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FAST DISINTEGRATING TABLETS: A REVIEW

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ABSTRACT
Fast disintegrating tablets (FDTs) have received increasing demand from the last few years and the field has become a rapidly growing field in the pharmaceutical industry. Fast disintegrating tablets (FDTs) are those solid doses form which when put on the tongue gets rapidly dissolved, releasing the drug within a few second without need of water. The development of FDTs have been formulated for paediatric, geriatric and bedridden patients and for active patients who are busy and travelling and may not have access to water. Such formulation provide an opportunity for product line extension in the many elderly persons will have difficulties in taking conventional oral doses forms(viz, solution suspensions tablet and capsules) because of hand tremors and dysphasia. This article focused on ideal requirements, need for development of FDTs, challenges in formulations, suitability of drug candidates super-disintegrants employed, various technologies developed for FDTs. Evaluation methods, and various marketed products.

KEYWORDS: Fast disintegrating tablets (FDTs), Solid dosage form, Conventional oral dosage form, Super-disintegrates, bioavailability, Patient's compliance.

1. INTRODUCTION

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation and is moving rapidly.[1] Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance.[2] Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self medication, pain avoidance and the most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules.[3,4] One important drawback of such dosage forms is "Dysphasia" or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy.[5,6] To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form.[7] Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance.[8] Fast-dissolving drug-delivery systemscame into existence in the late 1970's as an alternative to tablets, capsules andsyrups for paediatric and geriatric patients.

The Centre for Drug Evaluation and Research(CDER), US FDA defined Fast-dissolving/disintegrating tablets (FDDTs) are "*A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue*".

Recently European Pharmacopoeia also adopted the term "*Oro Dispersible Tablet*" defined as "*uncovered tablet for buccal cavity, where it disperses before ingestion*".[9]

Fast disintegrating tablets (FDT) are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapid melt, fast melts, oro-dispersible, melt-in-mouth, quick dissolving, porous tablets, EFVDAS or Effervescent Drug Absorption System.[10] Fast disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. When Faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), cross linked polyvinylpyrollidone

(crospovidone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva.[11]

1.1 Requirements for tablet disintegration[12]

1. Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
2. Allow high drug loading.
3. Be compatible with taste masking and other excipients.
4. Have a pleasing mouth feel.
5. Leave minimal or no residue in the mouth after oral administration.
6. Exhibit low sensitivity to environmental conditions such as humidity and temperature.
7. Be adaptable and amenable to existing processing and packaging machinery.

1.2 Advantages of fast disintegrating tablet's[13,16]

1. **Accurate dosing:** Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.
2. **Enhanced bioavailability:** Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus.
3. **Rapid action:** Beneficial in cases such as motion sickness, acute pain, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.
4. **Patient compliance:** No need of water to swallow the dosage form. Hence, it is convenient for patients who are travelling and do not have immediate access to water.
5. **Ease of administration:** Convenient to administer especially for geriatric, paediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.
6. **Obstruction free:** No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.
7. **Enhanced palatability:** Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.
8. **Simple packaging:** No specific packaging required. It can be packaged in push through blisters.
9. **Business Avenue:** Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.
10. **Cost effective:** Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

1.3 Disadvantages of fast disintegratingtablet's[16]

1. High doses cannot be incorporated.
2. Dose uniformity is a technical challenge.

1.4 Challenges in Formulatingfast Disintegrating Tablet's

Palatability-As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasingthe active ingredients which come in contactwith the taste buds; hence, taste-masking ofthe drugs becomes critical to patientcompliance.[17,18]

Aqueous solubility-Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, 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. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.[19,20]

Hygroscopicity-Several orally disintegrating dosage forms 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.[21]

Amount of drug-The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.[22]

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.[23]

Mouth feel-FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.[24]

Sensitivity to environmental conditions-FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water [24].

1.5 Mechanism of Disintegration of FDT's[25,72]

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of a drug mainly depends on physiochemical properties of the drug. The rate of drug dissolution is greatly influenced by disintegration of the tablet. Disintegrants are

important excipients of the tablet formulation, they are always added to tablet to induce breakup of tablet when they are comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together.

