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Review Article

FAST DISSOLVING TABLETS (FDTs): CURRENT STATUS, NEW MARKET OPPORTUNITIES, RECENT ADVANCES IN MANUFACTURING TECHNOLOGIES AND FUTURE PROSPECTS

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ABSTRACT

Fast dissolving tablet technology is a topic of current interest in pharmacy and therapeutics.

Tablet swallowing difficulty primarily affects the geriatric and paediatric populations whereas unpalatable taste of drugs leads to patient non-compliance. Swallowing problems also are common in young individuals because of their underdeveloped muscular and nervous systems. Fast Dissolving Tablets (FDTs) are one of the fruitful results of continuous technological advancements in the pharmaceutical industry. FD tablets play a major role in improving the patient's compliance. A variety of drugs can be administered in the form of FD tablets as they give the advantage of the liquid medication in the solid preparation. These novel types of dosage forms have found acceptance among the geriatric, paediatric and dysphasic patients. Fast-Dissolving Tablet (FDT) is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. It has been developed for oral administration, also called as fast-melt, rapid-melts, porous tablets or fast disintegrating or orally disintegrating tablets (FDTs). Fast or mouth dissolving tablets 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 tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. Fast dissolving tablets can be prepared by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, Cotton Candy Process and sublimation. In 1986, the first lyophilized fast-dissolving technology Zydis® was introduced (By Cardinal formerly R. P. Scherer) and several technologies are still improving.

Keywords: Fast dissolving tablets, Patented technologies, Development approaches, Taste masking approaches, Mechanism of disintegration, Future prospects and research trends.

INTRODUCTION

Patient compliance is one of the most important aspects in the pharmacy practice. Now days, pharmacy companies are coming up with development of new drug delivery systems to ensure the delivery of the drugs to the patients efficiently and with fewer side effects. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. This objective led to the emergence of the concept of Fast Dissolving Tablets. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintrigrants in the oral cavity without the need of water or chewing. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. [1]

Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. It has been reported that dysphagia (difficulty in swallowing) is common among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. FDTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population.

The role of technologies related to formulation of effective drug delivery systems with enhanced patient compliance is unique and fascinating. Over the long period of time, it has been observed that more than 50 percent of Pharmaceutical products are orally administered for several reasons; many of these products contain drugs which have an unpleasant taste, often very bitter. The major consequence of the bitter taste is to restrict greatly the further development of oral preparations and clinical applications of these drugs. Along with the continuing improvement in the social standard of living, it is no longer acceptable for useful medicines to have bitter taste. [2] People supposed to take effective drugs that have a nice taste and can be administered easily. Accordingly, it is important to mask the unpalatable taste of a drug in order to improve the product quality. This will also increase the value of the finished product as well as patient compliance, especially where infants, children and elderly are concerned. Hence, Pharmaceutical Industries invest time, money and resources into developing palatable and pleasant tasting products and Industries also adopt various taste masking techniques to develop an appropriate formulation.

FDTs offer several advantages over other dosage forms like effervescent tablets, dry syrups and chewing gums/tablets, which are commonly used to enhance patient's compliance. Administering effervescent tablets/granules and dry syrups involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage form, if the taste masking coat ruptures during mastication. [3] Administration of an oral drug delivery system having bitter taste and acceptable level of palatability has always been challenge in developing a formulation for paediatric and geriatric purpose. The bitterness of drug or drug product is minimized or eliminated by various physical, chemical and physiological means such as use of flavours, sweeteners, amino acids; and by using various techniques such as lipophilic vehicles, coating, inclusion complexation, ion exchange, effervescent agents,

rheological modification, solid dispersion system, group alteration and prodrug approach, freeze drying process, wet spherical agglomeration technique and continuous multipurpose melt technology. Developing a formulation with pleasant taste and rapid patient compliance has leaded the Pharmaceutical sector to work with newer and effective techniques for taste masking and product development. Therefore, formulation of taste masked products is challenge to Pharmacists.

The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. [4] Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide.

The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. Earlier reports revealed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste. The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water. [5]

Definition [6]

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

✓ A fast dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

✓ A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water.

✓ The fast disintegrating tablets are synonymous with fast dissolving tablets; melt in mouth tablets, rapid melts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.

Criteria for Fast dissolving Drug Delivery System: [7]

The tablets should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- 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.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.
- 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 quick 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 increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Benefits of fast dissolving tablets [8]

- Administered without water, anywhere, any time.
- Suitability for geriatric and paediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.
- Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- FDT passes all the advantages of solid dosage forms like good stability, easy manufacturing, unite and accurate dosing, easy handling etc.
- Provides rapid drug therapy intervention.
- There is no risk of physical obstruction due to dosage form.
- The possibility of an improved bioavailability due to rapid absorption and faster onset of action.
- Ease of administration to patients who are unable or refuse to swallow a tablet, such as paediatric, geriatric and psychiatric and disabled patients.
- Ability to provide advantages of liquid medication in the form of solid preparation.

- Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
- Allows high capacity of drug loading.
- FDTs helps avoids hepatic metabolism by allowing pregastric drug absorption thus reducing the dose of drug required.
- Adaptable to existing processing and packaging machinery.
- Cost-effective.
- Gives accurate dosing as compared to liquids Free of need of measuring, an essential drawback in liquids.
- Provides new business opportunities such as,

a. Product differentiation,

b. Line extension and life-cycle management,

c. Exclusivity of product promotion and patent-life extension.

