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A Brief Discussion on Fast Dissolving Tablet- A Recent Technology

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ABSTRACT

Oral delivery is at this time the gold standard in the drug manufacturing where it is considered as the safest, most convenient and greatest economical method of drug delivery. One 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 superdisintegrant or maximizing pore structure in the formulation. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. Mouth dissolving tablets are solid dosage forms containing drugs that disintegrate in the oral cavity within less than one minute leaving an easy-to-swallow residue. This is seen to affect about 35% of the general population and associated with a number of circumstances like Parkinsonism, mental disability, motion sickness, unconsciousness, unavailability of the water etc. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled, and patients who are uncooperative, on reduced liquid-intake plans, or are nauseated. To overcome such difficulties, mouth dissolving tablets have been developed. The aim of this review article is to give an overview on desired characteristics, advantages, preparation techniques and patented technologies of FDTs formulation.

Keywords: FDT, Patients compliance, super disintigrants, Technology, Evaluation.

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INTRODUCTION

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[1]. Drug delivery systems are becoming increasingly sophisticated as scientists acquire a better understanding of the physicochemical parameters pertinent to their performance[2].

The demand for developing new technologies has been increasing annually[3]. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and is also seen in swallowing conventional tablets and capsules, which results in high incidence of non-compliance and ineffective therapy[4,31].

Common complaints about difficulty in swallowing tablets in order of size, surface, shape and taste of tablets[5]. Fast dissolving tablets are useful in patients, like pediatric, geriatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style[6,35].One important drawback of conventional dosage form (tablet and capsule) is that it possesses higher disintegration time and pharmacological action is achieved after 30-45 min. of dosage form administration[7]. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients[8]. Should next generation drugs are predominantly protein or peptide based, tablets may no longer may be the dominant format give the difficulty of dosing such moiety[9]. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide[10]. US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"[11]. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem[12,48]. These dosage forms disintegrate/dissolve in oral cavity within a minute without need of water or chewing,

anywhere, anytime[13]. ''Fast dissolution'' or ''fast disintegration'' typically requires dissolution or disintegration of a tablet withinoneminute[14]. FDTs are beneficial for patient having swallowing problems usually during travelling and/or mentally retarded patients[15,47]. The new

business opportunity like product differentiation, product promotion, patent extension, and life cycle management become easy after the intervention of FDTs[16]. FDDS include tablets and films[17]. Some FDTs are designed to dissolve in the saliva usually within <60 seconds[18]**.** Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts porous tablets, quick dissolving etc[19]. These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds[20]. In case of patients who are mentally ill, uncooperative, nauseated patients and those with acute episodes of coughing or asthma the time of response should be very rapid which indicates that the drug should be absorbed into the systemic circulation as early as possible[21]. All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets[22]. These dosage forms are also used to attain instant a higher concentration of drug in body for immediate actions[23]**.** The basic approach used in the development of the fast-dissolving tablets is the use of superdisintegrants eg. Croscarmellose sodium, sodium starch glycolate, and crospovidone[24]**.** Most commonly used methods to prepare these tablets include; Freeze drying / Lyophilization, Tablet molding and Direct-compression methods[25]**.**

The disintegration time for good FDTs varies from several seconds to about a minute[26]. FDTs dissolve rapidly in the saliva without the need for water, faster the dissolution and provide quick onset of action. These dosage forms are also applicable when local action in mouth is desirable such as local anaesthetic for toothaches and oral ulcers etc[27]. Drug candidates that undergo pre-gastric absorption when formulated as MDTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing[28]**.** 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 undertreated patient populations[29]. The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible tablet", by the European pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing[30,40]. These fast-dissolving tablets ensure complete solubilization of tablet through surface erosion, resulting in elimination of lag time for disintegration thereby offering faster absorption and rapid onset of action[32]. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people[33]**.** FDT have been investigated for their potential in increasing the bioavailability of poor water soluble drugs through enhancing the dissolution profile of the drugs[34]. Most of the FDT technologies use unique forms of taste masking as well. The primary method of taste-masking include adsorption onto or complexation with carriers and spray coating of drug

