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FAST DISSOLVING TABLETS: PATIENT COMPLIANCE DOSAGE FORMS

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ABSTRACT

Recent advances in Novel Drug Delivery System (NDDS) aim to enhance safety and efficacy of already used drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. An oral route of drug administration is the most popular route of administration. It have wide acceptance up to 50-60% of total dosage forms. Tablet is the most popular dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, patients with underdeveloped muscular and nervous responses in young individuals and case of contrary patients, the difficulty in swallowing is a common problem which results in poor patient compliance. Orodispersible tablets (ODT) or fast dissolving tablets (FDT); has been proven as alternative oral dosage forms. The fast dissolving drug delivery systems is a modification that came into existence in the early 1970's and overcome the use of the tablets, syrups, capsules and the other oral drug delivery systems. These are novel types of tablets that disintegrate/dissolve/disperse in saliva within few seconds without uptake of water. Fast dissolving tablets (FDTs) have been in ever-increasing demand during the last decade, and the field is developing rapidly in the pharmaceutical industry. This article reviews the need, advantages, challenges, limitations, mechanism of superdisintegrants, various formulation technologies (conventional and patented), and marketed product of fast dissolving tablets.

KEY WORDS: Fast Dissolving, Tablets, Superdisintegrants, Disintegration time, Patented Technologies.

INTRODUCTION

Drug delivery systems combine one or more traditional drug delivery methods with engineered technology. These systems have the ability to specifically target where a drug is released in the body as well as the rate at which the drug gets released. Drug delivery systems (DDS) are a strategic approach for expanding markets/indications, extending product life cycles and generating contingencies. Despite of tremendous advancements in drug delivery, the oral route remains the preferred route for administration of drugs because of dose accuracy, low cost therapy, self-medication, non-invasive method and ease of administration leading to high acceptance.

Oral administration is the most popular route for systemic actions due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require stringent sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision of dosing, and manufacturing efficiency make tablets the solid dosage form of choice. The oral route remains the desired route for the administration of therapeutic agents because of the low cost of therapy, manufacturing ease and ease of administration lead to high levels of patient compliance.

Many patients face difficulty in swallowing tablets and hard gelatin capsules and as a result do not take medications as prescribed. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become an issue of public attention. The problem can be resolved by the introduction 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. In the latter case, the bioavailability of a drug from fast dispersing formulations may be even greater than that observed for standard dosage forms. In cases like motion sickness, sudden episodes of allergic attacks and unavailability of water, swallowing conventional tablets can be difficult. Particularly the hurdle is experienced by pediatric and geriatric

patients. Such complications can be resolved by using fast dissolving tablets. When placed on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva without the need of water. 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.

Taste-masking is one of the critically important properties in the formulation of an acceptable FDDT. Conventional tablet formulations generally do not address the problem of taste masking, because it is assumed that the dosage form will not dissolve until it passes the oral cavity. Many oral suspensions, syrups, and chewable tablets employ flavors, sugars and other sweeteners to mask the bitter taste of the drug. Current methods of taste masking in fast dissolving tablets include use of sweeteners and flavors; however, these are not a sufficient enough for taste-masking many bitter drugs. The primary methods of taste-masking include adsorption onto carrier or complexation with carriers and spray coating of solid dosage forms, which fulfills consumer choice, because of rapid disintegrate/dissolve in oral cavity within seconds and swallowed without the need of water or chewing. As tablet disintegrates in buccal cavity, this could enhance the clinical effects of the drug through pre-gastric absorption of drug from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism. Fast dissolving drug delivery can be accomplished by various methods like direct compression, wet granulation, compression moulding, volatization and freeze – drying. 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.

Ideal properties of fast dissolving systems[1,6]

The tablets should

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Allow high drug loading.
- Be compatible with taste masking and other excipients.

- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

Advantages of Fast Dissolving systems[3]

1. Ease of administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric and psychiatric patients.
2. No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
3. Rapid dissolution and absorption of the drug, which will produce quick onset of action .
4. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. in such cases bioavailability of drug is increased.
5. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
6. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
7. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
8. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
9. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
10. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

Excipients Used In Fast Dissolving Drug Delivery Systems[9]

Excipients counterbalance the properties of the drug in fast disintegrating tablets. This requires a thorough understanding of the chemistry of these excipients to impede interaction with the drug. The role of excipients is crucial in the formulation of fast dissolving tablets. These inactive food-grade ingredients, when consolidated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a extensive range of drugs, except some drugs that require taste masking agents.

