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A Review on Fast Dissolving Drug Delivery Systems- A Pioneering Drug delivery Technology

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ABSTRACT

Recently fast dissolving drug delivery system gaining popularity and acceptance in novel drug delivery system. It has shown more patient compliance because of easy administration, easy to swallow, economical and palatable taste. Paediatrics, geriatrics, motion sickness, mentally disable and bedridden patients are more benefited by such kind of delivery system it also enhances the bioavailability of drug. The aim of this article is to review the progress in methods of manufacturing, evaluation and various latest technologies involved in the development of Fast dissolving tablets which will be helpful to young researchers. Fast dissolving tablets are prepared by the addition of various super disintegrates with drug and various additives. As the conventional tablet needed water for swallowing but fast dissolving tablets are immediately dissolves in mouth with help of saliva within few seconds without need of water, so patient can take anywhere at any time this is one of the best advantage of this type of delivery system. Rather than this that kind of tablets are easy to manufacture and evaluate with offering uniform dosing.

Keywords: Fast Dissolving Tablet, Mouth Dissolving Tablet, DCL, ODT Technology.

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INTRODUCTION

Oral route of administration is the most convenient and preferred route of administration among the various other delivery system. More than 70% of drugs are available in the market in the form of oral drug delivery system due to pain avoidance and versatility [1] but a very elderly patient may not be able to swallow a daily dose of antidepressant. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H_2-blocker.Fast-dissolving/disintegrating tablets (FDDTs) are a perfect fit for all of these patients.[2]

A fast dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing [3] these systems were first developed in the late 1970s for the people 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 [4,5.] It improves 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[6,7]

The main proposal of the present review is to study the practicability of fast dissolving drug delivery and illustrate briefly the ideal properties, advantages and limitations, conventional and patented technologies, available marketed formulations in FDTs and evaluation methods.

The Centre for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."[8] FDTs disintegrate and/or dissolve instantaneously in the saliva without the use of water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely[9]

Advantages of Fast Dissolving Tablets[10]

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as paediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for

patients who are travelling and do not have immediate access to water.

- Rapid dissolution and absorption of the drug, which will produce fast onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is highly increased.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in paediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety

Limitations of Mouth Dissolving Tablets[11]

- 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

Requirements of Fast Dissolving Tablets[12]

- It should not require water for oral administration, yet dissolve / disperse/ disintegrate in mouth matter of seconds.
- The parent compound has to soluble, stable and able to easily permeate the mucosal barrier be rapidly dissolved while retaining a sufficiently long contact time at the administration site.
- Incorporating hydrophilic excipients.
- Able to rapidly absorb water for a rapid de-aggregation of the matrix.
- Tablet must be highly porous.

Criteria of Formulation for Fast Dissolving Tablets[13]

A**) Drug**

1. The dose must be lower than 20 mg.
2. The drug should be partially unionized at oral p_H.
3. Drug should permeate through the oral mucosal tissue

B) Excipients[18,19]

- **Bulk agents**

Bulk agents are significant in the formulation of fast-dissolving tablets. The material contribute functions of a diluents, filler and cost reducer. Bulk agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides adding bulk also reduces the

concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property. Mizumito et.al, classified sugar-based excipients on the basis of moulding and dissolution rate

Type 1 saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mould ability but low dissolution rate.

- **Emulsifying agents**

These are important excipients for formulating fast-melting tablets. They aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-dissolving tablet formulation, including alkyl sulphates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

- **Lubricants**

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

- **Flavours and Sweeteners**

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients aids in overcoming bitterness and disagreeable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the organoleptic characteristics of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose.