particles[36]. Fast disintegrating drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing[37]. The disintegration time for ODTs generally ranges from several seconds to about a minute[38,39]. Currently these tablets are available in the market for treating many disease conditions like hypertension, migraine, dysphasia, nausea, vomiting, Parkinson's disease, schizophrenia and pediatric emergency[41]**.** There are number of dosage forms available like effervescent tablets, dry syrups and chewing gum tablets, which are commonly used to enhance the patient's compliance but MD tablets that can dissolve or disintegrate in oral cavity have attracted a great deal of attention[42]**.** European Pharmacopoeia described orally disintegrating tablets as „uncoated tablets intended the placed in the mouth where they disperse rapidly before being swallowed" and as tablets which should disintegrate within 3 min[43,44]. To obviate the problems associated with conventional dosage forms, orally disintegrating tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters[45].

Orally disintegrating tablet formulations also provide advantages in the industrial field such as diversity of products and extension of patent time[46]. Fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging[49]. As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism[50,51]. various formulation technologies like Zydis Technology, Durasolve Technology, Orasolve Technology, Flash Dose Technology, Wow Tab Technology, Flash Tab Technology, Quicksolv Technology, Lyos Technology, Fast Melt Technology and Zip-lets Technology are used[52]**.**

Difficulties with Existing Oral Dosage Form :

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.
- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.

- Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult
- Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.
- Cost of products is main factor as parenteral formulations are most costly and discomfort[1,2,3].

Definition[4,5]

US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"	Orally Disintegrating Tablet (ODT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60seconds or less. ODTs are also called as Oro-disperse, mouth dissolving, rapidly disintegrating, fast melt, quick dissolve and freeze dried wafers, melt in mouth tablets, rapimelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.	Their growing importance was underlined recently when **European Pharmacopoeia** adopted the term "Orodispersible tablet" and described orally disintegrating tablets as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 min.

Advantages of ODTS:

Advantages of ODTs include:

- Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- The ODTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.
- Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.
- Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Good mouth feels, especially for pediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.
- Minimum risk of suffocation in airways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is possible.
- Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.
- No specific packaging is required. It can be packaged in push through blisters.
- Provide new business opportunities in the form of product differentiation, patent-life extension, uniqueness, line extension, and life-cycle management, and exclusivity of product promotion[6,7].

Selection of Drugs:

The ideal characteristics of a drug for in vivo dissolution from an ODT include:

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue Unsuitable drug characteristic for ODT;
- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release[8].

Factors to be Considered for Selection of Superdisintegrants:

- **Disintegration**:

  The disintegrant must quickly wick saliva into the tablet to generate the volume expansion

and hydrostatic pressure necessary to provide rapid disintegration in the mouth.

- **Compactibility:**

  It is desirable to have ODT with acceptable hardness and less friability at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed.

- **Mouth feel:**

  Large particles can result in a gritty feeling in mouth. Thus, small particles are preferred. If the tablet form a gel-like consistency on contact with water, However, it produces a gummy texture that many consumer find objectionable.

- **Flow:**

  In typical tablet formulation, suprdisintegrants are used at 2-5 wt % of the tablet formulation. With ODT formulation, disintegrant level can be significantly higher[9].

Important Criteria for Excipient used in Formulation of ODTs:

- It must be able to disintegrate quickly.
- Their individual properties should not affect the ODTs.
- It should not have any interaction with drug and other excipieints.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When selecting binder (a single or combination of binders) care must be taken in the final integrity and stability of the product.
- The metlting point of the excipients used should be in the range of 30-35ºC34.
- The binder may be in liquid, semi solid, solid or polymeric in nature[3,4].

Desired characteristics and development challenges:

- **Fast Disintegration:**

FDT dosage forms, also commonly known as fast melt, quick melt, orally disintegrating tablets, and orodispersible systems, have the unique property of disintegrating the tablet in the mouth in seconds.

- **Taste of Active Ingredients:**

Taste-masking technologies are increasingly focused on aggressively bitter-tasting drugs like the macrolide antibiotics, non-steroidal anti-inflammatory drugs, and penicillins.