Bulking Materials

Bulking agents enhance the textural characteristics that in turn enhance the disintegration in the mouth, besides adding bulking agents also reduces the concentration of the active ingredient in the composition. The recommended bulking agents for fast dissolving drug delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolysate for higher aqueous solubility and good sensory perception. Bulking agents are mostly added in the range of 10 percent to 90 percent with respect to the weight of the final composition. The following excipients are ranked in descending order in terms of their brittleness:

Microcrystalline cellulose >Spray dried lactose >Beta lactose >Alpha lactose >Alpha lactose monohydrate >Dicalcium phosphate dihydrate.

Mizumito et al has classified sugar-based excipients into two types on the basis of molding and dissolution rate:

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

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

Lubricants

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Flavours and Sweeteners

Flavours and taste-masking agents make the products more palatable and acceptable for patients. The incorporation of these ingredients facilitates in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used

to enhance the organoleptic characteristics of fast-disintegrating tablets. Formulators can select from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a palatable taste as well as adds bulk to the composition.

Disintegrants

It is an important excipient in the tablet formulation, which is always added to tablet to induce breaking of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which predominantly facilitates this process are known as disintegrants. The purpose behind the addition of disintegrants is to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

Bioavailability of a drug highly depends on the absorption of the drug, which is affected by the solubility of the drug in gastrointestinal fluid as well as the permeability of the drug across gastrointestinal membrane. The drug dissolves at a slower rate from a non-disintegrating/ slow-disintegrating tablet due to exposure of only limited surface area of the tablet to the fluid. The disintegration test is an official test which has standard limits and hence a batch of tablets must meet the stated or mentioned requirements of disintegration.

Mechanism of Action of Disintegrants

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

Water wicking

The capability of disintegrant to entrap water into the porous network of tablet is essential for effective disintegration process. Upon keeping the tablet into suitable aqueous medium, the medium enters into tablet porous network and replaces the air adsorbed on the particles which weakens the intermolecular bonds and breaks the tablet into fine particles. The ability of a system to draw water can be summarized by Washburn's equation:

$$L2 = (\gamma \cos\theta/2\eta) \times rt$$

The Washburn equation is too simplistic to apply to a complex tablet-disintegration process, but it does show that any change in the surface tension (γ), pore size (r), solid- liquid contact angle (θ) or liquid viscosity (η) could affect the water wicking efficiency. L is the length of water penetration in the capillary and t is the time. This process is also called as capillary action method.

Swelling

Although penetration of water is a necessary first step for disintegration, swelling is probably the most widely accepted mechanism of action for tablet disintegration in FDTs. Swelling of the disintegrant against the matrix results in the development of swelling force. A large number of internal porous networks in the dosage form, which contains spaces to accommodate the swelling, can reduce the effectiveness of the disintegrant. On the other hand, sufficient swelling force to cause swelling is exerted in the tablet with low porosity. It is lucrative to note that if packing fraction is very high, fluid will be unable to penetrate into the tablet and disintegration process is again reluctantly slows down.

Heat of wetting

When disintegrants with exothermic properties get wetted, localized stress is created due to capillary air expansion, which assists in disintegration of tablet. This mechanism, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

Due to release of gases

Carbon dioxide releases within tablets upon wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegration due to these disintegrants are highly sensitive to any small alteration in relative humidity level and temperature, stringent control of environment is required during preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

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 Particle repulsive forces

This is another mechanism of disintegration attempts to justify the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann proposed a particle-particle repulsion theory to explain that particles which do not swell extensively such as starch could still disintegrates tablets. According to this theory, water penetrates into tablet through hydrophilic pores which creates a continuous starch network that can facilitate transmitting contact of water from one particle to the next, imparting a sufficient hydrostatic pressure. The water then penetrates between starch grains because of its affinity for starch surfaces, thereby breaking hydrogen bonds and other forces binding the tablet together. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

Deformation recovery

Deformation recovery theory entails that the shape of disintegrant particles is distorted during compression and the particles return to their pre-compression shape upon wetting, thereby causing the tablet to disintegrate. Such a phenomenon may be an important aspect of the mechanism of action of disintegrants such as crospovidone and starch that exhibit little or no swelling.

By enzymatic reactions

Enzymes that are present in the body also act as disintegrants. These enzymes inhibit the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outward direction that causes the tablet to burst or the accelerated absorption of water results in excessive increase in the volume of granules to facilitate disintegration.

Superdisintegrants

A “Superdisintegrant” is an excipient, which is added to tablet or capsule blend to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. These advanced substances are more effective at lower concentrations along with greater disintegrating efficiency and mechanical strength. The use of superdisintegrant is the preliminary approach in the development of fast disintegrating tablets (FDTs). Superdisintegrants play a major role in faster dissolution and disintegration of the tablets. It is fundamental to choose an optimum concentration of superdisintegrants so as to ensure rapid disintegration and high dissolution rates of tablets.

Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrants can be selected according to the critical concentration of the disintegrants. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrants, whereas above this concentration the disintegration time remains almost constant or even increases.