Limitations of Mouth Dissolving Tablets [8]

- 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 relatively larger doses are difficult to formulate into MDT e.g. antibiotics like amoxicillin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for MDT.
- Similarly patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Patented technologies for fast dissolving tablets

Nowadays FD tablets are successfully evolved as the alternative way of administering tablets. There are number of patented technologies which were developed for the formation of FD tablets and are described as under:

Zydis Technology

Durasolve Technology

Orasolve Technology

Flash Dose Technology

Wow Tab Technology

Flash Tab Technology

Oraquick Technology

Quick–Dis Technology

Nanocrystal Technology

Shearform Technology.

Ceform Technology.

Pharmaburst technology

Frosta technology

Ziplet technology

Humidity treatment

Sintering

Zydis Technology: [9]

Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. 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 material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatine, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharide 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. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatine. The product is very lightweight and fragile and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pre-gastric absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. There are some disadvantages to the Zydis technology. As mentioned earlier, the Zydis formulation is very lightweight and fragile and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidities. It readily absorbs water and is very sensitive to degradation at humidities greater than 65%. The Zydis technology (ZT) is a patented technique which had been used for drugs like famotidine, enalapril, loperamide, piroxicam, oxazepam, lorazepam, domeperidone, brompheniramine, olanzepine, ondansetron and rizatriptan. In U.S., the FDT products available are: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis.

Durasolv Technology: [10]

Durasolv is the patented technology of CIMA lab's second-generation mouth-dissolving/disintegrating tablet formulation. Durasolv is an appropriate technology for product requiring low amounts of active ingredients. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). These can be packaged into conventional packaging system like blisters, pouches or vials. DuraSolv is Cima Produced in a fashion similar to OraSolv; DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabletting. The DuraSolv product is thus produced in a mouther and more cost-effective manner. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.

Orasolv Technology: [10]

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. OraSolv was Cima's first mouth-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special

handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolv formulations are not very hygroscopic. The major disadvantage of the OraSolv formulations is its mechanical strength.

Flash Dose Technology:

Flash dose technology has been patented by FUISZ. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shearform matrix termed as "floss". Shear form matrices are prepared by flash heat processing. The Flash Dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue.

Wow tab Technology: [11]

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". In this process, combination of low Mouldability saccharides (rapid dissolution) and high Mouldability saccharides (good binding property) (eg. Maltose, oligosaccharides) are used to obtain an adequate hardness and rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide and compressed into table. The Wow tab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market from a number of years. The Wowtab technology utilizes sugar and sugar-like (eg. mannitol) excipients. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The Wowtab product dissolves quickly in 15 seconds or less.

Flash tab Technology: [12]

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, micro encapsulation, simple pan coating methods and extrusion spheronisation. All the processing utilized conventional tabletting technology. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. The tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

Oraquick Technology [12]

The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more liable (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, psychotropic, and anti-infectives.

Quick–Dis Technology

The novel intra-oral drug delivery system, trademarked as Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. When 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 typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm.

NanoCrystal Technology [13]

For mouth dissolving 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 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds.

Shearform Technology ™ [13]

The Shearform technology is based on preparation of floss that is also known as 'shearform matrix', which is produced by subjecting a feedstock containing a sugar carrier 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 flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystalised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystalised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallisation. The shearform floss, when blended with the coated or uncoated microspheres, is compressed into Flashdose or EZ chew tablets on standard tabletting equipment.

Ceform Technology ™

In Ceform technology microspheres containing active pharmaceutical ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly-spinning machine. The centrifugal force of the rotating head of ceform machine throws the dry drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquefies the drug blend to form a sphere without adversely affecting drug stability. The microspheres are then blended and/or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microspheres can be incorporated into a wide range of fast dissolving tablets such as Flashdose, EZ chew, Spoon Dose as well as conventional tablets. [14]

Pharmaburst technology [14]

SPI Pharma, New castle, patents this technology. It utilizes the coprocessed excipients to develop ODT, 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.

Frosta technology [15]

Akina patents this technology. It utilizes the concept of formulating plastic granules and coprocessing 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 30s depending on size of tablet.

Ziplet technology [15]

In ziplet technology water insoluble drug(s) as coated micro particles are used. The addition of suitable amount of water soluble inorganic excipients combination with disintegrants are impart an excellent physical resistance to the FDT and simultaneously maintained optimal disintegration. The use of water soluble inorganic excipients offer better enhancement of disintegration in comparison to the most commonly used water soluble sugars or salts. Tablets primarily contain water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed reduces the rate of water diffusion into the tablet core.

Humidity treatment [15]

The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase mechanical strength is due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. When an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially. In a patent by Mizumoto et al a drug, a sugar, and an amorphous sugar capable of transforming from amorphous to crystalline state were mixed and compressed into tablets. The "amorphous sugar" is that which can form an amorphous state by spray drying, freeze drying, or other granulation methods. These amorphous sugars include glucose, lactose, maltose, sorbitol, trehalose, lactilol, and fructose. The relative humidity is determined by the apparent critical relative humidity of the mixture of a drug and an amorphous sugar. A relative humidity is greater than or equal to the critical relative humidity of this mixture which is to be chosen for the humidity condition. The advantage of using amorphous sugar is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems.

