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Review Article

A Review: Formulation of Fast Dissolving Tablet

Patel Zinkal K,* Patel Rahul R, Kanu R Patel, Mukesh R Patel
Department of Pharmaceutics,
Shri B.M.Shah College of Pharmaceutical Education and Research,
Dhansura Road College campus, Modasa, Arvali, Gujarat, India
*zinkal.pharm27@yahoo.in

ABSTRACT

As pharmaceutical scientists are attaining a better understanding of biochemical and physicochemical properties related to the drug action, the drug delivery systems are becoming simple. Recent advances in Novel Drug Delivery Systems (NDDS) aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery. Fast dissolving tablet is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets when put on the tongue. It readily dissolve or disintegrate in the saliva without chewing or water within <60 seconds. Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. This review includes requirements for fast disintegrating tablets, salient features, advantages, limitations, challenges in formulation, various technologies developed for fast disintegrating tablets, patented technologies, evaluation methods and various marketed products.

Keywords: Superdisintegrating Agents, Fast Dissolving Tablet, Enhanced Bioavailability, Oral Route.

INTRODUCTION

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery. Oral route of drug administration become popular route for systemic effects due to ease of ingestion, accurate dosage, self-medication, pain avoidance. Fast dissolving drug delivery system are Novel Drug Delivery techniques aim for designing dosage forms, convenient to be manufacture and administer without water, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance. [1] This segment of formulation is especially designed for pediatric, geriatric, bedridden, psychotic patients who are unable to swallow or refuse to swallow conventional oral formulation and also for active patients who are busy and traveling and may not have access to water. United States Food and Drug Administration (FDA) defined fast dissolving tablet (FDT) as “a solid dosage form containing medicinal substance or active ingredient which disintegrate or dissolve rapidly within seconds when placed upon the tongue.” Fast dissolving tablets are also known as mouth-dissolving tablets, rapid dissolving, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving, quick melt, and quick disintegrating tablets. [2]

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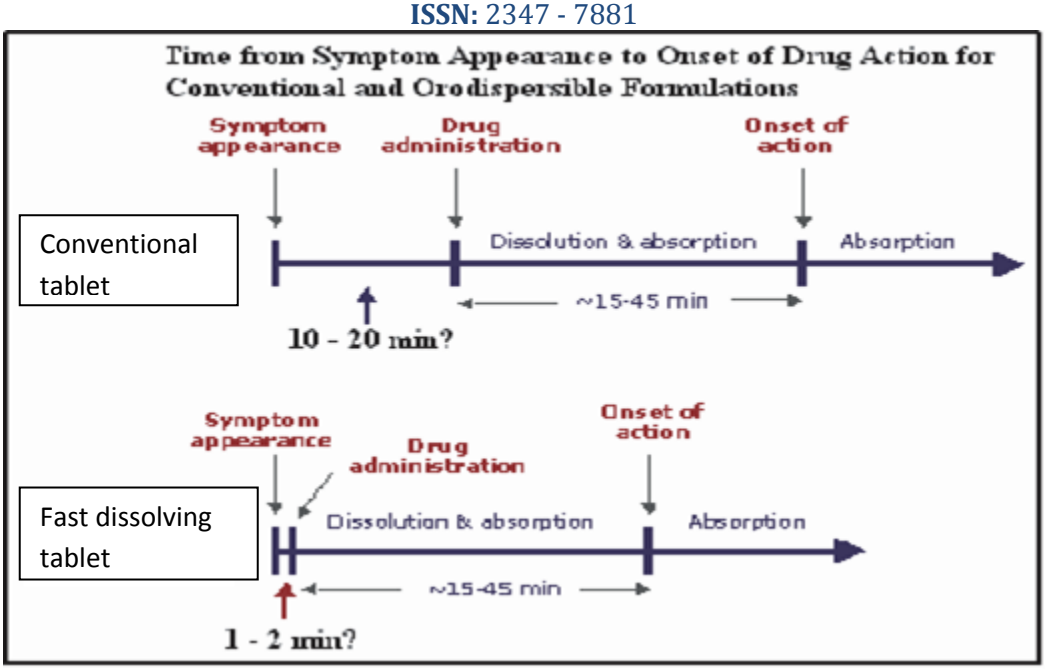

