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FAST DISSOLVING TABLETS: AN OVERVIEW

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ABSTRACT

Oral route is considered as safe and prefect route for administration of drug. Fast dissolving / disintegrating tablets are innovative approach for the patients who have difficulty in swelling the tablets and liquids. Traditional tablets and capsules are administered with an 8-oz. glass of water may be inconvenient or impractical for some geriatric and paediatric patients. Such problem can be solved in the novel drug delivery system by formulating "mouth dissolving tablets" (MDTs) which disintegrates or dissolves rapidly without water within few seconds in the mouth due to the action of super-disintegrant or maximizing pore structure in the formulation. Fast dissolving tablets dissolve or disintegrate rapidly in oral cavity without intake of water. On comparison with conventional dosage form FDT have several advantages. This review describes the various formulation aspects, benefits, limitations, patented and non patented technologies developed for MDTs, marketed formulation and drugs used in this research area.

KEYWORDS: Mouth Dissolving Tablets, Orally Disintegrating Tablets, Super-disintegrates, Bioavailability and Fast-Dissolving/Disintegrating Tablet (FDDTs).

INTRODUCTION

The oral route usually remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. Oral dosage forms are more popular than other dosage forms because of ease of administration, accurate dosage, self- medication, pain avoidance, patient compliance, etc. Despite of tremendous advancement in drug delivery the oral route of drug administration is the most important method of administration of drug for systemic effect. About 60% of all

dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenteral and liquid orals. But the liquid orals (syrup, suspension, emulsion etc.) have the problem of accurate dosing mainly and parenteral are painful drug delivery and need skilled persons for administration, which may cause patient noncompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. The most popular solid dosage forms are tablet and capsules.[1]

It may be inconvenience or impractical to swallow tablets or liquids, traditional tablets and capsules administered with approximately one glass of water. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking.[2]

Fast dissolving/disintegrating tablets (FDDTs) are a perfect fit for all of these patients. The Fast dissolving tablet (FDT) is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopoeia adopted the term "Oro dispersible Tablet" as a tablet that is to be placed in oral cavity where it disperses rapidly within three minutes in mouth before swallowing.[3]

USFDA define FDTs as "A solid dosage form containing medicinal substances or active ingredients which disintegrate rapidly within a few seconds when placed up on tongue. FDTs can be prepared by various conventional methods like direct compression, wet granulation, melt granulation, moulding, spray drying, freeze drying, sublimation and by addition of superdisintegrants. FDTs disintegrate and / or dissolve rapidly in the saliva without need for water, releasing the drug. 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 significantly greater than those observed from conventional tablet dosage form.[4]

This dosage form combines the advantages of dry and liquid formulation. Some novel FDT technology allow high drug loading, have an acceptable taste, offer a pleasant mouth felling, leaving minimal residue in the mouth after oral administration. FDT have been investigated for their potential in improving bioavailability of poorly soluble drug through enhancing the dissolution profile of the drug and first pass hepatic metabolism drugs.[5]

Requirements of Fast dissolving tablets

Fast dissolving tablets should not require water for oral administration, yet dissolve/disperse /disintegrate in mouth in a matter of seconds. It has pleasing mouth feel with an acceptable taste masking property. It should be harder and friable and exhibit low sensitivity to environmental conditions such as humidity and temperature. It should leave minimal or no residue in the mouth after oral administration.[6]

Salient Features of Fast Dissolving Drug Delivery System

Fast dissolving tablet are easy to administer to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients. There is convenience of administration and accurate dosing as compared to liquids. FDTs are not need water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water. Good mouth feels property of FDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.

These formulations have rapid dissolution of drug and absorption which may produce rapid, onset of action. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes and pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects are obtained by such FDTs.[7]

Benefits of fast dissolving tablets

FDTs can administered without water, anywhere, any time so these are suitable for geriatric and pediatric 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. FDTs are beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra-rapid onset of action required. Increase bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets. These are stable 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.[8]

Challenges to develop FDT

During formulation of FDTs, there is avoidance of increase in tablet size with sufficient mechanical strength in a good packaging design to protect from moisture is the major challenge. FDTs should give a rapid disintegration of tablet with minimum or no residue in mouth and compatible with taste masking technology**.** The formulation must not affected by drug properties.[8]

Limitations of Fast dissolving tablets

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.[9]

Mechanisms of Fast Dissolving Tablets

FDTs involve the following mechanisms to achieve the desired fast dissolving characteristics:

1. Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.
2. Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.
3. There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug.

