International Standard Serial Number (ISSN): 2319-8141
International Journal of Universal Pharmacy and Bio Sciences 3(3): May-June 2014
INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES
*IMPACT FACTOR 1.89****
*ICV 5.13****
Pharmaceutical Sciences **REVIEW ARTICLE……!!!**

AN OVERVIEW ON FAST DISSOLVING TABLETS

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KEYWORDS:

Fast dissolving tablets, absorption, bioavailability.

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ABSTRACT

The concept of Fast dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficulty for many patients to swallow tablets and hard gelatin capsules. Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Such problems can be resolved by means of Fast dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

INTRODUCTION:

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of administration, pain avoidance, versatility and patient compliance, less expensive to manufacture**.** The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance [1, 2, 3,4 and,5]. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy [6, 7, & 8]. Oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[9, 10].

The concept of Fast Disintegrating Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. 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. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva.

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[11, 12].

Fast disintegrating tablet disintegrate and/or dissolve rapidly in the saliva without the need for water. 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. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. 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. FDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage

forms[13,14]. Taste-masking is of critical importance in the formulation of an acceptable FDDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overwhelm or complement the bitter taste of the drug. FDTs are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of solid dosage forms, which increase consumer choice, for the reason of rapid disintegrate/dissolve in oral cavity within seconds and swallowed without the need of water or chewing.

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 [15].

1.1Definition

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

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water. The fast disintegrating tablets are synonymous with fast dissolving tablets; melt in mouth tablets, rapimelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.

1.2 Requirements of Fast disintegrating tablet of an ideal FDT should [16]

- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be optimum harder and less friable
- Leave minimal or no residue in mouth after administration
- Exhibit low sensitivity to environmental conditions (temperature and humidity).

1.3 Advantages [16, 18,& 37]

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients.

- Convenience of administration and accurate dosing as compared to liquids.
- No need of 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 feel property of MDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, and in such cases bioavailability of drugs in increased.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism.

Disadvantages

- The disadvantage of most ODT is that they are fragile and brittle.
- It needs special package for protection during storage and transportation.

1.4 Characteristics of fast disintegrating systems

a. Ease of administration

Fast disintegrating drug delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (Tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

b. Taste of the medicament

As most drugs are unpalatable, fast disintegrating drug delivery systems usually contain the medicament in taste masked form. These delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

c. Hygroscopicity

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

d. Friability

In order to allow fast disintegrating 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.

e. Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

1.5 Techniques that can be used for taste masking [17]

Mouth dissolving tablets come in contact with taste buds for a longer time as it dissolves in the oral cavity. Taste masking is an essential requirement for mouth dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques.

Polymeric coating strategies (microencapsulation):

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. In case of giving coating to the drug particles, it will result in an increase the particle size. The extent to which the particle size increase will affect the mouth feel and tablet size will depend on the dose of the drug. The amount of coating material required to achieve taste masking. In fact this process retards or inhibits dissolution and solubilization of drug, which allows time for particles to pass from mouth before taste is perceived in mouth.

Complexation with cyclodextrin:

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

Use of ion exchange resins:

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly. Bitter cationic drugs can get adsorbed on to the weak cation exchange resins of carboxylic acid functionality to form the complex, which is non bitter.

The complex of cationic drugs and weak cation exchange resin does not break at pH 6-7, of saliva with cation concentration of 40 meq/lit. But at high cation concentration of stomach pH of 1-3, free drug is immediately released.

Use of effervescent systems:

The effervescent agents are used for the taste masking of drugs. Generally these formulations contain a carbon dioxide generator for taste masking, optionally a taste bud desensitizing composition, sweetener, and flavoring agent.

Salt formation or functional group modification:

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water soluble drugs.

Incorporation of sweeteners and flavors:

Flavors, sweeteners, gelatin, acidic amino acids, lecithin or lecithin like substances and surfactants are used for taste masking of bitter drugs.