- **Drug Properties:**

The drugs belonging to Biopharmaceutical Classification System Class II, i.e., the drugs with poor solubility and high permeability are best suitable moieties for FDTs in a dose of 125 and

250 mg. Tizanidine HCl, Oxybutynin HCl, Rofecoxib, Ibuprofen, Promethazine Theoclate, prednisone, Indomethacin, Glyburide, Fentanyl citrate, Griseofulvin Hydrochlorothiazide, Crystallized Paracetamol, and Nimesulide are few examples of drugs that has been formulated as fast-dissolving drug delivery system.

- **Tablet Strength and Porosity:**

The FDTs comprise of two component frameworks of lyophilized matrix system that work together to ensure the development of a successful formulation. The first component is water-soluble polymers such as gelatin, dextran, alginate, and maltodextrin. This component maintains the shape and provides mechanical strength to the tablets (binder). The second constituent is matrix-supporting/disintegration-enhancing agents such as sucrose and mannitol, which acts by cementing the porous frame work, provided by the water-soluble polymer and accelerates the disintegration of the FDT.

- **Moisture Sensitivity:**

FDTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast-dissolving properties as well as to create good mouth feel[2,5].

THE NEED FOR DEVELOPMENT OF FAST DISINTEGRATING TABLETS [5]

- **Patient factors:**

❖ Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.

❖ Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.

❖ Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.

❖ Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.

❖ Mentally challenged patients, bedridden patients and psychiatric patients.

- **Effectiveness factor:**

Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts 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 pre-gastric segments of GIT[4,11].

EXCIPIENTS COMMONLY USED FOR FDT PREPARATION:

Mainly seen excipients in FDT are as per Table 1 at least one disintegrant, a diluent, a lubricant and optionally swelling agent, a permeablizing agent, sweeteners and flavoring agents.

Table 1: Name and Weight Percentage of Various Excipients[3]

Name of the excipients	Percentage used
Disintegrant	1-15%
Binder	5-10%
Anti static agent	0-10%
Diluents	0-85%

- **Superdisintegrants**

  Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation.

  Swelling Index = [(Final volume - Initial volume)/initial volume)] X 100

  Example: croscarmellose sodium, crospovidone, carmellose, carmellose calcium, sodium starch glycolate ion exchange resins (e.g. Indion 414). Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

- **Binders**

  Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage.

  Example: Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers.

- **Antistatic agent**

  An **antistatic agent** is a compound used for treatment of materials or their surfaces in order to reduce or eliminate buildup of static electricity generally caused by the triboelectric effect.

  Example**:** colloidal silica (Aerosil), precipitated silica (Sylod.FP244), talc, maltodextrins, beta-cyclodextrin etc.

- **Lubricants**

  Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

  Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

- **Flavours**

  Example**:** Peppermint flavour, clove oil, anise oil, eucalyptus oil. Flavoring agents include,

vanilla, citrus oils, fruit essences etc.

- **Sweeteners**

  Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose, Maltose, aspartame, sugars derivatives etc.

- **Fillers**

  Example: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc.

- **Surface active agents**

  Example**:** sodium doecylsulfate, sodium lauryl sulfate, Tweens, Spans, polyoxyethylene stearate[7,15].

Taste Masking Methods:

The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in ODT formulations. Following methods are used in Taste masking is given in Table. 7.

Table 7: Technologies Used for Masking the Taste of Active Ingredients[22]

Technology	Excipients	Active Ingredient	Method
Fluidized bed Coating	Methyl cellulose (MC), Acesulfame(AS), HPMC	Northindrone, tamoxifen, caffeine, acetaminophen, rilmazafone HCl	-MC and AS solution charged to fluidized bed drier containing sieved northindrone. -Internal temperature maintained at 115°F - Coating completed in 3,min.
Agglomeration Process	Sweetener:- Sodium saccharin; acesulfeme Dry blend;-HPMC Silica dioxide Polythiazide	Polythiazide	-Sweetener solution sprayed on dry blend to form agglomerated granules - Wet mixture was dried in a convection oven at 103°F for 17 hrs. -Dried product size reduced, sieved (#100
Pelletization Process	Dry Blend:- Aspartame, HPC and Gum arabic	Loratidine	Crushed ice was mixed with dry blend mixture to form spherical particles. - Wet spherical particles were dried in a tray drier at 55°C
Infusion method	Dry blend:- Sucralose, Fluoxetine and Polyvinyl pyrrolidone	Fluoxetine	-Propylene glycol: water (40:60) was used to mix dry blend, HPMC was added. Mixing was continued at high speed for 3 min. The particles obtained were screened (#100)