Figure: 1.1 Timely comparisons between Conventional & Fast dissolving tablet

CRITERIA FOR FAST DISSOLVING DRUG DELIVERY SYSTEM [3]

The tablets should:

- Not require water to swallow, but it should dissolve or disintegrate in the mouth within a seconds.
- Be compatible with taste masking.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity. [4]
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.
- Allow high drug loading.

ADVANTAGES OF FDT [5]

- Ease of Administration to the patient who cannot swallow and therefore improved patient compliance
- No water needed which is useful for patients who are traveling and do not have immediate access to water.
- Rapid dissolution, absorption of the drug and hence increase bioavailability
- Pregastric absorption of drug can increase oral bioavailability of drug, and as a result of reduces dose administration.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Good chemical stability as conventional oral solid dosage form.
- Convenience of administration and accurate dosing as compared to liquid formulation.
- Cost effective
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Advantageous over liquid formulation in terms of administration as well as transportation.[6]
- Reduced first pass metabolism.

LIMITATIONS OF FDT [7]

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● 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
● Drugs with larger doses are difficult to formulateinto FDT e.g. rifampin (600 mg), ethambutol (1000mg) etc.

DRUG SELECTION CRITERIA [8]

● Able to permeate the oral mucosa.
● At least partially non-ionized at oral cavity PH.
● Have the ability to diffuse and partition into the epithelium of upper GIT.
● Small to moderate molecular weight.
● Low dose drugs mostly less than 50 mg.
● Drug should have good stability in saliva and water.
● Drugs which have lower bioavailability, are good candidates for FDT.
● Short half life and frequent dosing drugs are unsuitable for FDT.
● Very bitter taste and unacceptable odor drugs are unsuitable for FDT.
● Pharmaceutical Companies have formulated FDT for various categories of drugs such as neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction.

THE NEED FOR DEVELOPMENT OF FDT [9]

Patient factors

FDTs are suitable for those patients (particularly pediatric and geriatric patients) who are unable to swallow traditional tablets and capsules. These include the following:
● Patients who have difficulty in swallowing oral tablet
● Patients incompliance due to fear of chocking
● A middle-aged patient undergoing radiation therapy may be too nauseous to swallow H_2-blocker
● A psychotic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic
● A patient with persistent nausea, who may be journey, or has little or no access to water. [10]

Effectiveness factor

Dispersion of drug in oral cavity causes pre-gastric absorption which avoids first pass hepatic metabolism which increase the bioavailability. Furthermore, safety profiles may be improved for drugs.

Manufacturing and marketing factors

As a drug nears the end of its patent life, it is possible for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form.

CHALLENGES IN FORMULATING FDT [11]

Palatability

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. FDT disintegrate or dissolve in patient's oral cavity, thus releasing API comes in contact with taste buds, so taste-masking become a critical to patient compliance

Mechanical strength

Order to allow FDTs to disintegrate in oral cavity, they are either vary porous or compressed into tablets with very low compression force, which makes tablets friable, difficult to handle and requiring specialized packing. These tablets have very poor mechanical strength

Hygroscopicity

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Several fast dissolving dosage forms are hygroscopic in nature and not able to maintain physical integrity under normal conditions of temperature and humidity. So, require special packaging

Amount of drug

The application of technologies used for ODTs 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.

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.

Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve

INGREDIETS MOSTLY USED IN FDT [12, 13]

Super Disintegrants

Disintegrants play a major role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. Sodium starch glycolate, Ac-di-sol (croscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised starch are some of examples of disintegrants.

Sugar Based Excipients

Sugar based excipients are used for taste masking and as bulking agents. Most of the dugs are having unpleasant or bitter taste. And the basic requirement for designing FDTs is that the drug should not have disagreeable taste. Sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking.

