's ratio[30]

Hausner's ratio also measure the propensity and the flow ability of powder. Hausner's ratio can be calculated from the bulk and tapped density.Hausner ratio given by the equation-:

Hausner's ratio=(Tapped density)/(Bulk density)

EVALUATION OF FAST DISSOLVING TABLETS

1. Thickness[31]-

Tablet thickness is an important characteristic and isexpressed in mm. The thickness and diameter of the tablets was determined using a micrometer screw gauge.

2. Weight variation test[32] –

For this test 20 tablets are generally selected randomly from the lot and weighted individually for checking weight variation. Weight variation specification as per I.P. is shown in table-:

Table-3: weight variation and accepted % deviation.

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

3. Hardness[32]-

Force required to break a tablet in a diametric compression testis called hardness (crushing strength). Hardness is measured by using a Monsanto Hardness Tester.

4. Friability[32]-

Roche friabilator is used for the measurement of friability using 20 tablets. Twenty tablets are weighed and rotated at 25 rpm for 4 minutes (100 revolutions). The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

% Friability=((Initial weight-final weight))/(Initial weight) X 100

5. Measurement of Tablet Porosity[33]-

Porosity of tablet can be determined by using mercury penetration porosimeter. The tablet porosity (ε) can be calculated by using following equation,

$\varepsilon=(1-m)/(\rho t\ V)$ X 100

Where, ρt = true density, m and V = weight and volume of the tablet, respectively.

6. Water absorption ratio[33]

A tablet is placed on the paper and the time required for complete wetting is determined by using following formula-

Water absorption ratio=(Wb-Wa)/Wb X 100

Where, Wa = weight of tablet after absorption, Wb = weight of tablet before absorption.

7. In-vitro disintegration time[34]

This test is performed on 6 tablets, by placing tablet into each tube (3 inches long and have 10 mesh screen) of apparatus using the distilled water (used as disintegration medium) at a frequency of 28-32 cycle/minute and $37^0C \pm 2^0C$ and the time in second was noted when no lumps remaining in the apparatus.

8. *In-vitro* dissolution study[35]

Dissolution study is carried out by using USP type-II apparatus. The dissolution test is performed using 900 ml of the dissolution medium at 50 rpm and 37°C ±0.5°C. 10 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium to maintain sink condition. The samples are analyzed spectrophotometrically at a particular wavelength.

9. **Stability studies[36]**

Stability testing of tablets is done to check whether it is a stable product or not and to check integrity of formulations during its shelf life. The formulation prepared should be packed in a special way, firstly the formulation is wrapped in a butter paper then aluminium foil is wrapped over it, then this is packed in an aluminium pouch and heat sealed. Storage conditions of formulation should be 45^oC/ 75% RH. Formulations should be stored for 3 months. During the course of stability study triplicate samples should be taken at three sampling intervals i.e. 0, 1 and 3 month, and tablets should be evaluated for physical changes and drug content.

Table 4: List of marketed fast dissolving tablets

S. N.	Brand name	Active ingredient	Application
1.	Benadryl® Fastmelt®	Diphenhydramine citrate	Sinus pressure relief
2.	Citalopram® ODT	Citalopram	Antidepressant
3.	Claritin®, RediTabs®	Loratadine	Antihistamine
4.	DuraSolv®, Alavert®	Loratadine	Allergy
5.	Excedrin® QuickTabs	Acetaminophen	Pain reliever

6.	Feldene® Melt	Piroxicam	Rheumatoid arthritis
7.	Gaster D®	Famotidine	Antiulcer
8.	Imodium Instant Melts®	Loperamide HCL	Antidiarrhoeal
9.	Kemstro™	Baclofen	Antispastic, analgesic
10.	Klonopin®	Clonazepam	Anticonvulsant
11.	Maxalt® -MLT	Rizatriptan benzoate	Migraine
12.	Metozolv ODT®	Metoclopramide	Antiemetic, Gastroprokinetic agent
13.	Nasea OD®	RamosetronHCl	Antiemetic
14.	Nimulid MD®	Nimesulide	Pain reliever
15.	NuLev®	Hyoscyaminesulfate	Antiulcer
16.	Pepeid® ODT	Femotidene	Anti-ulcer
17.	Propulsid® Quicksolv ®	Cisapride Monohydrate	Gastrointestinal prokinetic Agent
18.	Relivia®	Tramadol Hydochloride	*Pain* reliever
19.	Remeron® Soltab®	Mirtazapine	Antidepression
20.	Resperdal®, M-TabTM®	Resperidone	Schizophrenia
21.	Tempra®Quiclets	Acetaminophen	Analgesic
22.	Triaminic® Softchews®	Various combination	Pediatric cold cough,Allergy
23.	Vimovo®	Naproxen	NSAID
24.	Vometa® FT	Domperidone	Antiemetic, Prokinetic agent
25.	ZubrinTM (Pet drug)	Tepoxelin	Canine NSAIDs
26.	Zyperxa®	Olazepine	Psychotropic
27.	ZelaparTM	Selegiline	Parkinson’s disease
28.	Zofran® ODT	Ondansetron	Antiemetic
29.	Zomig® ZMT	Zolmitriptan	Migraine

CONCLUSION

FDTs are innovative dosage forms specially designed to get disintegrated in saliva without the need of water, due to the porous structure of the tablet matrix or on the addition of superdisintegrants and/or effervescent excipients.

Fast dissolving tablets have better patient compliancespecially geriatric and pediatric populations for and offer improved biopharmaceutical properties and efficacy and better safety when compared with conventional. The development of a fast-dissolving tablet also provides an opportunity for extension in the market place. Pharmaceutical marketing is another reason for the development of fast dissolving products. Hence, patient demand and the availability of various technologies have increased the acceptance of Fast disintegrating tablets, which in turn prolongs the patent life of a drug. There is need for improved manufacturing processes for fast dissolving tablets to make them mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablet.

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