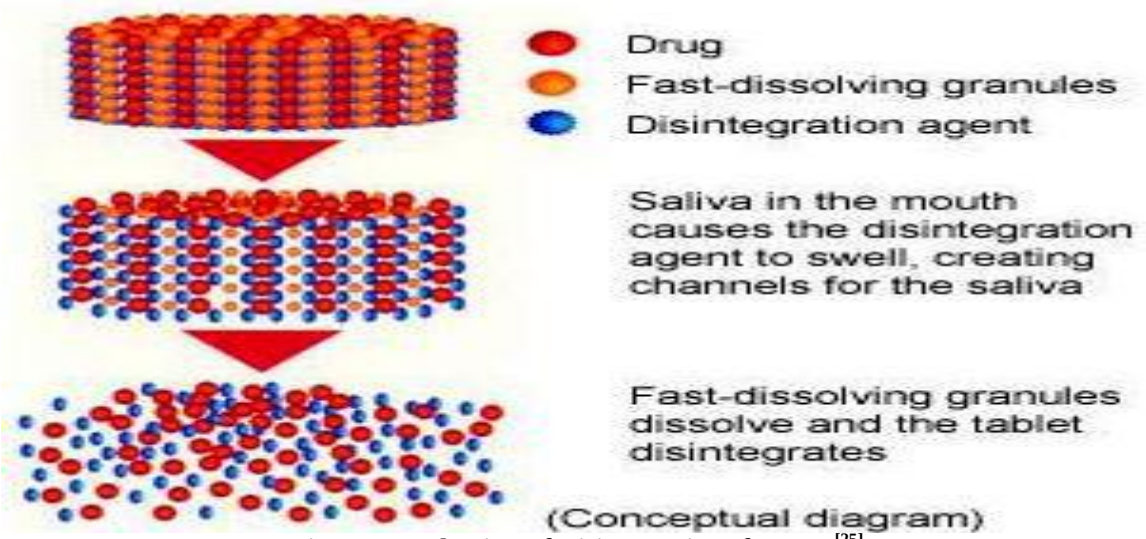

Fig. 1.1: Mechanism of Disintegration of FDT,s.[25]

1.6 General Excipients Used in FDT'S Preparation

Excipients used in FDTs contain at least one superdisintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavourings.

Table 1.1: Name and weight percentage of various excipients.[26]

Name of the Excipients	% Used
Superdisintegrants	1-15%
Binder	5-10%
Antistatic agent	0-10%
Diluents	0-85%

1.6.1 Superdisintegrants

Superdisintegrants are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs, some commonly used superdisintegrants are cross linked carboxymethyl cellulose (crosscarmellose), sodium starch glycolate, polyvinylpyrrolidone etc.

Table 1.2: List of Superdisintegrants.[26]

Superdisintegrants	Example	Mechanism of Action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and Wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant	-	-Does not contain any starch or sugar. Used in nutritional products
Calcium silicate		-Wicking Action	Highly porous, Optimum concentration is b/w 20-40%

1.6.2 Advantages of Superdisintegrants

1. Effective in lower concentrations
2. Compatible with commonly used therapeutical agents and excipients.
3. Less effect on compressibility and flowability.
4. Remarkable tendency on wetting causing rapid disintegration
5. Work equally effective in hydrophilic and hydrophobic formulations.
6. More effective intragranularly.
7. Does not stick to the punches and dyes.

1.6.3 Mechanism of action of superdisintegrants

Porosity and capillary action (Wicking): Disintegration by capillary action is always the first step.When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet andreplaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tabletinto fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipients and ontableting conditions. For these types of disintegrants maintenance of porous structure and lowinterfacial tension towards aqueous fluid is necessary which helps in disintegration by creating ahydrophilic network around the drug particles.

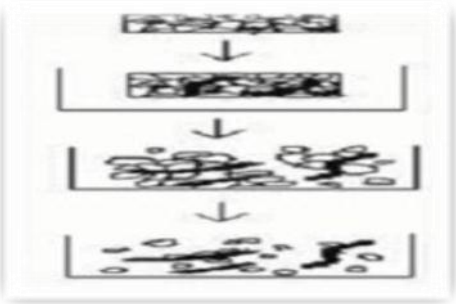

Fig. 1.2: Porosity and capillary action (Wicking).[27,28]

Swelling: The general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is to penetrate in the tablet and disintegration is again slows down.