Antiadherents

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches. They are also used to help protect tablets from sticking. Most commonly used is magnesium stearate.

Binders

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets. Binders are usually

- Saccharides and their derivatives: sucrose, lactose, starches, microcrystalline cellulose and cellulose ethers such as Hydroxypropyl cellulose (HPC) , xylitol, sorbitol or maltitol;
- Protein: gelatin
- Synthetic polymers: polyvinylpyrrolidone (PVP), polyethylene glycol (PEG).

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Disintegrants

Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. Disintegrant types include:

- Water uptake facilitators
- Tablet rupture promoters

Example: cross linked polyvinyl pyrrolidone (crospovidone), cross linked sodium carboxymethyl cellulose (croscarmellose sodium), sodium starch glycolate.

Fillers or diluents

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. A good filler must be inert, compatible with the other components of the formulation, nonhygroscopic, relatively cheap, and preferably tasteless or pleasant tasting. Plant cellulose (pure plant filler) is popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is another popular tablet filler. Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate, vegetable fats and oils

Flavours

Flavours can be used to mask unpleasant tasting active ingredients and improve the likelihood that the patient will complete a course of medication. Flavourings may be natural (e.g. fruit extract) or artificial. Example: mint, cherry, anise, peach, apricot, liquorice, raspberry, vanilla

Colours

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication.

Lubricants

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

Glidants

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction. Examples include fumed silica, talc, and magnesium carbonate.

Preservatives

Some typical preservatives used in pharmaceutical formulations are:

- Antioxidants like vitamin A, vitamin E, vitamin C, retinyl palmitate, and selenium
- Citric acid and sodium citrate
- Synthetic preservatives like the parabens: methyl paraben and propyl paraben.

Sweeteners

Sweetners are added to make the ingredients more palatable, especially in chewable tablets such as antacids or liquids like cough syrup. Therefore, tooth decay is sometimes associated with cough syrup abuse. Sugar can be used to disguise unpleasant tastes or smells.

Sublimating Agents

The use of sublimating agents including camphor, menthol, and thymol was explored. The addition of camphor lowered the disintegration time (<30 s) further, but the percent friability was increased.

SUPERDISINTEGRANTES [14]

Use of disintegrates in FDT is basic approach. It is essential to choose a suitable disintegrates, in an optimum concentration to ensure

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disintegration and dissolution.it provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Use of superdisintegrantes like cross-linked cellulose, cross-linked PVP, cross-linked starch, cross-linked alginic acid.

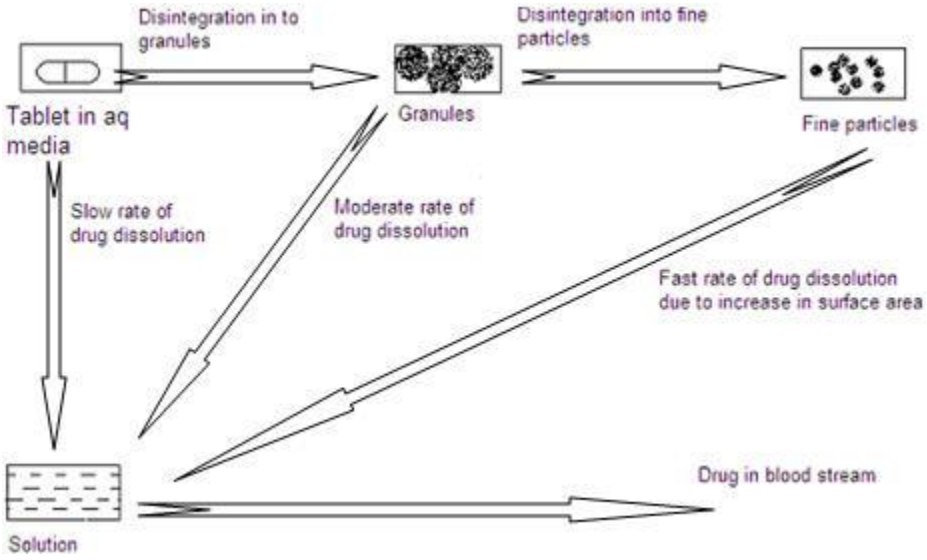
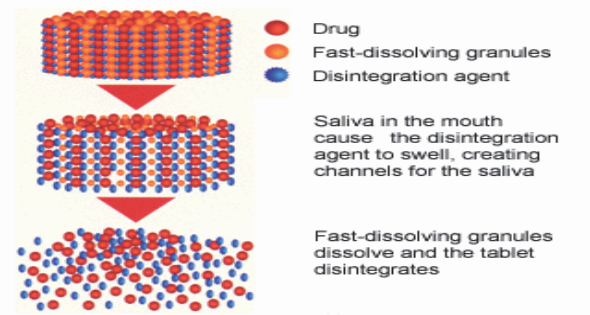