- Simple wet granulation method or roller compaction of other excipients. Spray drying can also employed to shroud the drug.
- Drugs can be sifted twice or thrice in small particle size mesh with excipients such as sweeteners and flavors etc

- Drug particles are coated directly.
- Granulation of the drug with certain excipients fallowed by the polymer coating.
- If the drug is tasteless or very low dose, direct blend of bulk drug substance into fast disintegrating matrix is straightforward.
- Formation of pellets by extrusion spheronization.
- Coacervation to form microencapsulated drug within a polymer.
- Cyclodextrins can be used to trap or complex, cyclodextrin help to solubilze many drugs.
- Drug complexation with resinates are insoluble and no taste in oral cavity. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.
- Other methods include hot melt and supercritical fluids.
- Adjustment of pH Values: Many drugs are less soluble at pH different from the pH value of the mouth, which is around 5.9. Solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules including a drug sildenafil dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone[22].

Table 2: Mechanism of superdisintegrants[4]

Mechanism of disintegration	Example of Superdisintegrants
Wicking	Cross linked cellulose, cross linked PVP, calcium silicate
Swelling	Cross linked starch
Both wicking and swelling	Cross linked PVP, Cross linked aliginic acid

Various ingredients for FDTs

Component	Example
Water-soluble excipients	Compressible sugars, binders, surfactants, flavouring agents
Water-insoluble excipients	Microcrystalline cellulose, di- or tri-basic calcium phosphate
Disintegrants	Modified celluloses (such as cross-linked sodium carboxy methyl cellulose), cross-linked polyvinyl pyrrolidone(PVP), microcrystalline cellulose, starch and modified starch (including potato starch, maize starch, starch 1500, sodium starch glycolate and starch derivatives), alginic acid and sodium alginate.

Mechanism of tablet disintegration:

Disintegrants are substances routinely included in tablet and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of dosage form in dissolution fluids. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Various mechanisms**(Table 2)**

proposed in this concern include water wicking, swelling, deformation recovery and repulsion. It seems likely that no single mechanism can explain the complex behaviour of the disintegrants. However, each of these proposed mechanisms provides some understanding of different aspects of disintegrant action.

❖ **Swelling**

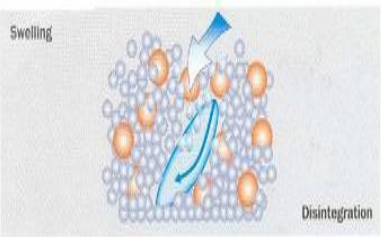

Figure:1 Swelling (Particles swell and break up the matrix form within; swelling sets up; localized stress spread throughout the matrix)

Although water penetration is a necessary first step for disintegration, swelling is probably the most widely accepted mechanism of action for tablet disintegrants. For swelling to be effective as a mechanism of disintegration, there must be a superstructure against which disintegrant swells.

❖ **Water Wicking**

When we put the tablet into suitable dissolution medium, the medium penetrates into tablet and replaces air adsorbed on the particles, which weakens intermolecular bond and break the tablet into particles. Water uptake by tablet depends upon hydrophilicity of drug, excipients and on manufacturing conditions.

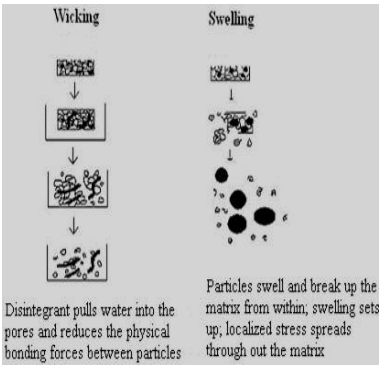

Figure:2 Disintegration of Tablet by Wicking and Swelling

❖ **Particle Repulsive Forces**

According to this, water penetrates into tablet through hydrophilic pores and a continuous starch network is created that can convey water from one particle to the next, imparting a significant hydrostatic pressure. water then penetrates between starch grains because of its affinity for starch surfaces, thereby breaking hydrogen bonds & other forces holding the tablet together.