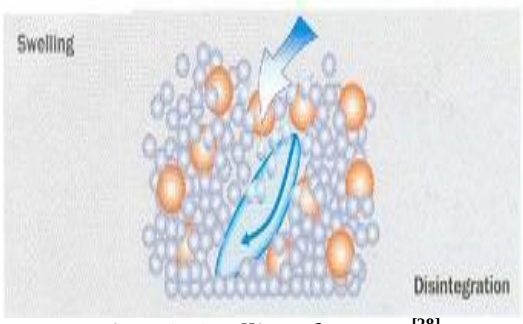

Fig. 1.3: Swelling of FDT, s.[28]

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. Researchers found that repulsion is secondary to wicking.

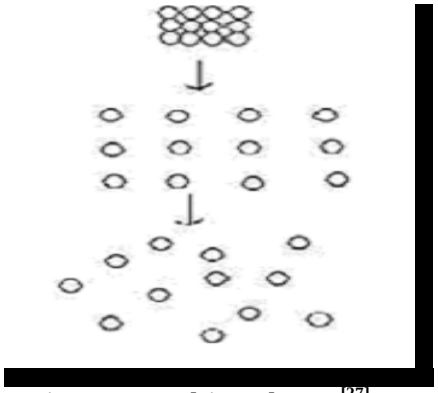

Fig. 1.4: Repulsion Theory.[27]

Due to deformation-During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

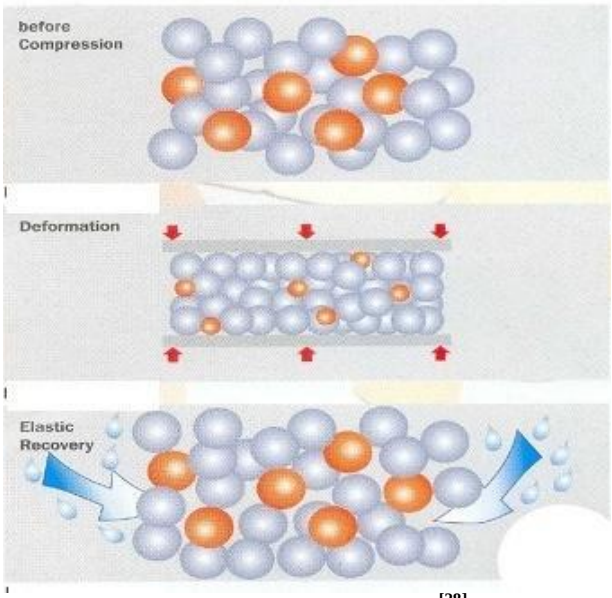

Fig. 1.5: Elastic recovery.[28]

Due to release of gases-Carbon dioxide released within tablets on wetting due to interaction between bicarbonate

and carbonate with citric acid or tartaric acid. The tablet disintegrates due togeneration of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet, as these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in two separate fraction of formulation.

By enzymatic reaction-Here, enzymes present in the body act as disintegrants. These enzymes destroy thebinding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

1.7 Techniques for Preparing Fast Dissolving Tablets[29]

Freeze-Drying or Lyophilization: Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Moulding: Moulding process is of two types i.e., solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30oC under vacuum. The mechanical strength of moulded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilization technique, tablets produced by the moulding technique are easier to scale up for industrial manufacture.

Spray Drying[69]: In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crosspovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation: To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents.