Figure: Tablet Disintegration and Subsequent Drug dissolution

Mechanism of Action of Superdisintegrats



By Capillary Action

When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

By Swelling

Perhaps the most widely accepted 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 unable to penetrate in the tablet and disintegration is again slows down.

Because of Heat of Wetting (Air Expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

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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 to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

By Enzymatic Reaction

Enzymes presents in the body also act as disintegrants. These enzymes destroy the binding 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.

Due to Disintegrating Particle/Particle Repulsive Forces

Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling 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.

Due to Deformation

Hess had proved that during tablet compression, disintegrated particles get deformed and these regain 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 break up of the tablet

MAJOR THEORIES IN FDT TECHNOLOGY

1. Mechanisms of granule aggregation

The binding mechanisms of agglomeration were first defined and classified by H. Rumpf. The mechanisms can be divided into five major groups.

Solid bridge: The solid bridge can be formed through sintering. If the temperature of the mixture rises above approximately two thirds of the melting temperature or softening range of the solid, diffusion of an atoms or molecules from one particle to another occurs at the point of contact. Formation of solid bridges can also occur by a chemical reaction or a hardening binder.

Adhesion and cohesion forces: Some materials, such as finely divided solids, can easily attract free atoms or molecules from the surrounding atmosphere. A thin adsorption layer can be developed on each particle and such layers contact and penetrate each other to form a strong bond.

Surface tension and capillary force: Free water or capillary condensation can develop liquid bridges. They often lead to formation of solid bridges.

Attraction force between solid particles: At extremely small distances between the adhesion partners these forces can be very high but, due to their short-range effect, they diminish quickly with increasing distance at the coordination points. Van der waals forces attract the particles at close range. Unsatisfied valences exist on newly created surfaces during grinding or compression.

Interlocking Bonds: Interlocking bonds occur if the particulate solids have elongated shape. In high- pressure agglomeration, another interlocking mechanism may occur if a mixture of rigid and plastic materials is compacted

2. Disintegration

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The complete disintegration defined by U.S. Pharmacopoeia XX is "The state in which any residue of the unit, except fragments of insoluble coating or capsule shell remaining on the screen of the test apparatus is a soft mass having no palpably firm core." Several mechanisms like

Evolution of gas: The basis of effervescent tablets is the reaction of sodium bicarbonate with citric or tartaric acid to yield carbon dioxide upon contact with water. Release of gas generates enough pressure to disintegrate a tablet

Adsorption: The heat of wetting of the ingredients that occurs when the tablet is immersed in a fluid causes the entrapped air in the tablet to expand and disintegrate a tablet. This proposal, however, is questionable. It is not clear whether the amount of heat generated can cause sufficient increase in the volume of air to cause pressure build up thus breaking a tablet apart. This mechanism can provide only a partial explanation.

Effect of water absorption (wicking): Disintegrants such as starch introduce water into a tablet and form a large system of capillaries inside the tablet to cause tablet disintegration.