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations.

1.6 Different Approaches for Preparing Of Fast Disintegrating Tablets:

1.6.1. Freeze drying[19]:

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. The influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in freeze dried form was investigated by Corveleyn and Remon[20] . who concluded that maltodextrins are useful in the formulation of fast dissolving tablets made by freeze drying. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability.

Jaccard and Leyder[21] employed lyophilization technique in making an oral pharmaceutical preparation and found increased absorption and bioavailability of drugs like Spiranolactone, Nicergoline and Trolendomycin in comparison to their conventional formulation.

The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

 International Standard Serial Number (ISSN): 2319-8141

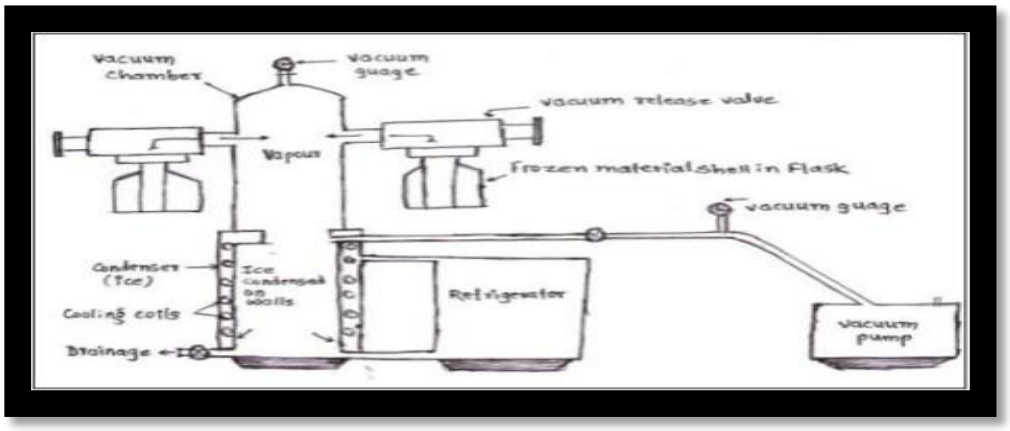

Figure No: 1.1 Freeze dryer

1.6.2. Molding

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

Molded forms are also prepared using a heat-molding process that involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at -30°C under vacuum. Another process used is called no-vacuum lyophilization, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure. Pabley et al., evaporated a frozen mixture containing a gum (e.g., acacia, carrageen, guar, tragacanth, or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol, or maltodextrin), and a solvent in a tablet shaped mould[28]. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs Moulded tablets usually are prepared from soluble ingredients by compressing a powder mixture previously moistened with solvent (usually ethanol or water) into mould plates to form a wetted mass (compression molding). Recently, molded forms also have been prepared directly from a molten matrix in which the drug is dissolved or dispersed (heat molding) or by evaporating the

solvent from a drug solution or suspension at standard pressure (no-vacuum lyophilization). Tablets produced by molding are solid dispersions. The physical form of the drug in the tablets depends on whether, and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. It can dissolve totally in the molten carrier to form a solid solution, or dissolve partially in the molten carrier while the remaining particles stay undisclosed and dispersed in the matrix.

The characteristics of the tablets (such as disintegration time, drug dissolution rate, and mouth feel) will depend on the type of the dispersion or dissolution. Because the dispersion matrix is, in general, made from water soluble sugars, molded tablets disintegrate more rapidly and offer improved taste.

These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the molding process are used. Unfortunately, molded tablets typically do not possess great mechanical strength. Erosion and breakage of the molded tablets often occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases.

FDTs, having both adequate mechanical strength and good disintegration, recently have been prepared by molding techniques using nonconventional equipment and/or multistep processes. The nonconventional approach, however, does cost more. Compared with freeze-drying, FDTs prepared by molding techniques can be produced more simply and efficiently at an industrial scale, although they cannot achieve disintegration times comparable with those of lyophilized forms.