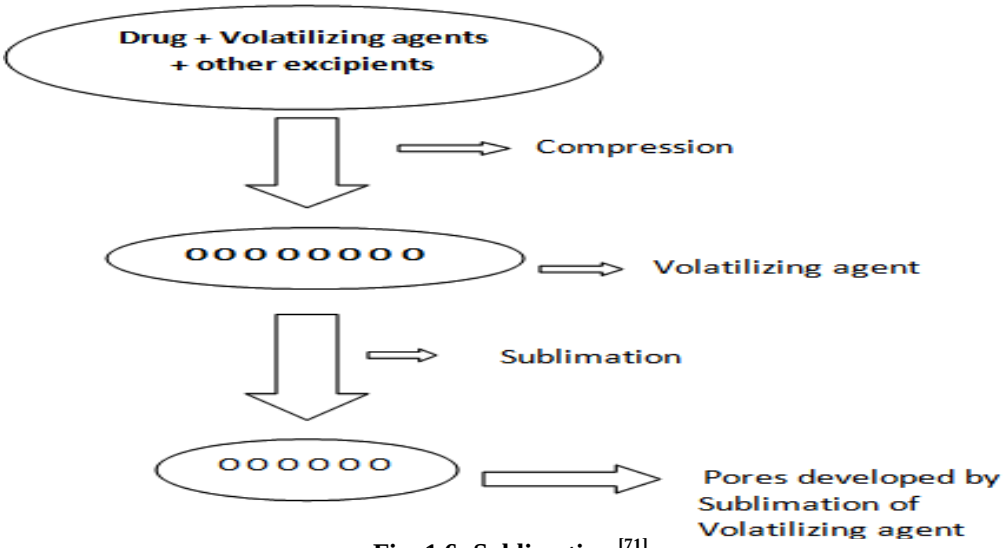

Fig. 1.6: Sublimation.[71]

Direct Compression: Direct compression represents the simplest and most cost effective tablet manufacturing technique. In this method, tablets are prepared directly by compression of the mixture of drug and excipients without any preliminary treatment. The mixture which is to be compressed must have good flow properties (**Fig 7**). This method complete within 3 steps i.e.

a. Milling of drug and excipients
b. Mixing of drug and excipients
c. Tablet compression

Fig. 1.7: Direct compression.[71]

Nanonization: A recently developed Nanomelt technology involves reduction in the particle size 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. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/ dissolution of nanoparticles leading to increased absorption and hence 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).

Fast Dissolving Films: In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinylpyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste.

1.8 Important patented technologies for fast disintegrated tablet's[6,30,31,32]

Zydis Technology[33,35]**:** Zydis® was introduced By R. P. Scherer Corporation in 1986. 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. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form 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 asglycines 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.

Orasolv Technology: *CIMA labs* have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

OraQuick Technology: *KV Pharmaceutical* claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

Quick-Dis Technology: *Lavipharm Laboratories Inc.* (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, 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.

Durasolv Technology[36]: DuraSolv is Cima‟s second-generation fast-dissolving/ disintegrating tablet formulation. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tableting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.

Wowtab Technology[37]: Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". The active ingredients may constitute upto 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldabiity saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs.

Flashtab Technology[38]: The Flashtab technology is yet another fast dissolving/disintegrating tablet formulation. Prographarm laboratories have patented the Flashtab technology. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute.

Advatab Technology[39,41]: Advatab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is distinct from other ODT technologies as it can be combined with Eurand‟s complimentary particle technologies like its world leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

Flash Dose Technology[42]: Flash dose technology has been patented by Fuisz. Nurofenmeltlet, a new form of Ibuprofen as melt-in-mouth tablets. Flash dose tablets consist of self binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

Sheaform Technology[43]: The technology is based on the preparation of floss that is also known as "Shearform Matrix", which is produced by subjecting a feed stock containing a sugar carrrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide aciform flow properties and this facilitate blending the recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet.

Pharmaburst Technology[44]: Pharmaburst™ is a "Quick Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch faces mouldablilty saccharine are used to obtain rapid melting

strong tablet. The active ingredient mixes with low mouldablilty saccharides.

Dispersible Tablet Technology[45,46]: Lek in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxinemethanesulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.

Nanocrystal Technology[47,48]: For fast disintegrating tablets, Elan's proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nanocrystal technology. Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. Nanocrystal Fast Dissolving Technology provides for Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix. Product differentiation based upon a combination of proprietary & patent-protected technology elements.