Swelling: Disintegrants such as Ac-Di-Sol and various starches are reported to swell when moisturized. Swelling of these disintegrants will produce enough pressure to disintegrate a whole tablet. The tablets made at low pressure have high porosity. When starches swell, it will not generate enough pressure because of the high empty space. Medium pressure creates just enough space that allows water to come in and exert high pressure when starches swell. High pressure is thought to squeeze most porosity away and the water cannot flow into a tablet.

3. Water absorption

The affinity that a substance has for absorbing water from its vapor state is generally referred to as Hygroscopicity. Even the relatively weak bond of physical sorption, for which the heat of adsorption is comparable to the heat of condensation, can provide this driving force over a large range in relative humidity. For water- soluble substances, dissolution of the molecules at solid surfaces can occur once multilayer condensation is established.

TECHNIQUES FOR FDT [15]

Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing techniques. It is easiest way to manufacture tablet. Conventional equipments, commonly available experiments and limited number of processing steps are involved in direct compression.[17]

Superdisintegrants

A disintegrate is a substance in a tablet formulation that enables the tablet to break up into smaller fragments. Superdisintegrants are used at a low level in the solid dosage foam, typically 1-10 % by weight relative to the total weight of the dosage unit. Example of superdisintegrants are crosscarmellose sodium, crospovidone and sodium starch glycolate. Microcrystalline cellulose and low substituted hydroxypropyl cellulose were used as disintegrate agents in the range of 8:2-9:1 to prepare fast dissolving tablet. Agar powders used as disintegrate for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment.

Sugar based excipients

This is another approach to manufacture FDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch-hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence

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impart taste masking property and a pleasing mouth feel. [18]

Advantages of direct compression

- High doses can be accommodated and final weight of the tablet can exceed that of other methods.
- Easiest way to manufacture the tablets.
- Conventional equipment and commonly available excipients are use.
- A limited no. Of processing steps are involved.

Cost-effectiveness

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. This method generally used for drying the heat sensitive drug. 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 aluminum 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.

Spray Drying [16]

In this technique, gelatin can be used as a supporting agent and as a matrix ,citric acid as acidic ingredient, sodium bicarbonate as alkaline ingredients, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, ammonium carbonate, benzoic acid, phthalic anhydride, camphor etc. to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc. can also be used as pore forming agents. Fast dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.

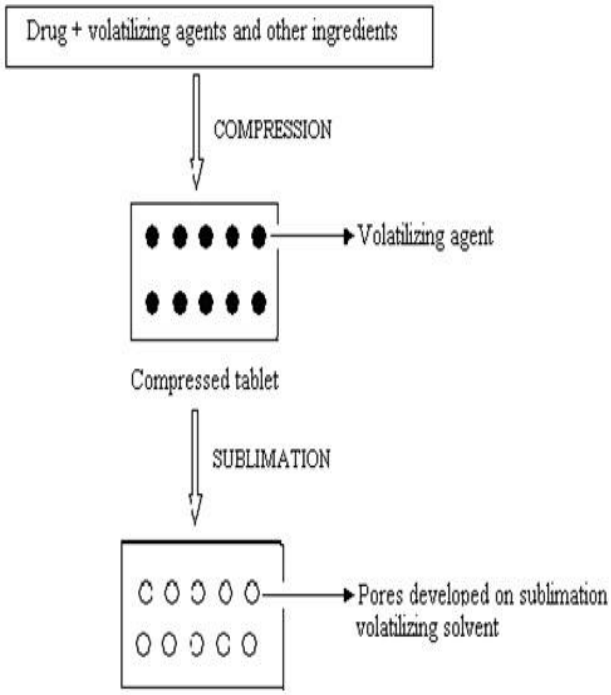

Fig. : schematic diagram of sublimation technique.

