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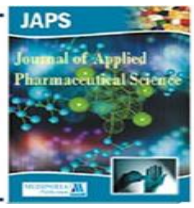

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A comprehensive review on fast dissolving tablet technology

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ABSTRACT

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Fast dissolving tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. This review describes the various formulation aspects, disintegrants employed and technologies developed for FDTs, patent formulation, evaluation tests, and marketed formulations.

Key words: Fast Dissolving tablet, Desired Characteristics, Manufacturing technology, Evaluation.

INTRODUCTION

The oral route of administration is considered as the most widely accepted route. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients (Sastry et al., 2000). Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients (Bhusan et al., 2000 and Wadhwani et al.,2004).Thus, a new delivery system known as oral fast dissolving/disintegrating (FDDS)/melt-in-mouth tablets gaining importance. These oral dosage forms dissolve rapidly in saliva and can be swallowed without the need of drinking water (Redkar et al., 2002). Elimination of bitterness is an important criterion in product formulation of mouth dissolving tablets (Yunxia et al., 1999). Superdisintegrants are added in formulation to increase the dissolution characteristics thus increasing bioavailability of drug (Kaushik et al., 2004). There are three methods of addition of disintegrant into the formulation, intra-granular (Internal addition), extra-granular (External addition), partly intra-granular and extra-granular addition (Sekar et al., 2008). The time for disintegration of orally disintegrating tablets is generally considered to be less than one minute (Liang and Chen., 2001, Morita et al., 2002, Schiermeier and Schmidt., 2002 and Siewert et al., 2003) although patients can experience actual oral disintegration times that typically range from 5-30 sec. Fast dissolving tablets are prepared by various techniques such as Direct compression, solid dispersion and moulding. The simple process and cost effectiveness of direct compression process prefer this process over other process (Chang et al., 2000).

DESIRED CHARACTERISTICS OF FAST DISSOLVING TABLETS

Because administration of FDTs is different from administration of conventional tablets, the FDTs should maintain several unique properties, as listed below.

Fast Disintegration

FDTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 mL) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

Taste of Active Ingredients

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the FDT formulations.

Drug Properties

For the ideal FDT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablets characteristics, such as tablet strength and disintegration. The FDT technology should be versatile enough to accommodate unique properties of each drug.

Tablet Strength and Porosity

Because FDTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.

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. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect FDTs from various environmental conditions (Seager., 1998, Dobetti., 2001 and Chang et al., 2000).

Table 1: Various Super-disintegrants and Their Properties (Cremer., 2003, Parakh SR and Gothosakar., 2003 and Duriez and Joshi., 2004)

Superdisintegrants	Commercially available grades	Mechanism of action	Special comment
Crosslinked Cellulose	Crosscarmellose® Ac-Di-Sol®, Nymce ZSX® Primellose®, Solutab®, Vivasol®, L-HPC	Swells 4-8 folds in < 10 seconds. Swelling and wicking both	Swells in two dimensions. Direct compression or Granulation Starch free.
Crosslinked PVP	Crosspovidon M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression but act by capillary action.	Water insoluble and spongy in nature so get porous tablet.
Crosslinked starch	Explotab® Primogel®	Swells 7-12 folds in < 30 seconds.	Swells in three dimensions and high level serve as sustain release matrix
Crosslinked alginic Acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation.
Soy polysaccharides	Emcosoy®		Does not contain any starch or Sugar. Used in nutritional products
Calcium silicate		Wicking action	Highly porous, Light weight,

ADVANTAGES OF FAST DISSOLVING TABLETS

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients.
- Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to

water.

- Good mouth feel property of Mouth dissolving drug delivery system helps to change the basic view of medication drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension (Kuchekar et al., 2003 and Bradoo., 2001).

LIMITATIONS OF FAST DISSOLVING TABLETS

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Tablet 2: List of marketed fast dissolving films (Arun Arya et al. 2010)

S. No	Product	Manufactured By
1	Dextromethorphan HBr (cough suppressant),Diphenhydramine Citrate (cough and cold),Breath Strips	MonoSolRx
2	Doneprezil rapid dissolving films, Ondansatron rapid dissolving films	Labtec Pharma
3	Life-saving rotavirus vaccine to infants	Johns Hopkins undergraduate biomedical engineering students
4	Methylcobalamin fast dissolving films, Diphemhydramine HCl fast dissolving films,Dextromethorphan fast dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films	Hughes medical corporation
5	Altoid cinnamon strips, Boots vitamin c strips, Cool shock peppermint strips, Benzocaine films, Caffeine films	Dow chemical company
6	Listerine Pocket Paks Breath Freshening Strips	Pfizer's Warner-Lambert consumer healthcare division
7	Energy strips - Caffeine 20mg, Acetyl Salicylic Acid (ASA), Ondansetron HCl, Dexamethasone, Nitroglycerine, Risperidone Vitamin B12, melatonin, folic acid, biotin Benzocaine, Diphenhydramine HCl, Dextrometorphan	ODF Technologies Inc.