1.6.3. Sublimation

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed by Heinnemann, et al.,[25]. Inert solid ingredients (ex. urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. A method of producing fast disintegrating tablet using water as the pore forming material has been described by Makino, et al. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Koizumi, et al, have developed a new method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material.

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence. To generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies

conducted by Heinemann and Rothe, Knitsch et al.,[24] and Roser and Blair,et al.,[23] inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a table[30,31].The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

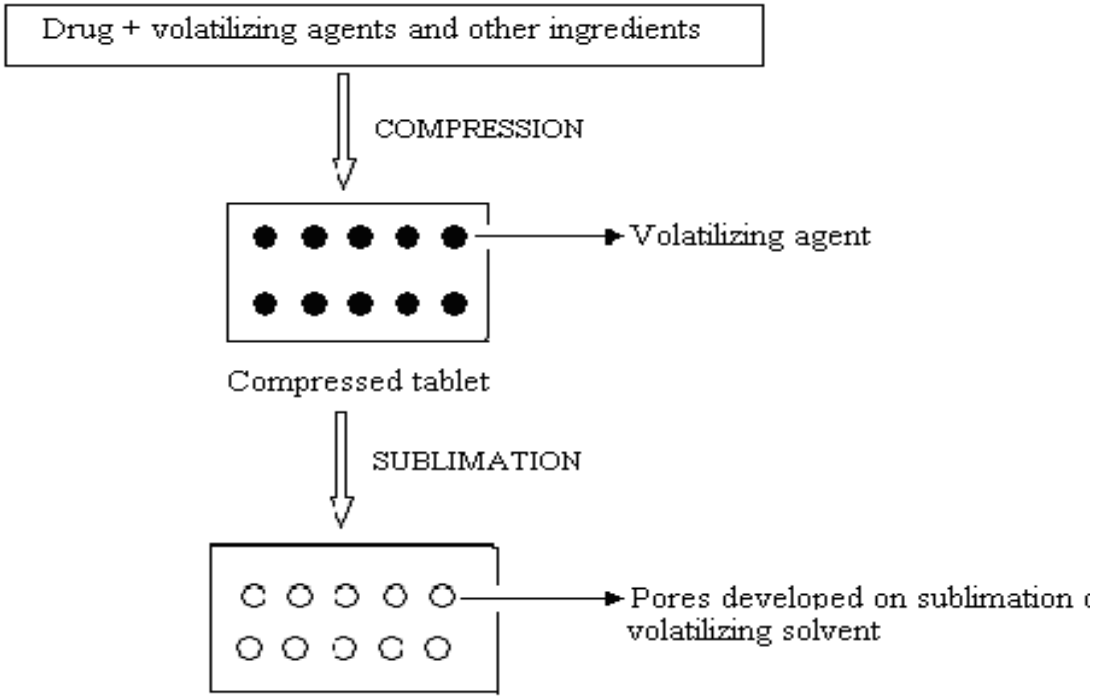

Figure No: 1.2 Schematic Diagram of Sublimation Technique for Preparation of FDT

1.6.4. Spray Drying

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets. Allen et al [26] used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 seconds.

1.6.5. Direct Compression:

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action

of disintegrates, water soluble excipients and effervescent agent. Disintegrate efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

Disintegrant addition:

Disintegrant addition technique is one of the popular techniques for formulating mouth -dissolving tablets because of its easy implementation and cost –effectiveness.

The basic principle involved in formulating mouth-dissolving tablets by disintegrants addition technique is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel.

Crospovidone (CP), Cross Carmellose Sodium (CCS), and Sodium Starch Glycolate (SSG) are most widely used superdisintegrants.In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level[27].

Sugar based excipients:

Sugar based excipients (sorbitol, mannitol, dextrose, fructose, maltose, poly dextrose) have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasant mouth feel and good taste masking.