Sintering [15]

When thermal energy is applied to a powder compact, the compact is densified and the average grain size increases. The basic phenomena occurring during this process is called sintering or densification and grain growth. Lagoviyer et al disclosed a process that tablet strength can be increased by sintering the tablet components at high temperatures and then resolidifying them at lower temperatures. A bulk agent in this formulation is used to provide bulk volume to the overall tablet and suitable agents include carbohydrates, calcium carbonate, and magnesium carbonate. Solvents can be chosen from water, ethyl alcohol, isopropyl alcohol or a mixture thereof. Binders are water soluble polymers such as polyethylene glycol (PEG), with a molecular weight of approximately 1000 to 1,000,000 Dalton. The granules are then lightly compressed to form tablets. These tablets are heated for a sufficient time and temperature to allow the binding agent to melt. The heating step is intended to melt the binding agent to create intra tablet bonds and helps to weld the product in to shape. Typically, a laboratory oven is set at around 50-100ºC. The heating time ranges from 3 to 45 minutes. The binding agents are resolidified as the temperature is reduced to ambient temperature. The disintegration time is generally within 3-60 seconds.

Table 1: List of Various Patented Technologies with their Company and Product Name [9- 10-15]

Tech.	Key attributes	methods	Company names	Activ ingredients & Brand names
Zydis®	Freeze-drying on-blister packing	Lyophilization	R. P. Scherer, Inc. [Cardinal Health]	Loratidine (Claratin) ®Reditab Fanotidine Pepcid®ODT Selegiline ZelaparTM Rizatritpan benzoate Maxalt-®MLT Ondansetron Zofran®ODT
Durasolv	Direct compression using water-soluble excipients	Direct Compression	Cima Labs, Inc.	Zolmitriptan(Zolmig Zmt) Hyoscyamine Sulfate Nulev® Baclofen KemstroTM
OraSolv	low compression force and an effervescent couple as a water-soluble disintegrating agent	Direct Compression	Cima Labs Inc.	Paracetamol(Tempra Quicklets) Mirtazapine Remeron®SolTab TempraFirs Tablet
Flashdose	-	Cotton Candy Process	Fuisz Technology Ltd.	Tramadol HCL (Relivia Flashdose) Fluoxetine FluoxetineODT Zolpidem Tertrate Zolpidem ODT
WOWTAB®	High- and low-moldability saccharides	Direct Compression	Yamanouchi Pharma	Famotidine(Gaster D) Ramosetoron HCl Nasea OD Diphenhydramine Citrate Benadryl®Fastmelt
Flashtab	Granulation of excipients by wet or dry granulation method and followed by compressing into tablets	Direct Compression	Ethypharm France.	Ibuprofen(Nurofen Flashtab)
Oraquick	Micromask Taste masking		K V Pharma. Co. Inc.	Hyoscamine Sulfate ODT
Quicksolv		Lyophilization	Jansen Pharma	Risperidone (Risperdal MTab)
Pharmabrust	Direct compression of powder mixture		SPI Pharma	
Advatab	Direct compression using external lubrication system	Microcaps & diffuscap CR Technology	Eurand International	Advatab Cetrizine, Advatab Paracetamol
Lyoc	Freeze-drying on the shelves of freeze dryer	Lyophilization	Farmalyoc Laboratories L. Lafon, Maisons Alfort, France	Phlorglucinol hydrate(SpasfonLyoc)
Advantol™ 200	Directly compressible excipient system	Direct Compression	SPI Pharma	

Techniques used formulation of fast dissolving tablets (FDTs)

The fast dissolving property of the FDTs is attributed to quick ingress of water into tablet matrix resulting in rapid disintegration. Hence, the basic approaches to develop FDTs include: Maximizing the porous structure of the tablet matrix

Incorporating the appropriate disintegrating agent/agents

Using highly water soluble excipients in the formulation

So far, several techniques have been developed on the basis of different principles.

1. Freeze drying / lyophilization

2. Tablet Moulding

3. Spray drying

4. Sublimation

5. Direct compression

6. Mass extrusion

7. Cotton candy process

8. Nanonization

Freeze-Drying or Lyophilization: [16]

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. The saliva goes into the matrix resulting in the dissolution of the matrix. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer, such as suspending agents, wetting agents, preservatives, antioxidants, colours and flavours which improve the process characteristics or enhance the quality of final product. 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. Essential characteristics for Freeze drying formulations include small particle size with low dose and water-insoluble, chemically stable drug molecule. 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. This technique forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture FDTs. Lyophilization is also used to develop an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability of several drugs.

The major advantage of this technology is that it offers less disintegration time but the technique is quite expensive and special packaging procedures are required. The storage conditions should be properly maintained as these tablets are less stable to changing environment; hence special packaging procedures are required. During lyophilization, formulation excipients and process variables play an important role. Hydrochlorothiazide was used as a model drug for detecting the influence of various formulations and process parameters on the characteristics of FD tablets. According to them, maltodextrins are useful for the formulation of tablets formed by lyophilisation technique. Similarly results revealed the role of formulation excipients in the development of lyophilised fast disintegrating tablets. It was concluded that the use of 5% gelatin in combination of mannitol is the ideal formulation. Carbopol 974P-NF and Pluronic F127 (6%) were concluded to have the best viscosity modifying properties.