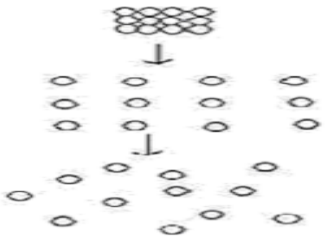

Figure:3 Repulsion Theory (Water is drawn into the pores and particles repel each other due to the resulting electrical force)

❖ **Deformation (elastic recovery):**

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media.

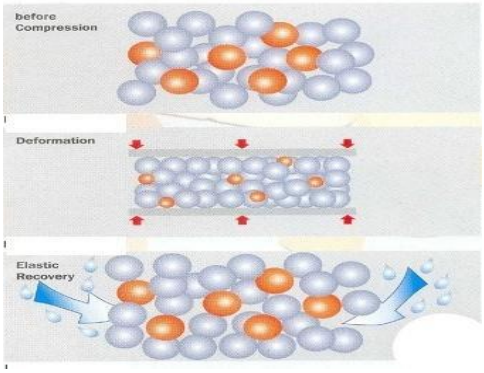

Figure 4: Steps involve in Elastic recovery

❖ **Due to Release of Gases**

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet.

❖ **By Enzymatic Reaction**

Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

❖ **Because of Heat of Wetting (Air Expansion)**

When disintegrants with exothermic properties gets wetted localized stress is generated due to capillary air expansion, which helps in disintegration of the tablet[36,37,38].

Technologies used to manufacture mouth dissolving tablets:

❖ **Conventional technologies for odts**

1. Freeze drying

ZYDIS® (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of fast disintegrating dosage forms. This method involves of drug in water soluble

matrix, which is then transferred to the preformed blister with peelable foil, as the zydis units are not strong enough to withstand being pushed through the lidding foil of a conventional blister. Freeze drying is then done to remove water by sublimation.

2. Moulding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly.

i. Compression molding:

The manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by compressing into mold plates to form a wetted mass, which is, then air dried to remove the solvent.

ii. Heat molding:

A molten matrix in which drug is dissolved or dispersed can be directly molded into ODTs. The tablets prepared using heat molding process involves settling of molten mass that contain a dispersed or dissolved drug.

iii. Molding by vacuum evaporation without lyophilization:

This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

3. Spray Drying

The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20sec. in an aqueous medium.

4. Direct Compression Method (Disintegrant Addition)

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The evolution of carbon dioxide as a disintegration mechanism called OROSOLV and DURASOLV have been described in two US Patents assigned to CIMA Lab.

5. Sublimation

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g. ammonium

bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, phthalic anhydride, urea and urethene) have been used for this purpose. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix.

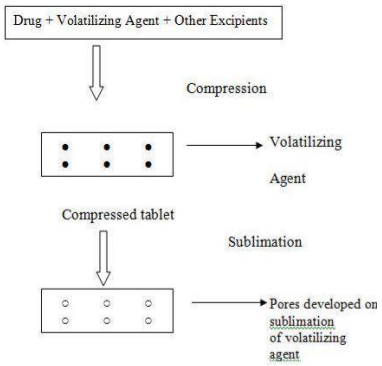

Figure 5.: Steps Involved in Sublimation.

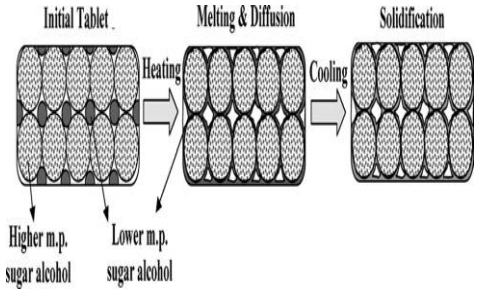

Figure 6: Schematic illustration of a fast disintegration tablet prepared by the phase transition method using a higher melting (erythritol) and a lower melting (xylitol) sugar alcohol

6. Phase transition process:

In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. The combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, is important for making ODTs without any special apparatus.

7. Melt granulation:

Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder that can be a molten liquid, a solid, or a solid that melts during the process.

8. Mass Extrusion:

This technology consists of softening the active blend using a solvent mixture of water soluble polyethylene glycol with methanol and expulsion of softened mass through the extruder or syringe to obtain cylinder of the product into even segments employing heated blade to form tablet.