However, not all sugar-based materials have a fast dissolution rate and good compressibility and compatibility.

1.6.6. Melt granulation:

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublizes rapidly leaving no residues.[28]

1.6.7. 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.[29]

1.6.8. Mass extrusion method

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and extrusion 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 can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.Rapidly disintegrating domperidone tablets were formulated by Dandagi P.M using two methods as mass extrusion technique and treated agar. In mass extrusion formulations sodium starch glycolate, eudragit E-100, low substituted hydroxyl propyl cellulose, lactose and in treated agar formulations mannitol, treated agar, lactose, aspartame were used as excipients.

1.6.9.Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy.Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. The candy floss matrix is grinded and blended with drug and excipients and then compressed to ODT. This process is more helpful for high doses of drug and also increases mechanical strength of tablet. But high temperature process limits the use of this process.

1.7 Patented technologies for mouth dissolving drug delivery system:[31]

The mouth dissolving tablets are also known as fast disintegrating and quick disintegrating tablets; however the function and concept of all these dosage forms are similar. Though several technologies are available, a few have reached for commercial marketed products such as Flash dose, Flash tab,

Oraquick, Orasolv, Zydis and WOW Tab.FDA considers these mouth dissolving tablets as a new dosage form .

1.7.1. Zydis Technology: [30, 32]

Gregory and Scherer have patented the Zydis technology. Zydis is the first mouth dissolving dosage form available in the market. This technology based on the concept of forming porous matrix network containing the active ingredient.

These are freeze dried products containing water soluble matrix material and drug, which is performed in blister pockets and freeze dried to remove the water by sublimation. The resultant structures are very porous in nature and rapidly disintegrate or dissolve upon contact with saliva. Zydis must be produced in blister packs with peelable backing foil, because the units are not strong enough to with stand being pushed through the backing foil of a conventional blister. A secondary moisture proof foil punch is often required because this dosage form is very moisture sensitive.

Polymers generally used to form the matrix in Zydis are Gelatin, Dextrins or Alginates. Mannitol or sorbitol may be added to impart crystallinity and hardness. The use of water as the medium ensures the formation of porous dosage form. Preservatives may be added in appropriate concentrations to prevent microbial growth in aqueous solutions (during manufacture). Suspending agents and pH-adjusting excipients may be added if necessary. Cryoprotect agents such as glycerin prevent the shrinkage of the Zydis units and may be useful additives. This technology has certain limitations.

A water insoluble drug can be incorporated only up to 400 mg per tablet or less, on the other hand water soluble drug can be incorporated only up to 60 mg. A lyophilized disk is so lightweight and fragile, so that it is unsuitable for conventional blister packing.

The use of matrix forming agents such as gelatin and sugar based excipients in the formulations could overcome this problem. Freeze drying is a relatively expensive and time consuming process. Other drawbacks of freeze dried disk include fragility and poor stability during storage under stressful conditions. The particle size of the insoluble drugs should be less than 50 µm and not more than 200 µm to prevent sedimentation during processing.

Most compounds in a Zydis formulation are claimed to be bioequivalent to their respective existing solid oral dosage forms.

Zydis Products:

Zyprexa Zydis: Olanzapine (5, 10, 15 or 20 mg), gelatin, mannitol, aspartame, sodium methyl parabene, sodium propyl parabene.

Claritin Reditab: Micronized Loratadine (10 mg), citric acid, gelatin, mannitol and mint flavor.

ZOFER MD ODT: Ondansetron (4 or 8 mg), aspartame, gelatin, mannitol, sodium methyl parabene, sodium propyl parabene, straw berry flavor.

Feldene Melt: Piroxicam (10 or 20 mg), gelatin, mannitol, aspartame, citric anhydrous.

Pepcid RPD: Famotidine (20 or 40 mg), gelatin, mannitol, aspartame.