Table 2: Excipients and their uses in the manufacture of FDT using freeze drying technique [16]

Excipient	Use	Examples
Polymer	Strength and rigidity	Gelatine, alginate and dextrin
Polysaccharides	Crystallinity, hardness, and palatability	Mannitol and sorbitol
Collapse protectants	Prevents shrinking	Glycerine
Flocculating agents	Uniform dispersion	Xanthum gum and acacia
Preservatives	Prevent microbial and fungal growth	Parabens
Permeation enhancer	Tran mucosal permeability enhancer	Sodium lauryl sulphate
pH adjusters	Chemical stability	Citric acid and sodium hydroxide
Flavours and sweeteners	Patient compliance	-
Water	Porous unit formation	-

Tablet Molding: [17]

Molding process is of two type's i.e. solvent method and heat method. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The mechanical strength of molded 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 molding technique are easier to scale up for industrial manufacture.

Following are the different tablet moulding techniques:

a) Compression Moulding Process: Solvent method

This manufacturing process involves moistening the powder blend with a hydro alcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

b) Heat-Moulding Process:

Heat-moulding process involves setting the molten mass containing a dispersed drug. This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30°C under vacuum.

c) Moulding by Vacuum Evaporation without Lyophilization:

This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique as in the former, the evaporation

of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process. Unlike lyophilization, vacuum drying helps to densify the matrix and thereby improves the mechanical strength of the product. In comparison to lyophilisation process, tablets produced by moulding technique are easier to adapt to the industrial scale. Moulded tablets are cheaper and have poor mechanical strength. They can break or get eroded during the process of handling and storing. To overcome the poor taste, drug containing discrete particles was incorporated, which was formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

Spray drying: [17-18]

Spray drying process is widely used to provide products with high porosity in fine powder because the processing solvent can be easily dried. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol and lactose as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate) 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.

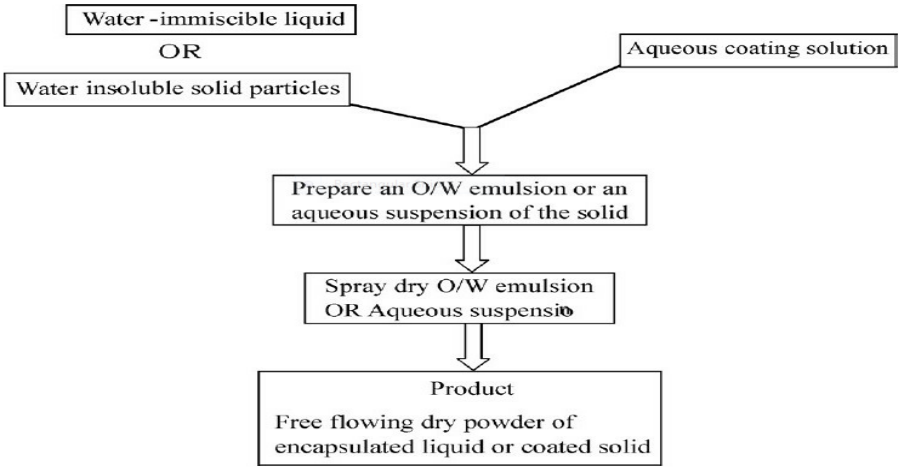

Fig. 1: Flowchart for coating liquid and solid particles using spray-dry process [17]

Sublimation: [18]

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. Sublimation of camphor was done in vacuum at 80 C for 30 minutes to develop pores in the tablets. Another technique describes use of water to produce fast dissolving tablets. Active ingredient and carbohydrates such as glucose or mannitol were moistened with water (1-3% w/w) and compressed into tablets. Removal of water yielded highly porous tablets.

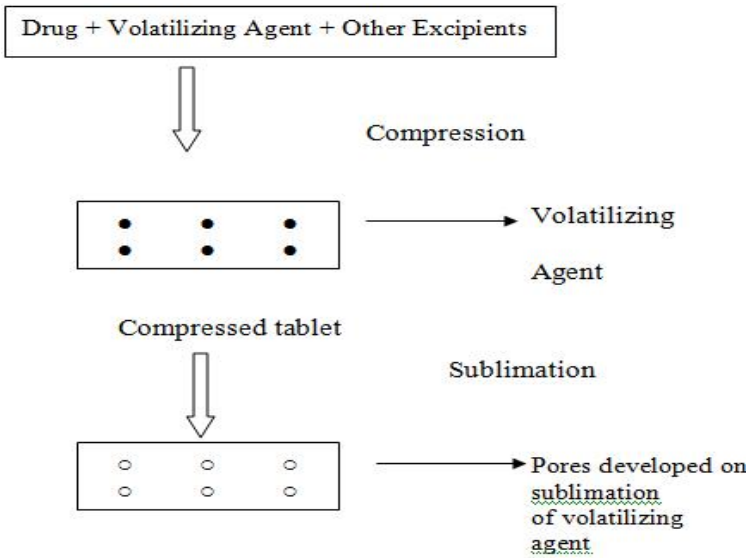

Fig. 2: Schematic Diagram of Sublimation Technique for Preparation of FDT [18]

Ex. Aceclofenac (NSAID), Amlodipine besylate (Dihydropyridine calcium antagonist), Ebastine (Second generation non–sedating H1 receptor antagonist), Cinnarzine (Histamine H- receptor antagonist), prepared by sublimation method

Direct Compression: [19-20]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of FDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of Superdisintegrants principally affects the rate of disintegration and hence the dissolution.