POTENTIAL CANDIDATE FOR FDT's[14,15,16,17,]

S.no.	Drug category	Examples of Drug
1.	Analgesic and anti-inflammatory agents	Ibuprofen, Indomethacin, Naproxen, Oxaprozin, Phenylbutazone, iroxicam, meloxicam, ketoprofen etc.
2.	Anti-anginals	Metoprolol,Amlodipine, Niefidipine
3.	Anti-coagulants	Phenindione, Nicoumalone, Dipyridamole, Dicoumarol
4.	Anti-depressants	Trimipramine, Trazodone, Nortriptyline, Mianserin, Maprotiline.
5.	Anti-bacterial	Trimetoprim,Tetracycline,Sulphapyridine,Sulphafurazole.
6.	Anti-gout agents	Sulphinpyrazone, Allopurinol, Probenecid
7.	Anti-fungal agents	Clotrimazole, Econazole Nitrate, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole
8.	Anti-hypertensive agents	Amlodipine, Carvedilol, Prazosin, Benidipine, Darodipine,Diltiazam, Diazoxide,Felodipine,Minoxidil, Nifedipine,Nimodipine,Terazosin
9.	Anti-malarial agents	Proguanil,mefloquine,halofant- trine,chlorproguanil,chloroquine
10.	Anti-neoplastic agents	Busulphan,Chlorambucil,Cyclosporin,Dacarbazine,Etoposide,Melphalan,Methotrexate,Procarbazine,Tamoxifencitrate,Mitomycin
11.	Anti-migraine agent	Dihydroergotamine mesylate, Sumatriptan,Ergotamine maleate
12.	Anti-protozoal agents	Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole
13.	Anti-thyroid agents	Carbimazole, Propylthiouracil
14.	Anxiolytic, sedative, hypnotics and neuroleptics	Alprazolam,Amyiobarbitone,Barbitone,Chlormethiazole,Chlorpromazine, Clobazam, Clozapine, Diazepam, Droperidol, Lorazepam, Haloperidol, Oxazepam
15.	Diuretics	Acetazolamide, Amiloride, Bumetanide, Chlorothiazide.
16.	Local anaesthatics	Lidocaine

SUPER-DISINTEGRANTS[20]

Superdisintegrants are the agents added to tablet formulations to promote the breakup of the tablets into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug. The list of superdisintegrants are given in Table 2

Table 1: List of Superdisintegrants

Superdisintegrants	Example	Mechanism of action
Crosspovidone-M® Kollidon® Polyplasdone®	Cross-linked PVP	Swells very little and returns to original size after compression but act by capillary action
Crosscarmellose® Ac-Di-Sol®, Nymce ZSX®, Primellose®Solutab®,Vivasol®L-HPC	Cross-linked Cellulose	Swells 4-8 folds in < 10 seconds. - Swelling and wicking both.
Sodium starch glycolate Explotab®, Primogel®	Cross-linked Starch	Swells 7-12 folds in < 30 seconds
Calcium silicate		Wicking Action
Alginic acid NF Satialgine®	Cross-linked alginic acid	Rapid swelling in aqueous medium or wicking action
Soy polysaccharides Emcosoy®	Natural super Disintegrant	

MECHANISM OF SUPERDISINTEGRANTS

There are four major mechanisms for tablet disintegration as follows:

- **Swelling**

General mechanism of action for tablet disintegration which is most widely accepted is swelling. Tablets with high porosity due to lack of adequate swelling force show poor disintegration. Sufficient swelling force with low porosity is exerted in the tablet. If the packing fraction is very high, fluid is unable to penetrate in the tablet & disintegration is again slows down.

- **Porosity and Capillary Action (Wicking)**

Effective disintegrates that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the preparation of fluid into tablets. The disintegrates particles themselves act to enhance porosity and provide pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the inter-particulate bonds causing the tablet to break apart.

- **Due to disintegrating particle/particle repulsive forces**

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

- **Due to deformation**

Disintegrated particles get deformed, during tablets compression and when these deformed particles come in contact with aqueous media or water they get into their normal structure. Swelling capacity of starch was improved during compression. Due to this increase in size of the deformed particles produces a breakup of the tablet.