9.Oral Disintegrating Thin Films:

In this technique, water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.) drug and other taste masking ingredients are dissolved in nonaqueous solvent to prepare non-aqueous solution, which forms a film after evaporation of solvent.

Patented Technologies for ODTs

1.Zydis®technology(Cardinal HealthInc.):

Zydis® was first marketed technology and introduced by R. P. Scherer Corporation (Cardinal Health, Inc.) in 1986. It is a unique freeze-dried oral solid dosage form, that can be administered without water and it dissolves instantly on tongue in less than 3 seconds.

2.Orasolv® technology (Cima Labs, Inc.):

Orasolv® is Cima Lab's first orally disintegrating dosage form. This technology is based on the direct compression of effervescent agent and taste masked drug at low compression force in order to minimize oral disintegration and dissolution time.

3.Durasolv® technology (Cima Labs, Inc.):

Durasolv® is Cima's second-generation fast- dissolving/ disintegrating tablet formulation. Durasolv® has much higher mechanical strength than Orasolv due to the use of higher compaction pressures during tableting. Durasolv® product is thus produced in a faster and more cost-effective manner.

4.Lyoc Technology (Cephalon Corporation):

Lyoc technique was owned by Cephalon Corporation. Lyoc utilizes a freeze-drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves.

5.Flashtab technology (Prographarm):

Flashtab technology was developed by Prographarm. A disintegrating agent and a swelling agent are used in combination with coated taste-masked microgranules of drug.

6.Wowtab technology (Yamanouchi Pharma Technologies, Inc.):

Wowtab technology was developed and patented by Yamanouchi Pharma Technologies. 'Wow' means 'without water'. The active ingredients may constitute up to 50 % w/w of the tablet.

7.Frosta technology (Akina):

Akina patents this technology. It utilizes the concept of formulating plastic granules and co-processing at low pressure to produce strong tablets with high porosity.

8.AdvaTab technology (Eurand):

In this technology, microencapsulation process is used for coating the drug particles with gastro soluble polymer to mask the taste along with restriction of drug dissolution in mouth cavity.

9.Flashdose technology (Fuisz Technologies, Ltd.):

This technology is patented by Fuisz Technologies, Ltd. This technology utilized cotton candy process. This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy.

10.Nanocrystal technology (Elan Corporation):

This technology has patented by Elan, King of Prussia, and is based on concept that decreasing particle size increases the surface area, which leads to an increase in dissolution rate.

11.OraQuick technology (KV Pharmaceutical Co. Inc.):

OraQuick utilizes its own patented taste masking technology i.e. MicroMask®. In MicroMask® technology, taste-masking process is done by incorporating drug into matrix microsphere.

12.Pharmaburst technology:

SPI Pharma, New castle, patents this technology. It utilizes the co-processed excipients to develop ODT, which dissolves within 30-40 seconds.

13.Quick-Dis technology (Lavipharm):

Lavipharm Laboratories Inc. has invented an ideal intraoral fast dissolving drug delivery system called as Quick-Dis™. This is a thin, flexible, and quick- dissolving film.

14.EFVDAS technology (Elan Corporation):

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 has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use.,

15.Multiflash technology (Prographarm):

Multiflash is a multi-unit tablet composed of coated microgranules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the esophagus after being swallowed with a minimum amount of water.

16. Shea form Technology:

The technology is based on the preparation of floss that is also known as „Shear form Matrix", which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing.

17. Ceform Technology:

In ceform technology microspheres containing active ingredient are prepared[39,40,41,42].

PREFORMULATION STUDIES FAST DISSOLVING TABLET:

It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

1. Bulk Density (Db):

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

$$Db = M / Vb$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

2. Tapped Density (Dt):

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

$$Dt = M / Vt$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

3.Angle of Repose (q):

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder**.(see table-3)**

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan (q) = h / r$$

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

Where, q is the angle of repose.

h is the height in cms

r is the radius in cms.

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

Table 3: Angle of Repose as an Indication of Powder Flow Properties[6,7]

Sr. No.	Angle of Repose	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

4.Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give(Table 4)

$$I = (Dt - Db)/ Dt * 100$$

Dt is the tapped density of the powder

Db is the bulk density of the powder.