The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) 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 impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

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

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

Similarly, the use of sugar-based recipients like dextrose, fructose, isomalt, lactilol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol is appreciated in masking the bad taste of the tablets and impart sweetness while formulating FD tablets.

Examples of FDTs prepared by direct compression method: Albendazole (Broad spectrum antihelmintic), Chlorpromazine hydrochloride (Antiemetic), Aceclofenac (NSAID), Cetrizine Hydrochloride (Selective H1 receptor antagonist) Clonazepam (Antiepileptic), Etoricoxib (NSAID), Granisetron hydrochloride, Isoxsuprine hydrochloride (Vasodilator), Lornoxicam (NSAID), Losartan potassium (Antihypertensive), Levo-cetrizine hydrochloride (Non sedative anti-histaminic), Meclizine hydrochloride (Antiemetic), Metoprolol tartrate (Antihypertensive), Naproxen (NSAID), Famotidine (Histamine H2- receptor antagonist), Montelukast sodium (Antineoplastic), Telmisartan (Antihypertensive), Repaglinide (Antidiabetic), Rosiglitazone maleate (Antidiabetic), Salbutamol sulphate (β2 receptor agonist).

Mass-Extrusion:

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste. Ex. Rizatriptan benzoate (Serotonin 5-HT receptor agonist).

Cotton Candy Process: [21]

This method involves Shearform technology, use of a combined form of excipients, either alone or with drugs which are known as floss for preparation of matrix. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F.

However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermo labile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva.

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).

Table 3: List of Superdisintegrants [20]

Superdisintegrants	Example	Mechanism of action	Comment
- Crosscarmellose - Ac-DI-Sol	Cross linked cellulose	-Swells 4-8 folds in <10 sec - Swelling and wicking both	-Can be used in Direct compression or granulation-Starch free
-Sodium Starch Glycolate - Expotab® - Primogel®	Cross linked starch	-Swells 7-12 folds in <30 sec	- Swells in three dimension and high level as sustain release matrix
- Crosspovidone - Crosspovidon M - Kollidon - Polyplasdone	Cross linked PVP	- Swells very little and returns to original size after compression -Act by capillary action	- Water insoluble and spongy in nature so get porous tablet
- Alginic acid NF - Satialgine	Cross linked alginic acid	- Rapid swelling in aqueous medium	-Promote disintegration in both dry and wet granulation
Soy polysaccharides - Emcosoy	Natural super Disintegrants	- Wicking action	- Highly porous, optimum concentration is between 20-40%

Table 4: List of commercially available Fast dissolving tablets [17-19]

S. No.	Trade Name	Active Drug	Manufacturer
1.	Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
2.	Claritin redi Tab	Loratidine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
4.	Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merck and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7.	Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
8.	Zeplar TM	Selegilline	Amarin Corp., London, UK
9.	Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
10	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
11	Nimulid MDT	Nimesulide	Panacea Biotech, New delhi, India
12	Torrox MT	Rofecoxib	Torrent pharmaceuticals, India
13	Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
14	Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
15	Propulsid Quicksolv	Cisapride Monohydrate	Janssen pharmaceutics
16	Risperdal MTab	Risperidone	Janssen pharmaceutics
17	Spasfon Lyoc)	Phloroglucinol Hydrate	Farmalyoc
18	Nurofen FlashTab	Ibuprofen	Ethypharm
19	Tempra-Quicklets	Paracetamol	Cima Labs,Inc.
20	Zolmig Repidmelt	Zolmitriptan	Cima Labs,Inc.
21	NuLev	Hyoscyamine Sulfate	Cima Labs, Inc.
22	Gaster D	Famotidine	Yamanouchi Pharma Tech. Inc.
23	Cibalgina DueFast	Ibuprofen	Eurand International
24	Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd.
25	Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc.
26.	Abilify Discmelt	Aripiprazole	Otsuka America/Bristol-Myers Squibb
27	Allegra ODT	Fexofenadine	Sanofi Aventis
28	Aricept ODT	Donepezil	Eisai Co.

Table 5: Drugs to be promising in corporate in fast dissolving tablets [20-21]
There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient.