The mechanisms are-

- High swell ability of disintegration
- Chemical reaction
- Capillary action.[10]

Swelling: The most widely accepted general mechanism of action for tablet disintegration is swelling and tablets having high porosity show poor disintegration due to lack of adequate swelling force. Sufficient swelling force is exerted in the tablet with low porosity.

Porosity and capillary action (wicking): Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the preparation of fluid into tablets. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture in particulate bonds causing the tablet to break apart. Disintegration by capillary action is always the first step.

Disintegrating particle/particle repulsive forces: A further mechanism of disintegrants attempts to explain the swelling of tablet made with 'non swell able disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The disintegration is based on electric repulsive forces and presence of water is required to exert this effect.[11]

TECHNOLOGIES USED FOR MANUFACTURING OF FDTs

In the recent past, several new advanced technologies have been introduced for the manufacturing of FDTs with ideal properties like less disintegration time, pleasant mouth feel, exceptional taste masking and sugar free tablets for diabetic patients. There are several patented and non patented technologies for manufacturing of FDTs.[12]

❖ Non patented technologies

1. Disintegrates addition

Disintegrate addition technique is one popular technique for formulating Fast-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved is formulating by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel.[13]

2. Freeze Drying or Lyophilization

Lyophilization consists of freezing of material followed by sublimation of ice or frozen moisture under vacuum of 100-300 microns at temperature -10°C to - 30°C. Lyophilization is technology which allows drying of heat sensitive drugs and biological at very low temperature, which results in preparation of highly porous, with a very high specific surface area, dissolve rapidly and great absorption and bioavailability. All the constituents of the material remain frozen in their original positions. Thus original product remains in their original size and shape with high porosity, which resulting in improved solubility in water. Various technologies which used in this method for manufacturing of FDT's are Zydis, Ouick solv and Lyoc. The freeze drying operation consists of few steps, it includes preparation and pre treatment, pre freezing to solidify the water, sublimation of ice under vacuum, removal of residual moisture under high vacuum and packing.[14]

3. Tablet Moulding

Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on whether and to what extent it dissolves in the wetted mass. The drug can exist as discrete particles or micro particles in the matrix. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel depends on the type of dispersion. Different moulding techniques can be used to prepare Mouth-dissolving tablets:

- **Compression moulding:** The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.[15]
- **Solvent method:** The powder blend is moistened with a hydro alcoholic or aqueous solvent. Using low compression pressure, the powder blend is moulded to form a wetted mass. Pressure used is lower than the pressure used in the preparation of conventional tablets. Air drying is done to remove solvent. Such tablets possess a poor mechanical strength.
- **Heat method:** Suspension is prepared containing drug, sugar and agar. It is prepared by pouring the suspension in blister packaging and then allowing it to solidified at room temperature to form a jelly and drying it at 30^0C under vacuum.[16]

  The mechanical strength of moulded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.[17]

4. Sublimation

The basis of this technique is to add inert solid ingredients that volatilize readily (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.[18]

These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Conventional methods like dry granulation, wet granulation and direct compression with highly soluble excipients, superdisintegrants and/or effervescent systems can also be used.[12]

5. Spray-Drying

In this technique, processing solvent is evaporated rapidly and can produce highly porous and fine powder, which was compressed into tablets. Hydrolyzed and non hydrolysed gelatin used as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium.[19]

6. Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. FDT can be prepared by using this technique because of the availability of improved excipients especially super-disintegrants, effervescent agents and sugar based excipients.

Super-disintegrants: The rate of disintegration gets affected by the addition of superdisintegrants and hence the dissolution. Other ingredients like water-soluble excipients and effervescent agents also increase the disintegration.

Sugar based excipients: The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel.

Sugar-based excipients classified 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 but low dissolution rate.[20]

Effervescent Agents: The evolution of CO_2 as a disintegrating mechanism forms the basis of the patented Orasolv technology (OT) and is frequently used to develop over-the-counter formulations. The product contains microparticles and is slightly effervescent in nature. Saliva activates the effervescent agent which causes the tablet to disintegrate. The OT had been utilized in fabrication of six marketed products: four Triaminic Softchew formulations, Tempra Firs Tabs and Remeron Sol Tab.[21]

7. Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder canalso be used tocoat granules of bitter tasting drugs and there by masking their bitter taste.[22]

8. 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 (foss)- sucrose, dextrose, lactose and fructose at temperatures ranging between 82ºC-130ºC by simultaneous action of flash melting and 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.[23]

However, other polysaccharides such as poly maltodextrins and polydextrose can be transformed into fibers at 30-40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile 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 the presence of saliva.[24]

The manufacturing process can be divided into four steps as detailed below.