Melt Granulation

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In this process, FDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) like PEG-6-stearate. Super polystate is a waxy material with melting point of 33-37°C. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of FDTs by melt granulation method where granules are formed by the molten form of this material

Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking

Effervescent Agent Addition Method

In this method a mixture containing tartaric acid and an alkaline substance such as sodium bicarbonate is prepared by mortar pestle and preheated at 80°C. It is helpful in removing the residual or absorbed moisture. The mixture is then mixed with superdisintegrants and finally compressed to form tablets

Taste Masking Method

Usually, microencapsulation is used to mask the bitter taste of drug. The active drug is encapsulated in an immediate release matrix. In FDTs, the rapid disintegration is achieved by using effervescent agents. The taste masking method involves the compression of taste masked microcrystal of active drug compound along with swelling and disintegrating agent.

Tablet Molding

In this technology water soluble ingredients are used, so that tablet disintegrate and dissolve rapidly. Molding process is of three types:

Solvent method: Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution.

Heat method: The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum.

No vaccum lyophillization: This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

The mechanical strength of molded tablets is a matter of great concern,

Phase Transition Process

Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and

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spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDTs

Nanonization

Involves size reduction of drug to nano size 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. It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

IMPORTANT PATENTED TECHNOLOGIES FOR FDT [19]

● **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. To impart strength and resilience 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 while 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.

● **Wow Tab Technology**

Yamanouchi patented this technology. WOW means without water. This technology utilizes conventional granulation and tableting methods to produce FDTs employing low- and high-mouldability saccharides. Low mouldability saccharides are lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides are used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (eg. Maltose, oligosaccharides) and compressed into table. Thus tablets obtained showed adequate hardness and rapid disintegration. Because of hardness, shows fast salvation in mouth and offer a very pleasant the tablet is more stable in the environmental conditions mouth feel. The general manufacturing method of tablets than the Zydis or Orasolv and is fit for both usual bottle by this technology involves preparation of sucrose and blister packaging.

Durasolv Technology

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants. Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture. The tablets have disintegration time less than 60 seconds. In this technology more amounts of hydrophobic lubricants, can be used in the formulation. Low compressive force is

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required to compress the tablet. The production cost is significantly less because direct compression method and conventional package equipment are employed.

Orasolv Technology

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the FDTs. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight. The particle coating which is used for taste masking purpose is not cracking at the time compression force. As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv, a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression. Paksolv offers moisture, light, and child resistance packing.

Dispersible Tablet Technology

Lek, Yugoslavia patents this technology. It offers development of FDTs with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration. Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improves disintegration of tablets usually less than 1 min

Frosta Technology

This technology patents by Akina. It utilizes the concept of formulating plastic granules and compressing 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 usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet.

Pharmaburst Technology

SPI Pharma, New Castle, patents this technology. It utilizes the coprocessed excipients to develop FDTs, which dissolves within 30-40 s. This technology involves dry blending of drug, flavour, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

Lyoc

Lyoc technology is patented by Pharmalyoc. Oil in watr emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity 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.

Flashtab Technology

Prographarm labs have a patent over this technology. In this technology, microgranules of the taste-masked active drug are used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusions-pheronisation. All these processes utilize conventional tableting technology. These taste-masked micro crystals of active drug, disintegrating agent, a swelling agent and other excipients like soluble diluents etc. are compressed to form a multiparticulate tablet that disintegrates rapidly. Disintegrating agents include reticulated polyvinylpyrrolidine or carboxy methylcellulose. Swelling agents

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include carboxy methylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

Nanocrystal Technology

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.

NanoCrystal™ Fast dissolving technology provides for:

a. Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix

b. Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters).

c. Wide range of doses (up to 200mg of API per unit).

d. Employment of non moisture sensitive substances.

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. It is considered that this technology reduces the particle size, which is beneficial to enhance the dissolution, hence bioavailability

Advatab Technology

During the production process of FDTs, the lubricant is coated on each tablet surface by a spray. The produced tablets are stronger and harder than conventional due to which saliva cannot penetrate easily [10]. High drug loading is possible in this technology. Additionally, there is no requirement of special packaging and, also, the tablet can be packaged in both push-through blisters and standard bottles. It is reported that AdvaTab tablets disintegrate within less they than 30 seconds due to quick penetration of saliva in pores of tablet in mouth.