Table-4 : Relationship between % compressibility and flow ability[8,9]

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

5.Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-

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

Dt is the tapped density.

Db is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

6:Identification of drug sample:

It was confirmed by melting point determination and also by FT-IR spectral analysis

7:Drug excipient Compatibility study:

Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study[44,45,46,47].

EVALUATION OF FAST DISINTEGRATING TABLETS:

Tablets from all the formulation were subjected to following quality control test.

- **General Appearance:**

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

- **Size and Shape:**

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

- **Tablet thickness:**

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

- **Weight variation:**

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in following **table- 5**.

Table 5: Weight variation specification as per I.P[14,15]

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

- **Hardness:**

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

- **Friability (F):**

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

$$F = (W_{int} - W_{fin}) / W_{int}$$

Wint - Weight of tablets before friability.

Wfin - Weight of tablets after friability.

- **Wetting Time:**

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

- **Water absorption Ratio:**

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

$$R = 10 (wa/wb)$$

wa is weight of tablet before water absorption &

wb is weight of tablet after water absorption.

- **In vitro dispersion time:**

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

- **In vitro Dissolution test:**

The development of dissolution methods for FDTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent FDT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for FDT much in the same way as their ordinary tablet counterparts. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used.

- **Stability testing of drug (temperature dependent stability studies):**

The fast disintegrating tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(1) 40 ± 1 °C

(2) 50 ± 1°c

(3) 37 ±1 ° C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation.

Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

- **Packaging:**

The products obtained by lyophilization process including various technologies such has Zydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For the above reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome-shaped blister, which prevents vertical movement of tablet within the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv. WOW Tab, Pharmaburst oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles[50,51].

Table. 8: Some ODT technological patents[44,45]:-

ODT Technologies	Technological basis	Patent owners
Zydis	Lyophilisation	R.P. Scherer Inc.
Quicksolv	Lyophilisation	Janseen Pharmace
Flashtab	Multiparticulate compressed tablets	Prographarm
Lyoc.	Lyophilisation	Cephalon Corporation
Orasolv.	Compressed tablets	Cima Labs Inc
Durasolv.	Compressed tablets	Cima Labs Inc
Wowtab	Compressed molded tablets	Yamanouchi Pharma Technologies, Inc.
Flashdose.	Cotton candy process	Fuisz Technologies, Ltd
AdvaTab	microencapsulation	Eurand
Multiflash	Multi-unit tablet composed of coated microgranules	Prographarm
EFVDAS	Effervescent system	Elan Corporation

Table 9: Examples of fast dissolving tablets currently available on the market[50,51,52]:-

Drug product	Active ingredient	Indication	Marketing company	Technology	Technology Company
Alavert	Loratadine	Allergy	Wyeth	OraSolv/DuraSolv	Cima Lab
Aricept	Donepezil	Alzheimers	Eisai		
Benadryl Fast	Diphenhydramine pseudoephedrine	Allergy, cold, sinus	Johnson and Johnson	WOWTAB	Astellas Pharma (formerly Yamanouchi)
Claritin	RediTabs	Loratadine	Allergy	Schering-Plough	Zydis Cardinal Health
Prevacid SoluTab	Lansoprazole	Duodenal ulcer	TAP		

Remeron SolTab	Mirtazapine	Depression	Organon	Durasolv	Cima Lab
Maxalt-MLD	Rizatriptan benzoate	Migrane	Merck	Zydis	Cardinal Health
Zofran ODT	Ondansetron	Nausea	Glaxo Smith Kline	Zydis	Cardinal Health
Zomig ZMT	Zolmitriptan	Migrane	Astra Zeneca	OraSolv/DuraSolv	Cima Lab
Zyprexa Zydis	Olanzapine	Schizophrenia	Eli Lilly	Zydis	Cardinal Heal

CONCLUSION:

The clinical studies show FDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. Considering the many benefits of FDTs, it is only a matter of time until a majority of oral formulations are prepared in FDT forms. By paying close attention to advances in technologies, pharmaceutical companies can take advantage of FDTs for product line extensions or for first-to-market products. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for FDTs in the days to come. The successful marketed FDTs have good taste and rapid release properties. With rapid acceptance of FDTs by patients and pharmaceutical companies, the market for this dosage form is promising, and the product pipeline continues to grow.

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