- Floss Blend
- Floss Processing
- Floss Chopping and Conditioning
- Blending and Compression.[25]

9. Melt granulation

In this process, FDTs can be prepared by incorporating a hydrophilic waxy binder (super poly state) PEG-6-stearate. Super poly state is a waxy material with melting point of 33°C- 37°C and a hydrophilic- lipophilic balance of 9. It acts as a binder and increases the physical resistance of tablets, and also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super poly state was incorporated in the formulation of

FDTs by melt granulation method where granules are formed by the molten form of this material.[26]

10. Phase-transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.[27]

11. Nanonization

Nano melt technology involves reduction in the particle size of drug to nano size by milling the drug using a proprietary wet-milling technique. The nano crystals 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 indose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug/unit).[28]

12. Three-dimensional Printing (3DP)

Three dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device with loose powders was fabricated using the three dimensional printing (3DP) process.[29]

13. Fast dissolving films

In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxyl methylcellulose, hydroxylpropyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film.[25]

❖ **Patented Technologies for Fast Dissolving Tablets**

1. Ceform Technology

The crux of this process is placing a dry powder containing pure drug and excipients into a rapidly spinning machine. Centrifugal force of the rotating head of this ceform machine, through small heated opening at high speed blends dry drug powder. This drug blend is liquefied to form a sphere, owing to the microburst of heat attained by carefully controlled temperature. This does not affect the stability of the drug. In the preselected oral dosage forms the microspheres are blended and/or compressed.[30]

2. Durasolv Technology

Durasolv is the patented technology of CIMA Labs, Inc. (Minnesota, United States). The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.[31]

3. Orodis technology

Orodis is compressed technology, have a fast disintegration time (15 to 30s). This technology produces very hard tablets, which are easy to handle. Tablets can be packed in push-through blisters. Materials used in this technology meet USP and EP standards.[32]

4. WOW tab Technology

WOW tab technology is patented by Yamanouchi Pharmaceutical Co., Japan. WOW means "Without Water ". In this process, combination of low mould ability saccharides and high mould ability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with low mould ability saccharine and granulated with a high mould ability saccharide and compressed into tablet.[33]

5. Dispersible technology

Lek in Yugoslavia has a patent over this technology. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methane sulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and

cyclodextrin polymers. Dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature.[34]

6. Orasolv Technology

This technology produces tablets by low compression pressure. This technique uses an effervescent disintegration pair that releases gas upon contact with water. The effervescent pair used usually includes acid and carbonate source that on combination produces effervescence.[35]

7. Flash tab Technology

Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.[29]

8. Flash dose Technology

Flash dose technology has been patented by Fuisz Technologies Ltd. (Chantilly, Virginia). Nurofen meltlets, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation (Canada). Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.[36]

9. Zydis Technology

This technology is the most well known example of the freeze drying method. The drug is physically trapped in water soluble matrix, and then freeze dried to give a product that rapidly dissolves.[37]

10. Pharmaburst technology

Pharmaburst™ is a “Quick Dissolve” delivery system patented by SPI Pharma (USA). Pharmaburst technology uses off the shelf coprocessed excipients to create an ODT that, depending on the type of active ingredients and loading, dissolves within 30- 40seconds. The quantity of pharmaburst required in a formulation depends on the active ingredients in the tablet. The process involves a dry blend of a drug, flavor and lubricant that are compressed into a tablet on a standard tablet press. The Manufacture process carried out under normal

temperature and humidity conditions. The tablets can be packaged in blister packs or bottle.[38][39]

11. EFVDAS

EFVDAS or Effervescent Drug Absorption System is a drug delivery technology that has been used in the development of a number of both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan Corporation (Ireland) has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use. The granular contents of the sachets can be added to boiling water to produce pleasant-flavored solutions. In these cases the effervescence of the granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, acetaminophen, cimetidine, naproxen, and acetaminophen and codeine combination product.[40]