TYPES OF SUPERDISINTEGRANT[9]

I. Natural

These are various plant based material. Plant based material serve as an alternative to synthetic products because of following reasons;

- Local accessibility
- Eco-friendly
- Bio-acceptable
- Renewable source and low price as compared to synthetic products

Example: Lepidus Sativum, Locust Bean Gum, Isapghula Husk (Plantago ovata), Hibiscus Rosa Sinesis Linn, Mucilage, Chitosan, Orange Peel Pectin etc.

II. Synthetic

Advantages of synthetic superdisintegrants:

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intra-granularly

Common super disintegrants used in formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmellose (NS-300), carmellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have superdisintegrants property and are widely used in pharmaceutical industry.

Techniques Employed In The Formulation Of Fast Dissolving Tablets

Many techniques have been reported for the formulation of Fast dissolving tablets or Orodispersible tablets.

A. Conventional Technologies of Fast Dissolving Tablets[11-13]

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Melt granulation
7. Mass extrusion
8. Cotton Candy process

1. Freeze-drying / Lyophilisation

The tablets that are prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve rapidly when come in contact with saliva. In this process, water is sublimated from the product after freezing. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weighing and pouring 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. First of all, the material is frozen to bring it below its eutectic point. Then primary drying is done to decrease the moisture to about 4% w/w of dry product. Lastly, secondary drying is made to reduce the bound moisture to the required volume. A major limitation of the final dosage form comprises lack of physical resistance in standard blister packs.

2. Tablet Moulding

Moulding process is of two types i.e. solvent method and heat method. Solvent method includes damping the powder blend using an alcoholic solvent and later on compressing at low pressure in molded plates to form a wet mass (compression moulding).The solvent is then removed by air-drying. The tablets prepared by this technique are less compact than compressed tablets and possess a porous structure that accelerates the dissolution. The heat moulding 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 30ºC under vacuum. Taste masking is an additional concern in fast dissolving systems. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based

tablet triturate form. Compared to the lyophilization method, tablets formed by the molding technique are easier to replicate for manufacturing in industry.

3. Spray Drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are assimilated by hydrolyzed and non-hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and/ or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

4. Sublimation

Inert solid ingredients like urea, urethane, ammonium carbonate, camphor, naphthalene etc, were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation results in a porous structure. The tablets disintegrate and dissolve in less than 20 seconds and exhibit sufficient mechanical strength. The key to rapid disintegration of orodispersible tablets is the presence of a porous structure in the tablet matrix. Hence to impart porosity in the matrix, volatile ingredients are used that are later exposed to a process of sublimation. In studies conducted by Heinemann and Rothe, Knitsch et al, and Roser and Blair, 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 including some other excipients into a tablet. The volatile material was then removed by sublimation, leaving behind a porous matrix.

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 incorporated and final weight of tablets can easily exceed as compared to the other production methods. The disintegration and solubilization of directly compressed tablets depends on single or combined action of disintegrants, water soluble excipients and effervescent agent's used. Breakage of tablet edges during handling and tablet crack during the opening of blister alveolus, all result from insufficient physical resistance. To establish a high disintegration rate, choice of suitable type and optimal amount of disintegrant is very important. Other components in formulation such as water soluble excipients or effervescent

agents can promote improved dissolution or disintegration properties. But the main problem faced upon using effervescent excipients is that they are highly hygroscopic in nature.

6. Melt Granulation

Melt granulation technique is a process by which the pharmaceutical powders are capably agglomerated by a meltable binder. The advantage of this technique compared to a traditional granulation technique is that no water or organic solvents is required. Since there is no drying step involved, the process is less time consuming and utilizes less energy than wet granulation. It is a technique useful to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.[10]

7. Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and consequent removal of softened mass through the extruder or syringe to get a cylinder of the product in even segments assisted by heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieving taste masking.

8. Cotton Candy Process

This process is so called as it makes use of a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves the formation of matrix of polysaccharides or saccharides by concurrent action of flash melting and spinning. The matrix formed is partially recrystallized to have better flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODT. This process can incorporate larger drug doses and offers improved mechanical strength.

B. Patented Technologies [14-17]

1. Zydis (R.P. Scherer, Inc.)
2. Wowtab (Yamanouchi Pharma Technologies,Inc.)
3. OraSolv (Cima Labs, Inc.)
4. DuraSolv (Cima Labs, Inc.)
5. FlashDose (Fuisz Technologies, Ltd.)
6. Flashtab (Prographarm Group)
7. OraQuick (KV Pharmaceutical Co, Inc.)