Maxalt-MLT: Rizatriptan (5 or 10 mg), gelatin, mannitol, aspartame, peppermint flavor.

1.7.2. Orasolv Technology: [33,]

CIMA Laboratories developed this patented Orasolv technology. This technology utilizes the effervescence materials and taste masked active ingredients, which on contact with saliva, rapidly disintegrates and releases the taste masked active ingredient. This technique requires only conventional manufacturing process like direct compression at very low compression forces in order to minimize oral dissolution time and equipment. The effervescence occurs due to chemical reaction between organic acid such as citric acid, fumaric acid or maleic acid and a base such as sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate, which result in generation of CO_2. The tablets produced by this technique are soft and friable and repackaged in specially designed "pick-and place system". "Paksolv" a proprietary packing system consisting of specialized tablet transfer, packaging equipment, and unique packaging materials and designs, is developed by CIMA Labs to pack the soft , friable tablets, to protect it from attrition and breakage during transportation. The concept of effervescence is well-known formulation art, utilized in several dosage forms. However the current technology uses this concept in a modified fashion where the micro particles are prepared by novel technique involving dispersion of active ingredients into suitable polymer dispersion together with other excipients such as mannitol and magnesium oxide. Orasolv dosage forms have been developed, containing more than 1000 mg of active load and are capable of combinations of multiple active ingredients in a tablet.

The main drawback of tablets produced by this technology is that, tablets are soft and friable and hence packaged using an integrated packaging line that uses a specially designed robotic "pick and pack" system. CIMA has carried out an internal study comparing an Orasolv Famotidine tablet with conventional famotidine tablet (Pepcid).

The plasma profiles of both the formulation do not alter the absorption kinetics of famotidine. There are six Orasolv formulations marketed worldwide. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 gm of drug have been developed. Their disintegration time is less than 30 seconds. The Orasolv formulation is not very hygroscopic.

Orasolv Products

RemeronR Sol tabs: Mirtazepine

TempraR First Tabs: Acetaminophen

1.7.3. Durasolv Technology [34]

Durasolv is another fast dissolving technology patented by CIMA laboratories. The tablets made by this technology consist of a drug, fillers and a lubricant. Durasolv tablets are prepared by using conventional tab letting equipment and have good rigidity (friability <1%). They can be packaged into conventional packaging systems like blisters, pouches or bottles. Durasolv is appropriate technology for products requiring low amount of active ingredients.

Durasolv products:

Undistred: Loratadine

Zooming ZMT: Zolmitriptan (2.5 mg)

1.7.4. Flash Dose Technology: [, 35, 36]

Fuisz has patented the flash dose technology. Nuroflen 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. Flash dose tablets consist of self-binding shear form matrix termed as "Floss". Shear form matrices are prepared by flash heat processing and are of two types. Single Floss or Unifloss consists of a carrier, and two or more sugar alcohols, out of which one is xylitol. Dual Floss consists of a first shear form carrier material (termed "base floss" contains a carrier and at least one sugar alcohol generally sorbitol), and a second shear form binder matrix

("Binder Floss", contains a carrier and xylitol). In Flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal forces and to a temperature gradient, resulting in discrete fibres. The preformed matrices obtained are partially crystallized and have good self binding and flow properties. Crystallization can be performed by using crystallization enhancers, e.g. ethanol, poly vinyl pyrrolidine, water and radiant energy, at a concentration of about 10%. Any crystallization modifiers (e.g. surfactants which include, lecithin, propylene glycol, spans, tweens and poly ethylene glycols) can be used up to 10% by weight of tablet composition.

Formed matrix are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. The shear form matrix is blended with drug (usually taste masked) and other tabletting ingredients, and compressed into tablets using conventional tabletting equipment. The tablets produced, dissolve rapidly in the saliva of mouth. The major drawback of these dosage forms are that the tablets are highly friable, soft and moisture sensitive. To protect this specialized packaging is required. These dosage form accommodate the drug up to 600 mg only.