Analgesics and Anti-inflammatory Agents:	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim, Flurbiprofen, Naproxen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Sulindac, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam.
Anthelmintics:	Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Pyrantel Embonate, Thiabendazole.
Anti-Arrhythmic Agents:	Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate.
Anti-bacterial Agents:	Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixic Acid, Nitrofurantoin, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxine, Sulphamerazine, Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Tetracycline, Trimethoprim.
Anti-coagulants:	Dicoumarol, Dipyridamole, Nicoumalone, Phenindione. Anti-Depressants: Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Trimipramine Maleate., Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide, Tolbutamide.
Anti-Epileptics:	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Phensuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Primidone, Sulthiame, Valproic Acid.
Anti-Fungal Agents:	Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole Nitrate, Terbinafine, Terconazole, Tioconazole, Undecenoic Acid.
Anti-Gout Agents:	Allopurinol, Probenecid, Sulphinpyrazone.
Anti-Hypertensive Agents:	Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.
Anti-Malarials:	Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate.
Anti-Migraine Agents:	Dihydroergotamine Mesyiate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate.
Anti-Muscarinic Agents:	Atropine, Benzhexol, Biperiden, Ethopropazine, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Tropicamide, Orphenadrine, Oxyphencylcimine.
Anti-Neoplastic Agents and Immunosuppressants:	Aminoglutethimide, Amsacrine, Azathiopnne, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitotane, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone.
Anti Protozoal Agents:	Benznidazole, Clioquinol, Decoquinate, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.
Anti-Thyroid Agents:	Carbimazole, Propylthiouracil.
Anxiolytic, Sedatives, Hypnotics and Neuroleptics:	Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam, Clotiazepam, Clozapine, Diazepam, Droperidol, Ethinamate, Flunanisone, Flunitrazepam, Fluopromazine, Flupenuiixol Decanoate, Fluphenazine Decanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, Perphenazine Pimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone.

Cardiac-Inotropic Agents:	Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.
Corticosteroids:	Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate, Flunisolide, Flucortolone, Fluticasone Propionatu, Hydrocortisone, Methyl prednisolone, Prednisolone, Prednisone, Triamcinolone.
Diuretics:	Acetazolarnide, Amiloride, Bendrofluazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid, Frusemide, Metolazone, Spironolactone, Triamterene.
Anti-Parkinsonian Agents:	Bromocriptine Mesylate, Lysuride Maleate.
Gastro-Intestinal Agents:	Bisacodyi, Cimetidine, Cisapride, Diphenoxylate, Domeperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Ranitidine, Sulphasaiazine.
Histamine H,-Receptor Antagonists:	Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, Dimenhydrinate, Flunarizine, Loratadine, Meclozine, Oxatomide, Terfenadine, Triprolidine.
Lipid Regulating Agents:	Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.
Local Anaesthetics:	Lidocaine.
Neuro-Muscular Agents:	Pyridostigmine.
Nitrates and Other Anti-Anginal Agents:	Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.
Nutritional Agents:	Betacarotene, Vitamin A, Vitamin B_2, Vitamin D, Vitamin E, Vitamin K.
Opioid Analgesics:	Codeine, Dextropropyoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine.
Proteins, Peptides and Recombinant Drugs**:**	Insulin (Hexameric/Dimeric/Monomeric Forms), Glucagon, Growth Hormone (Somatotropin), Polypeptides or Their Derivatives, (Preferably With A Molecular Weight from 1000 To 300,000), Calcitonins And Synthetic Modifications Thereof, Enkephalins, Interferons (Especially Alpha-2 Inter Feron For Treatment Of Common Colds).
Sex Hormones:	Clomiphene Citrate, Danazol, Ethinyloestradiol, Medroxyprogesterone Acetate, Mestranol, Methyl testosterone, Norethisterone, Norgestrel, Oestradiol, Conjugated Oestrogens, Progesterone, Stanozolol, Stiboestrol, Testosterone, Tibolone.
Stimulants:	Amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, mhazindol, pemoline.
*Oral Vaccines:-	
Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a representative Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, Aids, Measles, Lyme Disease, Travellers Diarrhea, Hepatitis A, B And C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhegic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Urinary Tract Infection Caused By E.Coli, Pneumoccoccal Disease, Mumps, and Chikungunya.	

There are no particular limitations on the amount of these drugs to be mixed as long as it is the usual effective treatment amount. It should be around 50% w/w or below of the entire tablet, and is preferably 20% w/w or below.

Approaches for taste masking of fast dissolving tablets [22, 23]

Fast dissolving tablet, which disintegrate or dissolve in the saliva produce a positive or negative taste sensation. Most of the drugs have unpalatable taste in which taste masking plays critical role in formulating OFDT. The negative taste sensation of drugs can be reduced or eliminated by various approaches which include:

1. Taste masking with flavours and sweeteners.
2. Taste masking by polymer coating.
3. Taste masking with ion-exchange resins.
4. Taste masking by formation of inclusion complexes with cyclodextrins.
5. Miscellaneous Taste-masking approaches.

Taste masking with flavours and sweeteners

Maximum patient acceptability with FDT is seen if they provide pleasant taste and mouth feel. To provide this property in tablets various sweeteners and flavours are employed. Usually sugar-based excipients are used as they are highly water soluble and dissolve quickly in saliva and provide pleasant taste and mouth feel to the final product.

Mannitol is most widely used excipient in formulating OFDT. Aspartame and citric acid are most commonly used along with various flavorants such as mint flavour, orange flavour, strawberry flavour, peppermint flavour to produce pleasant taste and mouth feel.

Taste masking by polymer coating

Some of the unpleasant drugs cannot be masked by incorporation of sweeteners and flavours, in such cases alternative method of masking the taste is by coating the drug. In fact this process retards or inhibits dissolution and solubilization of drug, which allows time for particles to pass from mouth before taste is perceived in mouth.