MECHANISM OF SUPER-DISINTEGRANTS

There are four major mechanisms for tablet disintegration as follows

Swelling

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

Porosity and Capillary Action (Wicking)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart.

Deformation

Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration 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 (Lachman and Liberman., 1990).

It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

APPROACHES FOR FAST DISSOLVING TABLET

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.
Various technologies used in the manufacture of Fast dissolving tablets include

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 (Dong et al, 2007). 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 solublises rapidly leaving no residues (Abdelbary et al., 2004).

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 (Kuno et al., 2005).

Sublimation

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., 1975, Knitsch et al., 1979 and Roser and Blair., 1998 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 tablet. 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.

Koizumi et al., 1997 applied sublimation technology to manufacture tablets that rapidly dissolve in saliva. Mannitol is used as a matrix former, and camphor was used as a sublimating agent.

The tablets dissolved in 10-20 seconds and displayed satisfactory handling properties. Makino et al., 1998 reported a method using water as pore-forming material. A mixture of drug and a carbohydrate (e.g. erythritol, glucose, sucrose, xylitol). The water was then removed, yielding highly porous tablets with satisfactory mechanical strength and a high dissolution rate.

Three-dimensional Printing (3DP)

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system (Yu et al., 2008). It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume (Ito and Sugihara., 1996)

Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste (Bhaskaran and Narmada., 2002).

Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen *et al.* have reported applying this process to the production of fast dissolving tablets. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatine as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 second in an aqueous medium. (Gupta and Patel., 2007 and Makino et al., 1998)

Tablet Molding

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30 ○C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for

industrial manufacture (Bhowmik et al., 2009).

Lyophilization or Freeze-Drying

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of FDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions (Bhowmik et al., 2009).

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. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially Tablet disintegrants and sugar-based excipients. Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction super-disintegrants and a better understanding of their properties have increased the popularity of this technology. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration.

Above the critical concentration level, however, disintegration time remains approximately constant or even increases. (Gupta and Patel., 2007).

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of first dissolving tablets. Bi *et al.* and Watanbe *et al*. used microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture rapidly disintegrating tablets. The ratios of MCC to HPC varied from 8:2 to 9:1. Ito and Sugihan investigated applying agar powder as a disintegrants because the powder absorbs water and swells considerably without forming a gel at physiological temperatures. Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by the overall cost of the product. Another approach to fast dissolving tablets by direct compression is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol), which display high aqueous solubility and sweetness, and hence, impart taste masking and a pleasing mouthfeel.

OraSolv and DuraSolv Technology

OraSolv technology (Cima Labs) produces tablets by low compression pressure (Lagoviyer et al., 2002 and Wehling and Schuehle., 1996). It uses an effervescent disintegration pair that releases gas upon contact with water. The widely used effervescent disintegration pairs usually include an acid source and a carbonate source. The acid sources include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids. The carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. The carbon dioxide evolved from the reaction may provide some “fizzing” sensation, which is a positive organoleptic sensation. The amount of effervescent agent is in general about 20–25% of the total weight of the tablet. Because of the soft and fragile nature of OraSolv tablets, a special packaging system, known as PakSolv, was developed to protect the tablets from breaking during transport and storage (Wehling et al., 1993). PakSolv is a “dome-shaped”blister package that prevents the vertical movement of the tablet within the depressions, because the diameter of the lower portion of the dome is too narrow to accommodate the tablet. PakSolv also offers light, moisture, and child resistance. As a second-generation technology, the DuraSolvR technology was developed by Ciba to provide stronger tablets for packaging in blisters or bottles (Amborn and Tiger., 2001).

The key ingredients in this formulation are non-direct compression filler and lubricant. The particle size of the non-direct compression filler is preferably between about 20 and 65 μm, while for direct compressible fillers at least 85% of the particles are over 100 μm in size. These non-direct compression fillers, such as dextrose, mannitol, sorbitol, lactose, and sucrose, have the advantage of quick dissolution and avoid some of the gritty or sandy texture usually present in direct compressible versions of the sugar. The amount of nondirect compression filler is usually about 60–95% of the total tablet weight. The tablets have low friability, which is about 2% or less when tested according to the USP, and the hardness of the tablets is at least about 15–20 N. The disintegration time is less than 60 seconds. It is interesting to note that in comparison with the conventional tablet formulations, higher amounts of hydrophobic lubricants, such as magnesium stearate, can be added to the formulation with non-direct compression fillers as the main component. About 1–2.5% of

lubricant can be added to the formulation, compared with 0.2–1% of lubricant in conventional tablets. The lubricant blending times can also be increased to 10–25 minutes or longer. Relatively modest compressive force is needed to compress the formulation. This method can produce tablets by the direct compression method and use conventional tableting methodologies and conventional package equipment. Thus, the production cost is significantly decreased.