Quicksolv Technology

Both the drug and excipients are dissolved in water and frozen. Add second solvent to the frozen mixture. And finally after a few hours, the second solvent is removed, which results in formation of a porous matrix. The second solvent may be acetone or ethanol. Always the matrix composition should be immiscible to the second solvent. The drug should be in fine size and have good stability in aqueous medium

Flashdose Technology

It utilizes Shearform technology along with Ceform technology to avoid the bitter taste of the drug. Shearform technology prepares the floss matrix. Matrix is composed of drug and excipients. Floss refers to fibrous material, which is similar to cotton-candy fibres. These cotton-candy fibres are prepared by saccharides such as lactose, sucrose, fructose and polydextrose. Tablets prepared by this technology possess high porosity. Also, as tablets contain sugar, it shows fast salvation in mouth and offer a very pleasant mouth feel. The general manufacturing method of tablets by this technology involves preparation of sucrose solution (80%) and addition of 1 % surfactant. Surfactant helps in maintaining the structural integrity of the floss fibres. Then this whole product is subjected to the flash heat process. In this process, the heat provokes an interior flow state of the carrier substance. Then this processed material is passed through an exit, where a spinning head operated at 2000-3600 rpm. The role of spinning head is to throw the floss under centrifugal force and produce long floss fibres. These fibres are

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generally amorphous in nature. Mix the drug and required excipients with floss fibres and finally compressed.

EVALUATION PARAMETERS [20]

Pre-compression Parameters

- **Bulk density (Db)**

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by:

$$D_b = M / Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder

- **Tapped density (Dt)**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by:

$$D_t = M / Vt$$

Where, M is the mass of powder, Vt is the tapped volume of the powder

- **Angle of repose(θ)**

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative 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

$$\tan (ø) = h / r$$

$$(ø) = \tan^{-1} (h / r)$$

Where, ø - is the angle of repose, h - height in cm, r - radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height(h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

SR.NO.	Angle of repose (^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

(Angle of Repose as an Indication of Powder Flow Properties)

- **Carr's index or %compressibility**

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} * 100$$

Where,
Dt is the tapped density of the powder and
Db is the bulk density of the powder.

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair Passable
23-35	Poor
33-38	Very Poor
< 40	Very Very Poor

(relationship between % compressibility and floe ability)

- **Hausner ratio**

Hausner ratio is an indirect index of ease of

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powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density.
Db is the bulk density.

Post-Compression Parameters

- **Weight variation**

20tablets 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 No.5

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

(Weight Variation Specification as per IP)

- **Hardness**

The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Monsanto tablet hardness tester). It is expressed in kg/cm^2 or pound.

- **Friability**

To achieve % friability within limits (0.1-0.9%) for an FDT is a challenge for a formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Friability of each batch was measure in "Electro lab friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min or total 100 times dropping a tablet at height of 6 inches in each revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation.

$$F = \frac{W_I - W_F}{W_I} \times 100$$

W_I = Initial Weight Of Tablet
W_F = Final Weight Of Tablet

- **Modified Disintegration Test:**

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

- **Dissolution test**

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

- **Wetting time**

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. To measure wetting time, five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus

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wetting is the important step for disintegration process to take place.

- **Water absorption ratio**

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

$R = 100 (Wa-Wb) / Wb$

Wb = The weight of the tablet before keeping in the petridish

Wa = The wetted tablet from the petridish is taken and reweighed.

- **Stability Study (Temperature Dependent):**

The fast dissolving tablets stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1°C

(ii) 50 ± 1°C

(iii) 37 ±1°C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization such as visual defects, Hardness, Friability, Disintegrations, and Dissolution etc. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

MARKETED FORMULATION OF FDT

BRAND NAME	API	COMPANY
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-Delhi, India
Tempra Quicklets	Paracetamol	Cima Labs,Inc.
Cibalgina DueFast	Ibuprofen	Eurand International
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
Felden fast melt	piroxicam	Pfizer Inc., NY, USA

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