OTHER EXCIPIENTS USED IN FDTs FORMULATION[21]

- **Flavours:** Peppermint flavour, cooling flavour, flavour oils, flavouring aromatic oil.
- **Sweeteners:** Aspartame, sugars derivatives.
- **Fillers:** Mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate.
- **Surface active agents:** sodium doecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters(Spans).
- **Binders:** Polyvinylpyrrolidone(PVP), polyvinylalcohol(PVA)
- **Colour:** Sunset yellow, amaranth etc.
- **Lubricants:** Stearic acid, magnesium stearate, zinc state, calcium state, talc.

METHODS OF MANUFACTURING FDT's

Freeze drying or Lyophilization

In this process after freezing water is sublimated from the product. Lyophilization is technology which allows drying of heat sensitive drugs and biological at very low temperature. Which results in preparation of highly porous, with a very high specific surface area, dissolve rapidly and great absorption and bioavailability. Lyophilization consists of freezing of material followed by sublimation of ice or frozen moisture under vaccum of 100-300 microns at temperature -10°C to - 30°C. All the constituents of the material remain frozen in their original positions. Thus original product remains in their original size and shape with high porosity, which resulting in improved solubility in water [22.]

The freeze drying operation consists of following steps:

1. Preparation and pre treatment
2. Pre freezing to solidify the water
3. Sublimation of ice under vacuum
4. Removal of residual moisture under high vacuum
5. Packing

Various technologies which used in this method for manufacturing of FDT's Zydis, Quicksolv and Lyoc [23]

- **The ideal drug characteristics for this process are**

Good aqueous stability in suspensions and relative water insolubility with fine particle size. With water soluble drugs primary problem is associated that is formation of eutectic mixture, due to freeze point depression and formation of glassy solid on freezing which might collapse on sublimation. Addition of cryprotectants like mannitol can prevent collapse of structure and mask the bitter taste. High cost of equipment and processing limits the use of this method.[24]

Spray Drying

Spray drying is the one step continuous process it involves transformation of feed from a liquid state (solution, suspension or paste) into a dried particulate form by spraying the feed into a hot drying medium. The primary preparation is atomized into a spray and contact between the spray and drying medium takes place resulting in moisture evaporation, continued till a dried product obtained. In this process, moisture flows through a droplet is by diffusional mechanism, supplemented by capillary flow [25] The tablets formed by this method are promised to disintegrates within 20 sec. The Formulation contained Gelatin can used as supporting agent and as a matrix, mannitol and/or lactose as a bulking agent and acidic ingredient (citric acid) and/or

alkaline ingredients (e.g. sodium bicarbonate) and crosspovidone or crosscarmellose or sodium starch glycolate are used as superdisintegrants. This spray dried powder after compression into tablet shows improved dissolution, disintegration and bioavailability [26.] Allen et al used this process to manufacture

FDT's. The spray drying process involves the following basic stages:

1. Atomization of feed into a spray
2. Contact of dry air and spray
3. Evaporation of aqueous medium from droplets
4. Separation of dried product from air [27.]

Sublimation Technique

Due to the use of this technique generate highly porous tablets. The basis of this technique is to add non reactive (inert) solid ingredients that volatilize readily such as camphor, naphthalene, urea ammonium bicarbonate, urethane, etc to other additives and the mixture is then compressed into tablets. Remove this volatile material through sublimation, which formed a porous structure [28] The tablets after sublimation which are highly porous which leads to rapidly disintegrate or dissolved within 15 sec in saliva.

Tablet Moulding technique

In tablet moulding technique, moulded tablets are prepared by using water soluble ingredients so that tablet dissolve completely and rapidly. With the use of hydro-alcoholic solvent.