1. Cost-effective manufacturing processes that utilize conventional, scalable unit operations.
2. Exceptional durability, enabling use of conventional packaging equipment & formats (bottles &/or blisters).
3. Wide range of doses (up to 200mg of API per unit).
4. Use of conventional, compendial inactive components.
5. Employment of non-moisture sensitive in-actives.

Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into FDT dosage forms because manufacturing losses are negligible.

Frosta Technology: *Akina*patents this technology. It utilizes the concept of formulating plastic granules and compressing them 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.

Ceform Technology: In this technology microspheres containing active ingredient are prepared. Basic requirement of this technology is placing dry powder containing either pure drug or special blend of drug and excipients. The microspheres then mixed and compressed into previously selected oral dosage form.

1.9 Evaluation of Fast Disintegrating Tablet's[49,50,71]

1.9.1 General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

1.9.2 Size and Shape

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

1.9.3 Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

1.9.4 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 following table.

Table 1. 3: Weight variation (According to IP).[70]

Average Weight of Tablet	% Deviation
80 mg or less	±10
80 mg to 250 mg	±7.5
250 mg or more	±5

1.9.5 Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and

handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

1.9.6 Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre -weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. The friability (F) is given by the formula.

$$F = \frac{W_{int.} - W_{fin}}{W_{int.}}$$

Where, W_{int}- Weight of tablets before friability.
W_{fin}- Weight of tablets after friability.

1.9.7 Wetting time[51]

Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured.

1.9.8 Disintegration test[52,53]

The time for disintegration of ODTs isgenerally less than one minute and actualdisintegration time that patient can experienceranges from 5-30 seconds. The standardprocedure of performing disintegration test forthese dosage forms has several limitationsand they are not suitable for the measurementof very short disintegration times. The methodneeds to be modified for ODTs asdisintegration is required without water; thusthe test should mimic disintegration in salivarycontents. A modified dissolution apparatus is applied to an ODT with a disintegration timethat is too fast to distinguish differencesbetween tablets when the compendial methodis used. A basket sinker containing the tablets is placed just below the water surface in acontainer with 900 ml of water at 37^0C, and apaddle rotating at 100 rpm is used. Thedisintegration time is determined when thetablet has completely disintegrated andpassed through the screen of the sinker. Various scientistshave developed new *invitro* methods that allow an accuratedetermination of disintegration test. Thedisintegration test is performed using a textureanalyzer instrument. In this test, a flat-endedcylindrical probe penetrates into thedisintegrating tablet immersed in water. As thetablet disintegrates, the instrument is set tomaintain a small force for a determined periodof time. The plots of some distance travelled by the probe generated with the instrument'ssoftware provide disintegration profile of thetablets as a function of time.

1.9.9 Dissolutiontest[54,73]

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. 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 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way astheir ordinary tablet counterparts. It has been suggested that USP 2 paddleapparatus is the most suitable and commonchoice for orally disintegrating tablets, with apaddle speed of 50 rpm commonly used.

1.9.10 Clinical studies[72]

In vivo studies have been performed on oral fast-disintegrating dosage forms to investigate their behaviour in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Zydis's residence time in the mouth and stomach, and its transit through the esophageal tract, was investigated using gamma-scintigraphy. Its dissolution and buccal clearance was rapid[55] the oesophageal transit time and stomach emptying time were comparable with those of traditional tablets, capsules, or liquid forms. A decreased intersubject variability in transit time was also observed.[56,57] Zydis also showed good therapeutic efficacy and patient acceptability - particularly in children[58,59] or when easy administration and rapid onset of action were required (such as for patients undergoing surgery.[60,61] The fastdisintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability.[62] Increased bioavailability and improved patient compliance were observed in Lyoc formulations for different drugs such as phloroglucinol[63], glafenine[63], spironolactone[64], and propyphenazone.[65] Using Zydis, all the drugs that can beabsorbed through the buccal and esophageal mucosa exhibited increased bioavailability andside-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism.[55] Finally, the suitability of ODTs for long-term therapy was also assessed. Lyoc formulations containing aluminium were positively tested in patients with gastrointestinal symptoms.[66]

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