WOWTAB Technology

WOWTABR technology employs a combination of low- and high-moldability saccharides to produce fast-dissolving tablets using conventional granulation and tableting techniques (Mizumoto and Masuda., 1996). According to the patent, saccharides were divided into two groups: those with high moldability and those with low moldability. Low moldability saccharides produce tablets with hardness between 0 and 2 kg, when 150 mg of such a saccharide is compressed under pressure of 10–50 kg/cm2 using a die 8 mm in diameter. The typical low-moldability saccharides include lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides produce tablets with hardness above 2 kg when prepared under the identical conditions. The typical high- moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When tablets are made by compressing a saccharide having low moldability or high moldability alone, the desired properties of adequate hardness and quick disintegration in the mouth cannot be achieved simultaneously. Moreover, if saccharides having low moldability and high moldability are mixed (physical mixture) before tableting, quick disintegration and dissolution in the mouth cannot be obtained. As clearly indicated in the patents, there is no single saccharide that can make tablets having both high strength and fast disintegration properties. For this reason, a saccharide having low moldability was granulated with a saccharide having high moldability as a binder. The low-moldability saccharides were used as the main component. The tablets show an adequate hardness and fast disintegration and dissolution when put in the mouth.

Flashtab Technology

Flashtab technology (Ethypharm, France) produces tablets by compression of granular excipients (Cousin et al., 1995). This technology uses almost the same excipients as do conventional compressed tablets. Excipients used in this technology comprise two groups of components: disintegrating agents, such as carboxymethylcellulose or insoluble reticulated polyvinylpyrrolidone; and swelling agents, such as carboxymethylcellulose, starch, modified starch, carboxymethylated starch, microcrystalline cellulose, and possibly directly compressible sugars. The mixture of excipients is prepared by either dry or wet granulation methods. The produced tablets are known to have satisfactory physical resistance and disintegrate in the mouth within 1 minute.

AdvaTab Technology

AdvaTab technology (Eurand) produces FDT tablets based on a proprietary tablet composition that was designed and patented by Kyowa Hakko Kogyo (Tokyo, Japan), (Ohta., 1997 and Hayakawa., 1999). in which the lubrication is dispensed onto each tablet by using a spray during the production process. Traditional tablets are produced using an internal lubrication system, which disperses lubricant on the inside and the surface of the tablets. This method can decrease tablet mechanical strength. AdvaTab is produced using 10–30 times less hydrophobic lubricant and can be 30–0% stronger than conventional tablets. As a result, the tablets are hard and durable yet do not impede liquid entry upon contact with saliva. AdvaTab can handle high drug loading and coated drug particles. Importantly, the technology does not require specialty packaging and, as a result, can be packaged in both standard bottles and push-through blisters.

Dispersible Tablet Technology

Lek (Kovacic et al., 1991) in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine (Milovac et al., 1991). and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methanesulphonate was observed with dispersible tablets containing 0.8– 10%,preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modifi ed starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.

Pharmaburst Technology

Pharmaburst technology (SPI Pharma, New Castle, Delaware) uses off -the-shelf coprocessed excipients to create an FDT that, depending on the type of active and loading (up to 700 mg), dissolves within 30–40 seconds. The quantity of Pharmaburst™ required in a formulation depends on the active in the tablet. It is necessary to carry out initial studies on a formulation by varying the amount of Pharmaburst™ from 50 to 80%, depending on the desired mouth feel and disintegration time. The process involves a dry blend of a drug, flavor, and lubricant that are compressed into tablets on a standard tablet press with stock tooling. T e manufacture process can be carried out under normal temperature and humanity conditions. The tablets can be packaged in blister packs or bottle (Kaushik et al., 2004).

OraQuick technology

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as

MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not 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 Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good tastemasking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives (Seager., 1998)

Quick –Dis technology

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within 30 seconds and 95% within 1 minute. (Dobetti., 2001 and Rish., 2004).

Nanocrystal technology

For fast dissolving tablets, Elan's proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nanocrystal technology. Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. (Kaushik et al., 2004)

NanoCrystal Fast dissolving technology provides for:

- 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 200mg of API per unit).
- Use of conventional, compendial inactive components.
- Employment of non-moisture sensitive in-actives.

Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) 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 FDT dosage forms because manufacturing losses are negligible.

Zydis technology

Zydis is a unique freeze dried oral solid dosage form that can be administered without water and it dissolves instantly on the tongue in less than 3 seconds. The drug is physically trapped in a water soluble matrix, and then freeze dried to produce a product that rapidly dissolves. The matrix usually contain excipients like polymers (e.g., gelatine, alginates, and dextrin) to provide strength and rigidity to tablets; polysaccharides (e.g.,mannitol and sorbitol) to impart crystallinity and hardness to the matrix and to improve palatability; collapse protectants (e.g, glycin) to prevent the product from shrinking in its packaging during manufacturing or storage; flocculating agents (e.g, xanthan gum and acacia) to provide uniform dispersion of drug particles; preservatives(e.g., parabens) to prevent microbial growth; permeation enhancers(e.g., sodium lauryl sulphate) to improve transmucosal permeability; pH adjusters(e.g, citric acid) to optimize chemical stability; flavours and sweeteners to improve patient compliance and water to ensure formation of porous units. Thirteen products are currently available based on zydis technology. In US, the zydis products available are Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran FDT, and Zyprexa Zydis. In the worldwide market, zydis formulations are also available for oxazepam, lorazepam, loperamide, and enalapril. (Allen Loyd., 1997)

Frosta technology

This technology is patented by Akina. Frosta technology utilizes the core concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. The process involves mixing the porous plastic material with water penetration enhancer and followed b y granulating with binder. The technology can be used for almost any drugs including

aspirin, loratidine, caffeine, and folic acid, vitamins and dietary supplements. Melting time varies from several seconds to about 10 seconds depending on the formulation. (Giri et al., 2010).

Table 3: List of Marketed Fast Dissolving Tablets (Yourong F et. al. 2004**).**

Trade Name	Active Drug	Manufacturer
Felden fast melt	Piroxicam	Pfizer Inc., NY, USA
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
Febrectol	Paracetamol	Prographarm, Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA
Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceutics
Risperdal MTab	Risperidone	Janssen pharmaceutics
Spasfon Lyoc	Phloroglucinol Hydrate	Farmalyoc
Nurofen FlashTab	Ibuprofen	Ethypharm
Tempra Quicklets	Paracetamol	Cima Labs,Inc
Zolmig Repimelt	Zolmitriptan	Cima Labs,Inc.
NuLev	Hyoscyamine Sulfate	Cima Labs, Inc
Gaster D	Famotidine	Yamanouchi Pharma Tech. Inc.
Cibalgina DueFast	Ibuprofen	Eurand International
Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd
Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc
Abilify Discmelt	Aripiprazole	Otsuka America/Bristol-Myers Squibb
Allegra ODT	Fexofenadine	Sanofi Aventis
Aricept ODT	Donepezil	Eisai Co.
Clarinex RediTabs	Desloratadine	Schering-Plough
Alavert Quick Dissolving Tablets	Loratadine	Wyeth
Clonazepam ODT	Clonazepam	Par Pharmaceutical
FazaClo	Clozapine	AzurPharma
Jr. Tylenol Meltaways	Acetaminophen	McNeil Consumer Healthcare
Loratadine Redidose	Loratadine	Ranbaxy
Mirtazapine ODT	Mirtazapine	Teva Pharmaceuticals
Niravam	Alprazolam	Schwarz Pharma
Ondansetron ODT	Ondansetron	Teva Pharmaceuticals
Orapred ODT	Prednisolone	Sciele Pharma
Parcopa	Carbidopa/levodopa	Schwarz Pharma
Prevacid SoluTab	Lansoprazole	Takeda Pharmaceuticals
Remeron SolTab	Mirtazapine	Schering-Plough
Risperdal M-Tab	Risperidone	Janssen
UNISOM SleepMelts	Diphenhydramine	Chattem
Zomig-ZMT	Zolmitriptan	AstraZeneca
Zyprexa Zydis	Olanzapine	Eli Lilly and Company
Citalopram ODT	Citalopram	Biovail
Metoclopramide Zydis	Metoclopramide	Salix Pharmaceuticals
Reglan ODT	Metoclopramide	Schwarz Pharma
Tramadol/Acetaminophen ODT	Tramadol/Acetaminophen	Biovail
Zolpidem ODT	Zolpidem	Biovail

CONCLUSION

The popularity of FDTs has increased tremendously over the last decade. FDT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in traveling, patients who are may not have access to water. Such products provide opportunity for the product line extension in the market place and extension of patent term of innovator. 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.

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