A. Compression moulding process

B. Heat moulding process

C. Moulding by vacuum evaporation without lyophilization

Melt granulation

In this process pharmaceutical powders are efficiently agglomerated by meltable binders. Water or organic solvent are not required for manufacturing of tablet this is the advantage of this system. For accomplishing this process, high shear mixers are utilized, temperature is raised above melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. Hydrophilic waxy binder (Superpolystate©, PEG-6 stearate) are used to prepare FDT with sufficient mechanical integrity. These waxy material is melt at 33-37°C that helps in disintegration of tablet as it melts in the mouth and solubilises rapidly leaving no residue s [29]

Supercritical fluid technology(SCF)

Novel supercritical fluid processes have developed by Ferro Corporation. Carbon dioxide is preferred medium for process. CO_2 is supplied to the reactor in a supercritical state or is heated

and pressurized in the reactor to attain a supercritical state. With the use of supercritical processes obtain stable aq. Suspensions of water-insoluble drugs, low bulk density porous particle for inhalation and composite particle comprised of porous particle of polymer that are infused with biologically active ingredients. The sizes of Particle obtain by this process are ranging from 10 nm to several microns.[26]

SCF extraction of emulsions (SFEE)

Drug with polymer are dissolve into organic solvent and dispersed in water using emulsifying agents to form emulsion. Using supercritical fluid organic solvents are extracted. This process can be used with small actives, polymers, lipids and some biological.[30]

Spray-freeze drying with CO_2

Drug and polymers are dissolving in water to form a solution that preparation then saturated with CO_2. This prepared solution is then sprayed using nozzle to form fine frozen droplets. Due to freeze drying water removed and porous or hollow particles are formed. This process is mostly used to formulate proteins.[22]

Expansion of SCF saturated solutions

The mixture of active ingredient and polymers are saturated with supercritical fluid creating a liquefied solution, this liquefied solution is then sprayed to form particles via cooling and SCF diffusion from the melt. Coating of particles is allows at mild temperature. [23]

Three-dimensional Printing (3DP)

This is rapid prototyping technology. It involves constructing specific layers that uses Processing of powder and liquid binding materials. This is based on computer aided design model. It was found that rapidly disintegrating with proper hardness can be prepared using TAG. The TAG tablets are disintegrates rapidly due to rapid penetration of water into tablet resulting from the large pore size and large overall pore volume. [29]

VARIOUS TECHNOLOGIES OF MANUFACTURING FDT'S

ADVANTOLTM 200

ADVANTOLTM 200 is developed by SPI Pharmaceutical it uses directly compressible excipients to produce "Soft-Melt" tablet by involving co-processing technology. The tablets are produced by conventional technique and equipment. The tablets produced are robust with good mechanical strength. [23]

ADVATAB

Advatab is developed by Eurand international the tablet having short disintegration time of 30 seconds and administered without water. Eurand international has its own registered

technological products Microcaps® and Diffucaps®. The combination product of Advatab and Microcaps has advantages such as ideal dosage form with superior taste and soft mouth feel but the disadvantage is taste masking of unpleasant drug.[29]

CEFORM TECHNOLOGY

Ceform technology involves microsphere formation of active ingredients along with excipients opening. The microspheres are formed in fast spinning machine; the centrifugal force is responsible for throwing the drug blend through small heated opening. The heat liquefies drug blend to form sphere. The spheres are compressed into tablets. The simultaneous drug and excipients processing offers unique microenvironment that enhances solubility and stability.[24]

COTTON CANDY TECHNOLOGY

The cotton candy process is patented by Fuise. This process involves spinning mechanism to produce floss like structure as appears in cotton candy. The floss formation increases the surface area very high that increases the dissolution rate. The flossy material mixed with excipients and then compressed into tablet. The tablet shows improved mechanical strength accommodate larger doses of drug but limitation is thermo labile substances as the process involves high temperature.[31]

DURASOLV (Cima Labs, Inc.)

Durasolve is second generation patented technology of CIMA labs Inc, it produces fast dissolving tablet using drug and excipients such as fillers, lubricants that are generally regarded as safe (GRAS). The tablets are produced using conventional technology by direct compression method and packaged using conventional packaging system such as blister, bottle, foil, pouches and vials. The marketed brands are NuLev and Zomig ZMT.[29]

The tablet offers following advantages and disadvantages

Advantages [32]

1. The tablets produced are rigid possess good mechanical strength.
2. The tablet can be produced with low doses of active ingredients.
3. The tablets produced are durable in nature.
4. As conventional methods are used the tablets are produced in cost effective manner.