1.7.5. WOW Technology

This technology is based on the combination of low and high mold ability saccharine to product fast dissolving tablets using a conventional manufacturing process. Tablets, produced from this

technology will have sufficient hardness to maintain the physical characteristics of the dosage from during production until it comes in contact with moisture such as saliva in mouth.

The active ingredients may constitute up to 50% W/W of the tablet weight.WOW –Tab technology is patented by Yamanouchi Pharmaceutical Co.WOW means without water. This process uses a combination of low mold ability saccharide (rapid dissolution) and high mold ability saccharide (good binding property) to obtain a rapidly melting strong tablet.

The active ingredient is mixed with a low mould ability saccharide (e.g. lactose, glucose, sucrose, maltose and xylitol) and granulated with a high mould ability saccharide (e.g. maltose, sorbitol, and oligo saccharide) and compressed into tablets.

The ratio of high mold ability saccharide used is 2-20% weight. In other process, low mold ability saccharide is granulated with high mold ability saccharide, and the resultant granules are mixed with active ingredient and subjected to compression using conventional tabletting equipment.

1.7.6. Flash Tab Technology:[36,39]

Prographarm laboratories have patented the Flash Tab Technology. This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like microencapsulation, coacervation, and extrusion-spheronization or simple pan coating method.

The micro crystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilizes the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than 1 minute.

1.7.7. Oraquick [37]

The Oraquick fast dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV pharmaceutical claims its microsphere technology known as micro mask has superior mouth feel over taste making alternatives.

The taste masking process doesn't utilize solvents of any kind, and therefore leads to faster and more efficient production. Also lower heat of production than alternative fast dissolving /disintegrating technologies makes Oraquick appropriate for heat sensitive drugs.

KV pharmaceuticals also claims that the matrix that surrounds and protects the drug powder in micro encapsulated particles is more pliable, meaning tablets can be compressed to active significant mechanical strength without disturbing taste masking. Oraquick claims quick dissolution in a matter of seconds, with good taste masking. There is no product using the Oraquick technology currently in market but KV pharmaceuticals has products in development such as analgesics, drugs for cough and cold, psychotropic and anti infectives .

1.7.8. Quick Solv:

Quick Solv is a porous solid form obtained by freezing and aqueous dispersion or solution of active containing matrix, then drying the matrix by removing the water using an excess of alcohol (solvent extraction).The final form disintegrates very rapidly but is limited to low drug content and can be used only with those actives that are insoluble in the extraction solvents.

1.7.9. Fast melt [40]

It constitutes of a highly porous, micro fine matrix tablet. The drug is in a size reduced form to ensure optimal solubility and dissolves rapidly. The combination of a mild effervescent base and drug processing ensures that the dosage form goes into solution in approximately 15-30 seconds. In this is particularly advantageous in case like migraine where a fast onset of clinical effect is required (Elan Corporation).

1.7.10. Nanocrystal Technology (Elan Corporation) [38]

This technology is based on concept that decreasing particle size increases the surface area, which leads to an increase in dissolution rate.

Nanocrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by wet milling the drug.

Nanocrystal™ fast dissolving technology provides

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix.
- Product differentiation based upon a combination of proprietary and patent-protected technology elements.
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations.
- Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters).
- Wide range of doses (up to 200 mg of API per unit).
- Utilization of non-moisture sensitive in actives.

Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach avoids manufacturing operations (e.g. granulation, blending, and tabletting) That generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into orally disintegrating dosage forms because manufacturing losses are negligible.

1.7.11. Lyoc [38,]

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.

The liquid solution or suspension preparation evolves fillers, thickening agents, surfactant, non-volatile flavoring agents and sweeteners along with drug. This homogeneous liquid is placed in blister cavities and subjected to freeze drying. To prevent in homogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the in process suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates are comparable to loosely compressed fast melt formulations.