Taste masking by ion-exchange resins [24]

Drugs are attached to the oppositely charged resin substrate, forming insoluble substance or resonate through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odours of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecules.

Ion-exchange resins are high molecular weight polymers with cationic and anionic functional groups. The most frequently employed polymeric network is a copolymer of styrene and divinyl benzene. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets and mask the taste. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution.

Ion-Exchange Resins can be classified into four major groups:

- ✓ Strong acid cation-exchange resin.
- ✓ Weak acid cation-exchange resin.
- ✓ Strong base anion-exchange resin.
- ✓ Weak base anion-exchange resin.

Taste masking complexation [24]

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most

suitable only for low dose drugs. Vander Waals forces are mainly involved in inclusion complexes. B-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch.

Miscellaneous taste-masking approaches [25]

✓ **By effervescent agent:**

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption.

It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide and optionally a taste bud desensitizing composition and other nonactive materials, such as sweeteners, flavouring components and fillers. The formulations contain the drugs in combination with effervescent agents to promote their absorption in the oral cavity and to mask their bitter taste.

✓ **Salt preparation:**

Salt preparation is one of the classical approaches to mask the bitter taste of drug by either decreasing solubility or by increasing hydrophobicity and thereby reducing contact of bitter drugs with taste buds. This approach differs from others to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thereby less stimulating to the taste buds, or to obtain a tasteless or less bitter form.

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid and tartaric acid.

✓ **Solid dispersion systems:**

Solid dispersion can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.

Mechanism of tablet disintegration

The tablet breaks to primary particles by one or more of the mechanisms listed below:

By capillary action (Wicking)

By swelling

Because of heat of wetting

Due to release of gases

By enzymatic action

Due to disintegrating particle/particle repulsive forces

Due to deformation.

By capillary action (Wicking) [26]

Disintegration by capillary action is always the first step. 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 tabletting 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 [26]

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling tablet 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 slow down.

Because of heat of wetting (air expansion) [26]

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 disintegrats and cannot describe the action of most modern disintegrating agents.

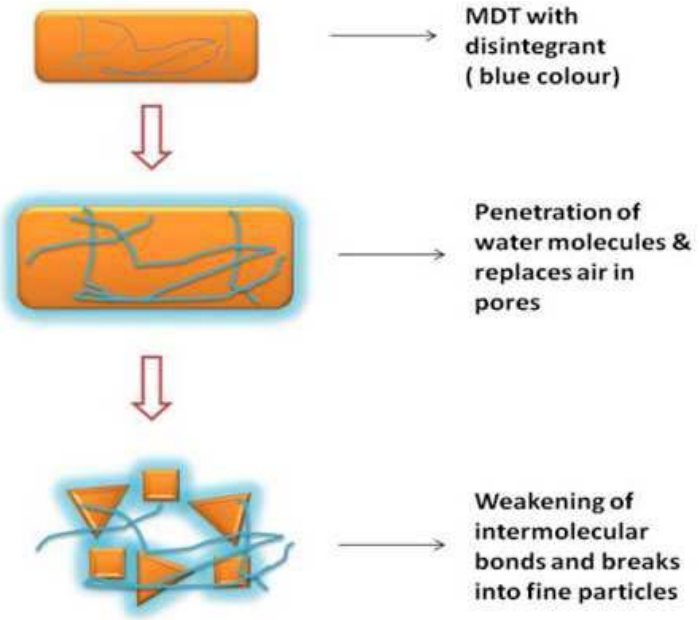

Fig. 1: Wicking mechanism. [26]

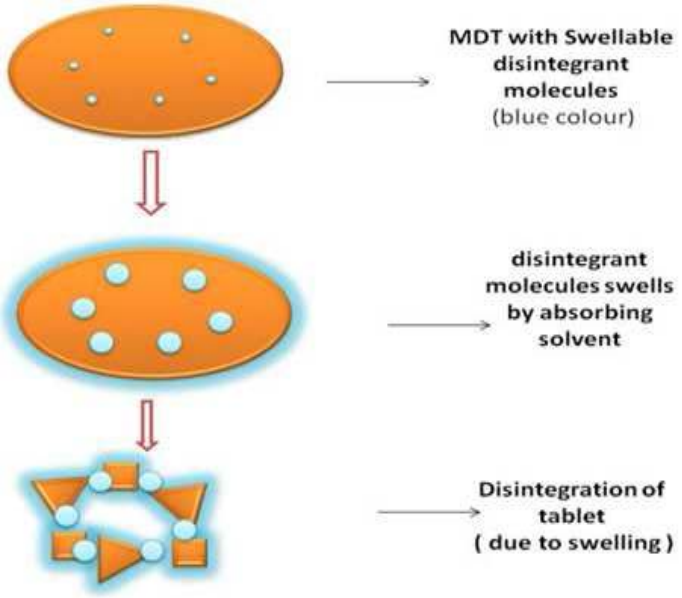

Fig. 2 the Swelling mechanism [26]