Disadvantages[29]

1. The tablet should not be exposed to moisture as it hygroscopic in nature.
2. During production process moisture levels should be monitored carefully, thus increases the cost of production.

FLASH TAB TECHNOLOGY

Flash tab technology to produce mouth dissolving tablet are patented by prographarm. In this technology the active pharmaceutical ingredient is used in the form of microcrystals along with excipients using conventional techniques like coacervation, micro encapsulation, and extrusion spheronisation. The tablets produced disintegrates fast in the mouth within one minute.[23]

FLASHDOSE (FUISZ)

The technology Flash dose has been patented by "Fuisz". A new form of ibuprofen as melting-mouth tablets, Nurofenmeltlet prepared using flash dose technology. " Biovail Corporation" launched first commercial product by name Nurofenmeltlet. Flash dose tablets consists of self binding shear form matrix termed known as "floss". Floss is compressed along with excipients and tablets are rigid possessing good mechanical strength. [30,23]

FROSTA TECHNOLOGY

Frosta technology patented by Akina. The technology consists of use of plastic granules that are compressed at very low compression pressure along with water penetration enhancer, and binder. The tablet produced possess excellent hardness and rapid disintegration intime the range of 15 to 30 sec. [28]

LYOC TECHNOLOGY (Farmalyoc)

Lyoc technology is patented technology of farmalyoc, marketed in USA that produces fast dissolving tablet by subjecting an aqueous solution, suspension, oil in water emulsion to freeze drying or sublimation process along with active pharmaceutical ingredients and excipients. The technique require large amount of inert filler which makes the tablet less porous thus increasing the disintegration time. The tablet produced becomes dense and possess poor mechanical strength. [26]

NANO TECHNOLOGY

Nanotechnology is technique that is applicable in fast dissolving tablet that involves Nano crystals. Nanotechnology is Elan's proprietary technology that uses particles of less than 2µ.The drug is compressed along with excipients. The technique is of choice for poorly water soluble drugs and with dose up to 200 mg. the tablet shows faster disintegration and dissolution and thus offers higher bioavailability and reduction in drug dose. The process involves use of conventional tablet equipment and packaging system.[24,25]

PHARMABURSTTECH (SPI PHARMA)

Pharmaburst™ is a "Quick Dissolve"delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipients system with specific excipients, which allows rapid disintegration and low adhesion to punches. Saccharides are used to obtain rapid melting strong tablet. The active

ingredient mixes with low mouldablilty saccharides[30]

QUICK–DIS TECHNOLOGY

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick- Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from Unit dose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. drug delivery system is 50% released within 30 seconds and 95% within 1 minute. [22]

SHEARFORM TECHNOLOGY

In this technology, a shear form matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. The flowing mass comes out through the spinning head that flings the floss. The produced floss is amorphous in nature. So by various techniques, it is further chopped and re-crystallised to provide a uniform flow, thus facilitate blending. Then the re-crystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before re-crystallising it. [24,28]

WOWTAB (YAMANOUCHI PHARMATECH. INC)

Wowtab Technology is patented by "Yamanouchi Pharmaceutical Co. "WOW" means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.[33] The tablets produced by Wowtab technique Offers Superior mouthfeel due to the smooth meltaction. It is suitable for both conventional bottle and blister packaging. Bit more stable to the environment than other techniques. [32]

ZYDIS TECHNOLOGY

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the

mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. polymers such as gelatin, dextran or alginates are incorporated. These forms a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.[32]

Evaluation of Fast Dissolving Tablets:

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in Table 3.

Table 3: Limits for the weight variation of tablets

Average weight of tablet	% deviation
80mg or less •	10
More than 80 mg but less than 250 mg •	7.5
250mg or more •	5

Tensile Strength

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using equation (1):

$$T = \frac{2F}{\pi dt} \quad \text{----- Eq-1}$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively[34.] Though, this is a widely used and accepted method for hardness testing, it is not applicable to very delicate tablets prepared by lyophilization technique wherein the liquid suspension of drug and excipients is freeze dried in the blister pocket and the dried tablets are finally sealed in the blister. Special aluminium(alu) blisters with peel off blister covers are used as packaging material for these tablets. Flash dose tablets prepared by cotton candy process are also poor candidates for this test[35, 36.] This test is best suited for tablets prepared by direct compression and moulding methods. However, the tensile strength of these tablets is always kept low which needs to be compromised to keep the disintegration time as minimum as possible.