12. Frosta technology

It utilizes the concept of formulating plastic granules and co processing at low pressure to produce strong tablets with high porosity. Plastic granules are composed of porous & plastic material along with 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.[41]

13. Nano crystal technology

Nano crystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling for fast dissolving tablets. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nano Crystal technology. NanoCrystal™ Fast dissolving technology provides pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix, exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters), wide range of doses (up to 200mg of API per unit) and employment of non moisture sensitive substances.[15]

14. Multiflash (Prographarm)

Multiflash is a multi-unit tablet composed of coated micro granules and fast-disintegrating excipients. This multi particulate tablet quickly disintegrates in the oesophagus after being swallowed with a minimum amount of water. This tablet avoids mucosal adhesion, and coated pellets can match various dissolution rates.[42]

15. Melt Ease technology

This technology is developed by nutrition formulators. Tablet dissolution can be achieved within 5seconds (average 400mg tablet). This technology provides the best mechanism available, to ensure compliance.[32]

16. Quicksolv Technology

This technology is patented by Janssen Pharmaceuticals (Beerse, Belgium). It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). The final product disintegrates almost instantly. This method is claimed to prevent or to reduce the incidence of cracking during the final preparation, having uniform porosity and also the adequate strength for handling.[43]

17. Lyoc Technology

It is a porous and solid galenic form based on lyophilization of an oil-in-water emulsion placed in the blister alveolus. It is manufactured by freezing a paste like emulsion containing drug as bulk or as coated micro particles. Lyoc disintegrates rapidly but possesses poor mechanical strength due to porous nature.[44]

18. Advatab

AdvaTab™ technology (Eurand) designed and patented by Kyowa Hakko Kogyo (Tokyo, Japan) produces orally dissolving tablets based on a proprietary tablet composition. Via spray during the production process, each tablet is well lubricated. AdvaTab™ is produced using 10–30times less hydrophobic lubricant and can be 30–40% stronger than conventional tablets. This technology results in tablets being hard and durable, yet allows easy wetting upon contact with saliva. High drug loading, coated drug particles for better mouth feel and no special packaging requirement are the major advantage offered by this technology. Unique

as it can be paired with Eurand's technologies like Microcaps (taste-masking) and Diffucaps (controlled release).[30]

Table 1: Various Patented Technologies.[45]

Patented Technology	Basic Technology	Technology Developed by Company	Active ingredient (Brand Names)
Zydus	Lyophilization	R. P. Scherer, Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
Quicksolv	Lyophilization	Janssen pharmaceutics (Beerse, Belgium)	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-Tab)
Lyoc	Lyophilization	Laboratoires Farmalyoc, (Maisons-Alfort, France)	Phloroglucinol Hydrate (Spasfon Lyoc)
Flashtab	Direct Compression	Ethypharm (France)	Ibuprofen (Nurofen Flash Tab)
Flashdose	Cotton Candy Process	Fuisz Technology, Ltd. (Chantilly, Virginia).	Tramadol HCl (Relivia Flash dose)
Orasolv	Direct Compression	Cima Labs, Inc. (Minnesota, United States)	Paracetamol (TempraQuicklets), Zolmitriptan
Durasolv	Direct Compression	Cima Labs, Inc. (Minnesota, United States)	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)
WoW tab	Direct Compression	Yamanouchi Pharma Tech. Inc. (Japan)	Famotidine (Gaster D)
Ziplets	Direct Compression	Eurand International (Pessano con Bornago, Italy)	Ibuprofen (Cibalgina Due Fast)
Advatab	Microcaps and Diffuscap CR Technology	Eurand International (Pessano con Bornago, Italy)	Adva Tabcetrizine, Adva Tab Paracetamol
Oraquick	Micromask Taste Masking	KV Pharm. Co., Inc. (Missouri, U.S.)	Hyoscyamine Sulfate FDT
Fuisz	Sugar based matrix known as Floss	Fuisz Pharmaceutical Ltd. (Chantilly, Virginia).	Diphenydramine & Pseudoeph

Selection of FDTs drug candidates

Several factors must be considered when selecting drug candidates for delivery as FDT dosage forms.

- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form e.g. selegiline, apomorphine, buspirone etc.
- The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.

- Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P>1, or preferable >2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.[46]
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
- Drugs which are having a short half-life and needs frequent dosing, which are very bitter or either having unacceptable taste whose taste masking cannot be achieved or which require controlled or sustained release are inappropriate for FDT formulation.[47]

Significance of Oral Disintegrating Tablets

FDTs offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

1. **Accurate dosing:** Being unit solid dosage form, provide luxury of accurate dosing, allows high drug loading and an ideal alternative for paediatric and geriatric patients.
2. **Enhanced bioavailability:** Pregastric absorption of drugs result in improved bioavailability and as a result of reduced dosage it improves clinical performance.
3. **Fast action:** Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity. Hence, it is beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing.
4. **Patient compliance:** No need of water to swallow the dosage form. Hence, it is convenient for travelling patients and busy people who do not have immediate access to water.
5. **Ease of administration:** Convenient to administer specially for geriatric, paediatric, mentally disabled and uncooperative patients who have difficulty in swallowing.
6. **Obstruction free:** No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.
7. **Improved palatability:** Leaves minimal or no residue in mouth hence provides good mouth feel and also, taste masking technique is used to avoid the bitter taste of drug.
8. **Good stability:** Has good stability because of less sensitivity to environmental conditions.
9. **Simple packaging:** It can be packaged in push through blisters and no need of specific packaging.

10. **Business avenues:** Provide new business opportunities in the form of product differentiation, product promotion, line extension, uniqueness and life cycle management.
11. **Cost effective:** Proves to be cost effective due to lower production, packaging and distribution cost compared to other commercially available products.
12. **Versatile technology:** As this technology is versatile therefore suitable for the development of enhanced products for veterinary medicines, OTC, Rx medicines.[48]

Excipients used in preparation of FDTs

Excipients in FDTs contain at least one superdisintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavourings.[3]

Table 2: List of Excipients.

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

Superdisintegrants

Superdisintegrants are effective at small concentration and have greater disintegrating capacity. These act by swelling and as result of 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.

Table 3: Various Types of Superdisintegrants.[3]

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

Superdisintegrant must causes tablet to dissolve in mouth when tablet meets saliva in the mouth. It should be compactable enough to produce less-friable tablets, good flow to form blend and produce good moth feel to patient for better patient compliance.

Taste masking agents

Less commonly, active pharmaceutical ingredients to be incorporated are tasteless and do not require taste masking. Taste-masking of bitter or with objectionable tasting drug substances is critical for any orally-administered dosage form drugs for FDT. Sugar based excipient are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste and the basic requirement for designing FDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases, sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used. There are various approaches of taste masking of bitter drugs for FDT.

Binders

Binders play vital role to keep the components of these fast melting tablets together during the compression stage. Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers it will be advantageous to select ethylcellulose, hydroxyl propyl cellulose (HPC), and (HPMC), alone or in admixtures, and the most commonly acrylic polymers are used are the ammonio-methacrylate copolymer (Eudragit RL and RS), polyacrylate (Eudragit.NE), and polymethacrylate (Eudragit E). The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30^0C–35^0C for faster melting properties. Further, its addition imparts smooth texture and disintegration characteristics to the system.[49]

Evaluation of Fast Dissolving Tablets

The FDTs shall be evaluated for different parameters.

1. **Pre-compression parameters**

- **Bulk density (D_b)**

It is the ratio of total mass of powder to the bulk volume of powder. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another. The bulk density of powder may be evaluated using a bulk density apparatus.[50]

It may be measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight 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.[51]

$$D_b = M/ V_b.$$

Where, M is the mass of powder, V_b is the bulk volume of the powder.

- **Tapped density (D_t)**

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume measured by tapping the powder for 750 times and the tapped volume 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 noted. Tapping 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[51][52]

$$D_t = M / V_t$$

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

- **Angle of Repose**

The frictional 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. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.[53]

The powder mixture allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose calculated by measuring the height and radius of the heap of powder formed. Relationship between angle of repose and powder flow property as shown in Table 4.[51]

Table 4: Angle of Repose[54]

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

- **Compressibility index and Hausner ratio**

The compressibility index (Carr's Index) and hausner ratio are measures of tendency of powder to be compressed and the flow ability of powder. As such, they are measures of the relative importance of inter-particulate interactions. Carr's index and Hausner's ratio may be calculated using following formula.[50]

$$\text{Carr's Index \% (I)} = (D_t - D_b) * 100 / D_t$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

$$\text{Hausner's ratio} = D_t / D_b$$

Where, D_t is the tapped density and D_b is the bulk density.