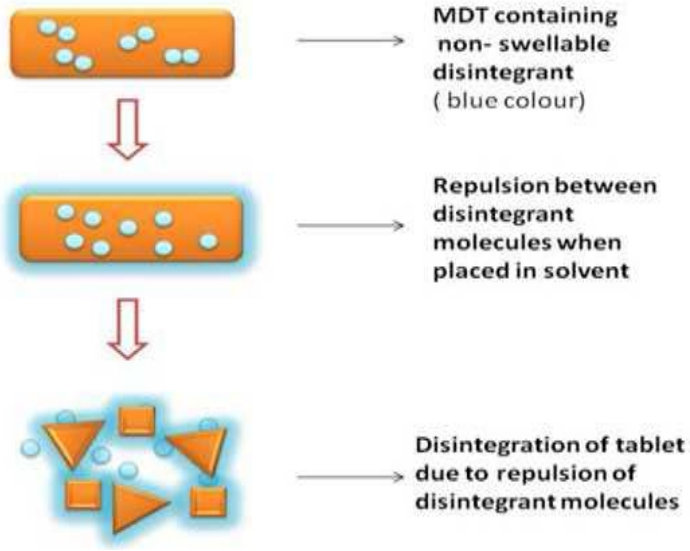

Fig. 3: Repulsion mechanism [26]

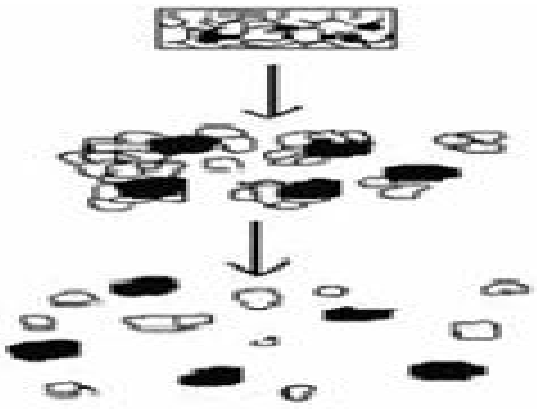

Fig. 4: By deformation [27]

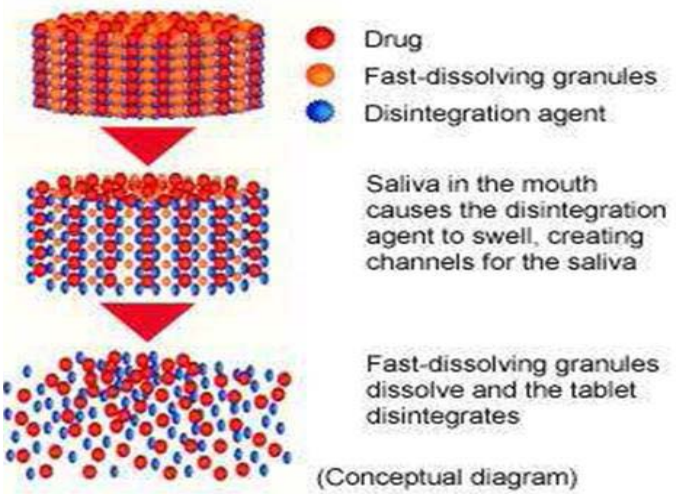

Fig. 5: Conceptual mechanism of FDT Disintegrating [27]

Due to release of gases [27]

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. 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 to two separate fraction of formulation.

By enzymatic reaction [27]

Here, enzymes present in the body 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 [27]

Another mechanism of disintegration 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.

Due to deformation [27]

Hess had proved that during tablet compression, disintegranted 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.

FUTURE PROSPECTS AND RESEARCH TRENDS IN FDTS [28]

There are several biopharmaceutical advantages such as improved efficiency over conventional dosage forms for Fast disintegrating tablets. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. There are still many aspects to improve in the FDT formulations. 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. 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. The future of FDTs lies in the development of FDTs with controlled release properties. 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 too severely. 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. In addition, the ability to formulate drugs in large doses will bring another important technological advance. In general, the FDT formulations require large amounts of excipients, and having large doses of drug will only make the final formulation too big to handle. An FDT formulation that would require fewer excipients than the drug itself would be a break through. While the problems to be solved are not easy, the history suggests that it is just a matter of time before they are solved.

The safety and efficacy profile of drugs in orodispersible tablet is same like their conventional tablet dosage form. Based on conventional techniques, new techniques are developed like Zydis, Wow Tab, Flashtab technology and many more, which leads to getting a patent and new market strategy for orodispersible tablets. This dosage form are gaining market share day by day and becoming a better choice of acceptance.

CONCLUSION

Fast disintegrating tablets have better patient acceptance and offer improved biopharmaceutical properties, improved efficacy and better safety as compared with conventional oral dosage forms. By using new manufacturing technologies, many drugs can be formulated in the form of fast disintegrating tablets to provide the advantages of liquid medication in the form of solid preparation. FDT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in travelling, patients who are may not have access to water. The clinical studies show FDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. The development of a

fast-dissolving tablet also provides an opportunity for a line extension in the market place; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage form. Pharmaceutical marketing is another reason for the increase in available fast dissolving/ disintegrating products. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. Fast dissolving/ disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer. Due to the constraints of the current FDDT technologies as highlighted above, there is an unmet need for improved manufacturing processes for fast dissolving tablets that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets. To fulfill these medical needs, formulators have devoted considerable effort to developing a novel type of tablet dosage form for oral administration, one that disintegrates and dissolves rapidly in saliva without the need for drinking water.

CONFLICT OF INTERESTS

Declared None

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