Friability

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for FDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flash dose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

Moisture Uptake Study

MDTs usually contain high concentration of hydrophilic excipients with the minimum possible hardness which together contributes to their increased susceptibility to moisture uptake. In order to maintain their physical integrity and surface texture, special attention is required during the storage and packaging of these dosage forms. Therefore, moisture uptake studies are strongly recommended for FDTs. The test can be carried out by keeping ten tablets along with calcium chloride in a dessicator maintained at 37°C for 24 h to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the dessicator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing. The materials with high moisture resistant properties should be used for packaging for e.g. alu strip pack, alu-alu blister or polyethylene sealing on blister. The use of appropriate quantity of desiccant in HDPE bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life [37]

Tablet Porosity

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non wetting liquid to climb up a narrow capillary.

The pressure difference across the interface is given by the Washburn equation II, where the pressure drop is inversely related to the pore size (perpendicular radius) [38]

$$\Delta P = -(2\gamma/r)\cos\theta \quad \text{..... Eq (2)}$$

where γ is the surface tension of the liquid, r is the perpendicular radius and θ is the angle of contact between the liquid and the capillary walls. Pore radius is calculated from eq II using

experimental data obtained in the form of P. In this test, the contact angle between mercury and the tablet is kept at 140° and the surface tension at the interface of mercury and the tablet is 0.486N/m. Pore sizes in the range of 0.06–360 μm, can be efficiently measured by this technique [39,40].Otherwise, the tablet porosity (ε) can also be calculated using equation III:

$$\varepsilon = \frac{1-m}{(\rho t V)} \ldots\ldots \text{Eq (3)}$$

Where ρt, is the true density, and m and V are the weight and volume of the tablet, respectively [39].Tablets prepared by spray drying, lyophilisation and cotton candy process generally possess high porosity and therefore, have extremely low disintegration time.

Wetting Time and Water Absorption Ratio

A study [41]on wetting time and water absorption ratio reported the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined according to equation IV:

$$R = \frac{100\ (Wa - Wb)}{Wb} \ldots\ldots\ldots \text{Eq (4)}$$

Where Wb and Wa are the weights of tablet before and after water absorption, respectively.

In vivo determination of disintegration time

The time for disintegration of ODTs is generally <1 minute and actual disintegration time that patient can experience ranges from 5 to 30 seconds. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth within salivary contents. Various disintegration methods developed are discussed.

Dissolution Test

The Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1N HCl and buffers (pH -4.5 and 6.8) should be evaluated for ODT much in the same way as conventional tablets.USP dissolution apparatus 1 and 2 can be used. USP 1Basket apparatus may have certain applications, but sometimes, tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. Kancke [42] proposed USP 2 Paddle apparatus, which is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of ODT is very fast when using USP monograph conditions; hence,

slower paddle speeds may be utilized to obtain a profile. The USP 2 Paddle apparatus at 50 to 100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste masked drug should match that of the finished product to maximize the value of the test. High performance liquid chromatography is often required to analyze dissolution aliquots[43] .

Table 6: Mouth dissolving tablet available in the market

Brand name	Active	Company
Zomig ZMT and	Zolmitriptanv	Astra Zeneca
Cibalginadue FAST	Ibuprofen	Novartis Consumer
Nulev	Hyoscyamine	Schwarz Pharma
Benadryl Fastmelt	Diphenhydramin	Pfizer
Pepcid ODT	Piroxicam	Pfizer
Feldene melt	Famotidine	Meark
Zyprexa	Olanzapine	Eli lilly
Zofran ODT	Ondansetron	GSK
Klonopin Wafers	Clonaxepam	Roche

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.

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.

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