Table 5: Compressibility Index and Hausner Ratio.[54]

Compressibility index (%)	Flow Character	Hausner Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair-aid not needed	1.19-1.25
21.25	Passable- may hang up	1.26-1.34
26-31	Poor- must agitate, vibrate	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

2. Post Compression Parameters

- **Shape of tablet:** The size and shape of the tablet can be dimensionally described, monitored and controlled.[55]
- **Tablet dimensions:** Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets should be taken and their thickness recorded using micrometer.
- **Determination of drug content:** Ten tablets should be weighed, taken in mortar and crushed to make powder. A quantity of powder weighing equivalent to specific amount of

drug shall be taken prescribed volume of solvent in volumetric flask. The solution shall be kept on shaking continuously for 24hrs on magnetic stirrer. Then the solution must be filtered and drug content must be estimated with UV-Visible spectrophotometer.[50]

- **Weight variation test:** Twenty tablets selected randomly from the lot and weighted individually to check for weight variation. The percentage difference in the weight variation should be within the permissible limits as per I.P., shown in table No.6.[56]

Table 6: Range of Weight Variation[56]

Average weight of tablet	Percentage Deviation
80 mg or less	±10
More than 80 mg and less than 250 mg	±7.5
250 mg or less	± 5

- **Friability:** This parameter is used to measure the mechanical strength of tablets. Roche friabilator is used to determine the 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. Ten pre-weighed tablets rotated at 25 rpm for 4 min or total 100 times dropping a tablet at height of 6inches in each revolution, the tablets then reweighed and the percentage of weight loss calculated by the following equation.[51][56]

$$F= (W_I - W_F) * 100/ W_I$$

Where W_I = Initial Weight of Tablet

W_F = Final Weight of Tablet

- **Hardness:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness also called crushing strength may be determined using pfizer and monsato hardness tester. It is expressed in kg/cm^2. The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth.[50][51]

- **In vitro disintegration time:** Disintegration time is very important for FDTs which is desired to be less than 60 seconds. This rapid disintegration assists swallowing of the tablet and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. In vitro disintegration time can be determined using disintegration test apparatus without disks. Carry out the test on six tablets. The distilled water at $37^0C \pm 2^0C$ is used as a disintegration media and time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus Time is noted in seconds for

complete disintegration of the tablet with no palpable mass remaining in the apparatus. Carry out the test in triplicate.[54][57]

- **Wetting time**: Wetting time of dosage form is related with the contact angle. A lower wetting time implies a quicker disintegration of the tablet. Circular tissue paper of 10cm diameter placed in a petridish with a 10cm diameter containing 6ml of simulated saliva pH 6.8. 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. Three trials for each batch and standard deviation should be determined.[57][58][59] [60]

  The pore sizes become smaller and wetting time increases with an increase in compression forces or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step in disintegration process.

- **Water absorption ratio**: Note the weight of the tablet before keeping in the Petri dish (Wb). After determining the wetting time, take the fully wetted tablet from the petridish and reweigh (Wa). The water absorption ratio R can be determined according to the following formula.[57]

  $R=100x\ (Wa – Wb\ )/Wa$

  Wa is weight of the tablet after wetting

  Wb is the weight of the tablet before wetting

- **In vitro dispersion time:** In vitro dispersion time measured by dropping a tablet in a beaker containing 10 ml of buffer solution at 37ºC ± 0.5ºC. Time require for complete dispersion of tablet is measured. Three tablets from each formulation randomly selected and in vitro dispersion time is performed.[61]

- **In Vitro dissolution:** In vitro drug release of the samples is carried out using USP–type II dissolution apparatus (paddle type). The 900ml of dissolution medium is placed into the dissolution flask maintaining the temperature of 37ºC ±0.5ºC and 50rpm. One tablet is placed in each flask of dissolution apparatus. 5ml of sample is withdrawn with help of filter tube at predetermined time intervals and same volume of fresh medium is replaced. These samples are analyzed by an UV spectrophotometer.[54][57]

CONCLUSION

Fast dissolving drug delivery system has gained more popularity from last decade. It is a novel technique for treatment of various patients who have difficulty in swallowing tablets or liquids, traditional tablets and capsules administered with 8oz of water. FDTs quickly disintegrate in oral cavity without the aid of water, along with sufficient mechanical strength. FDTs have tremendous scope as a delivery system for most of the drugs in the near future.

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