Table No: 1.1 List of Marketed Fast Dissolving Tablets [41]

S. No.	Trade Name	Active Drug	Manufacturer
1.	Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
2.	Claritin redi Tab	Loratidine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
4.	Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merck and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7.	Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
8.	Zeplar TM	Selegilline	Amarin Corp., London, UK
9.	Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
10.	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
11.	Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India

12.	Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
13.	Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
14.	Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
15.	Benadryl Fastmelt	Diphenhydramine	Warner Lambert, NY, USA
16.	Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceutics
17.	Risperdal MTab	Risperidone	Janssen pharmaceutics
18.	Spasfon Lyoc	Phloroglucinol Hydrate	Farmalyoc
19.	Nurofen FlashTab	Ibuprofen	Ethypharm
20.	Tempra Quicklets	Paracetamol	Cima Labs,Inc.
21.	Zolmig Repimelt	Zolmitriptan	Cima Labs,Inc.
22.	NuLev	Hyoscyamine Sulfate	Cima Labs, Inc.
23.	Gaster D	Famotidine	Yamanouchi Pharma Tech. Inc.
24.	Cibalgina DueFast	Ibuprofen	Eurand International
25.	Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd.
26.	Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc.
28.	Allegra ODT	Fexofenadine	Sanofi Aventis

29.	Aricept ODT	Donepezil	Eisai Co.
30.	Loratadine Redidose	Loratadine	Ranbaxy
31.	Mirtazapine ODT	Mirtazapine	Teva Pharmaceuticals
32.	Niravam	Alprazolam	Schwarz Pharma
33.	Ondansetron ODT	Ondansetron	Teva Pharmaceuticals
34.	Orapred ODT	Prednisolone	Sciele Pharma
35.	Parcopa	Carbidopa/levodopa	Schwarz Pharma
36.	Prevacid SoluTab	Lansoprazole	Takeda Pharmaceuticals
37.	Remeron SolTab	Mirtazapine	Schering-Plough
38.	Risperdal M-Tab	Risperidone	Janssen

Table No: 1.2: Therapeutic areas for fast disintegrating tablets[42]

S.No	Category	Examples
1	Antibacterial agents	Ciprofloxacin, tetracycline, erythromycin, rifampicin, pencillin, doxycyclin, trimethoprim.
2	Anthelmintics	Albendazole, mebendazole, livermectin, praziquantal,
3	Antidepressants	Trimipramine maleate, nortryptiline HCl, trazodone HCl, mianserin HCl, etc.
4	Antidiabetics	Glibenclamide, glipizide, tolbutamide,gliclazide,chlorpropamide, etc.
5	Analgesics/anti inflammatory agents	Diclofenac sodium, ibuprofen, ketoprofen, naproxen, piroxicam, etc.

6	Antihypertensives	Amlodipine, atenolol, nifedipine, prazocin HCl, diltiazem, etc.
7	Antiarrythmics	Disopyramide, quinidine sulphate, amiodarone HCl,etc.
8	Antihistamines	Cetrazine, cinnarizine, loratidine,
9	Anxiolytics, sedatives hypnotics	Alprazolam ,diazepam, clozapine, haloperidol, thioridazine, etc.
10	Diuretics	Acetazolamide, clorthiazide, furosemide, spironolactone,ethacrynic acid, etc.
11	Gastro intestinal agents	Cimitidine, famotidine, domeperidone, ranitidine HCl, omeprazole, ondansetron HCl,etc.
12	Corticosteroids	Betamethasone, hydrocortisone, prednisone, prednisolone, etc.

1.8 Mechanism of tablet disintegration[37]:

- Capillary action (Wicking).
- Swelling.
- Due to disintegrating particle/particle repulsive forces.
- Due to deformation.
- Due to release of gases.

Capillary action (wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles.

Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to

note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down

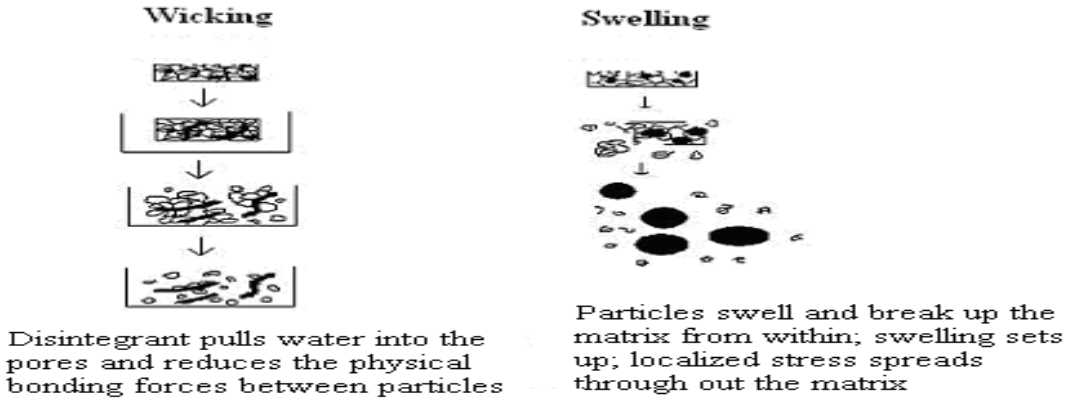

Figure No: 1.3 wicking and Swelling

Due to Disintegrating Particle/Particle Repulsive Forces:

Another mechanism of disintegratn attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to Deformation:

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

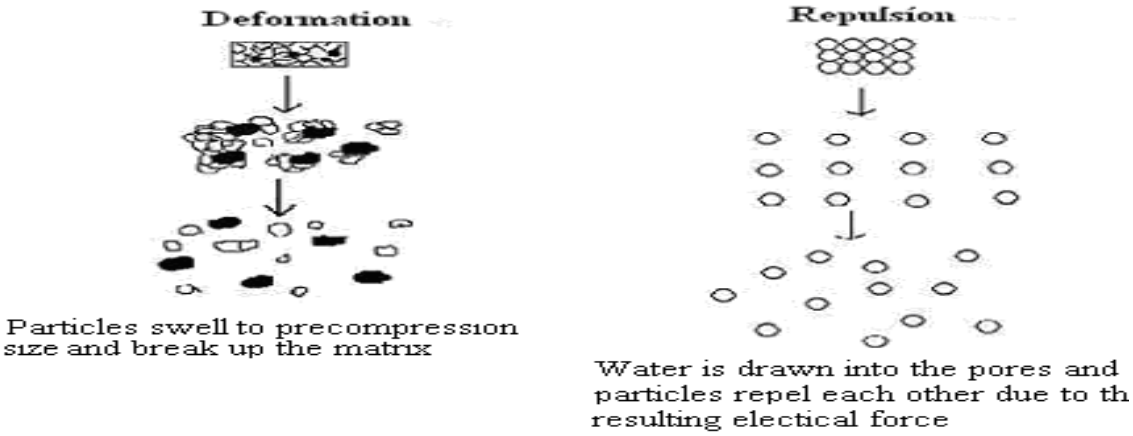

Figure No: 1.4 Deformation and Repulsive

Due to release of gases:

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

CONCLUSION:

Fast dissolving tablets (FDTs) are prepared by several different methods including crystalline transition, phase transition, sublimation, spray drying, and direct compression. Of these approaches, a conventional tablet compression method is used most widely because of its low cost and ease of manufacturing. The research on FDTs should be focused on decreasing the dissolution time of the tablets in the mouth, while maintaining sufficiently high mechanical strength to withstand handling during manufacturing, packaging and transportation. Natural polymers are preferred over synthetic polymers as they are nontoxic, easily available at low cost used in low concentration and as they are naturally extracted provide nutritional supplement. 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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