8. Quick –Dis Technology (Lavipharm Laboratories Inc.)
9. Ziplets/Advatab, (Passano con Barnago, Italy)
10. Lyoc technology (PHARMALYCO)
11. Pharmaburst technology (SPI Pharma, New Castle)
12. Frosta technology (Akina)
13. Nanocrystal Technology (Elan, King of Prussia)
14. Quick solv(Janssen Pharmaceuticals).

1. Zydis Technology

Scherer has patented the Zydis technology. Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. A Zydis tablet is produced by lyophilizing or freeze-drying the drug to form a matrix usually consisting of gelatin. The product is very light-weight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet.

2. Wowtab Technology

The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "With Out Water". It has recently been introduced into the U.S. The Wowtab technology makes use of sugar and sugar-like (e.g, mannitol) excipients. This process is a blend of low mouldable saccharides (rapid dissolution) and high mouldable saccharides (good binding property).The two different types of saccharides are mixed to attain a tablet formulation with ample hardness and fast dissolution rate. Due to its significant hardness, the Wowtab formulation is slightly more stable to the environment than the Zydis or OraSolv .

3. OraSolv Technology

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. In this system active medicament is taste masked. It also contains effervescent disintegrating agents. Tablets are made by employing direct compression technique at low compression force in order to minimize oral dissolution time. The limitation associated is that the tablets produced are soft and friable. An advantage that goes along with the low degree of compaction of OraSolv is

that the particle coating used for taste masking is not compromised by fracture during processing.

4. Durasolv Technology

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation developed in a similar fashion as that of the OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. The key ingredients in this formulation are filler and lubricant. The particle size of the filler is preferably between about 20 and 65 μm. The production cost is significantly less.

5. Flash Dose Technology

Flash dose technology has been patented by Fuisz Technologies Ltd. Nurofen meltlet, a new form of ibuprofen melt in mouth tablets prepared by 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.

6. Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. This technology engages in the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals, which are prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystal/micro-granules 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 utilized the conventional tablet technology, and the tablets produced showed good mechanical strength and disintegration time is less than 60 seconds.

7. Oraquick Technology

The OraQuick fast-dissolving/disintegrating tablet formulation employs a patented taste masking technology. KV Pharmaceutical claims it is microsphere technology, known as MicroMask, has better taste masking property. The taste masking process does not make use of any solvents and therefore leads to faster and more efficient production. OraQuick is appropriate for heat-sensitive drugs as it utilizes lower heat for the production than the competing fast dissolving technologies.

8. 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[12] and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the surface of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.

9. Ziplets/Advatab

This technology is patented by Passano con Barnago, Italy. It employs water-insoluble ingredient fused with one or more effective disintegrants to produce FDT with improved mechanical strength and optimal disintegration time at low compression force.

10. Lyoc

Lyoc technology is patented by PHARMALYCO. Lyoc utilizes a freeze drying process but it contradicts from Zydis in that the product is frozen on the freeze dryer shelves. In order to prevent homogeneity by sedimentation during this process, these formulations also require a large proportion of undissolved inert filler such as mannitol, to increase the viscosity of the in process suspension. The high proportion of filler used reduces the potential porosity of the dried dosage form and hence results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations.

11. Frosta Technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules are composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of the tablets.

12. Nanocrystal Technology

This is patented by Elan, King of Prussia. Nanocrystal technology comprises of lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled into blister pockets. This method refrains all the manufacturing processes such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous active ingredients.

Evaluation And Preformulation Studies Of Fast Dissolving Tablets[18-22]

Angle of Repose

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipients blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\text{Tan } \theta = h/r$$

Where, h= height of the pile of the blend

r= radius of the pile of the blend

Bulk Density (D_b)

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

$$D_b = \frac{\text{Mass of the powder (M)}}{\text{Bulk volume of the powder } (V_b)}$$

Tapped Density (D_t)

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

$$D_t = \frac{\text{Mass of the powder (M)}}{\text{Tapped volume of the powder } (V_d)}$$

Carr's Index (Or) % Compressibility

Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V) after hundred tapings of a sample in a measuring cylinder. CI was calculated using equation.

$$\text{Compressibility Index (CI)} = \frac{V_0 - V}{V} \times 100$$

Table no. 01: Relationship between % Compressibility and Flow Ability.

Per cent Compressibility	Flow ability
5-10	Excellent
12-16	Good
18-21	Fair Passable
23-25	Poor
33-38	Very Poor
< 40	Very Very Poor

EVALUATION OF TABLETS[23-26]

General Appearance

The general appearance of tablets includes size, shape, colour, odour, taste, surface texture.

Size, Shape, Thickness and Diameter

Size and shape of the tablet can be dimensionally described, monitored and controlled. Thickness of the tablet is an important characteristic for appearance and also in counting by filling equipment. The filling equipment utilizes the uniform thickness of the tablet as a counting mechanism. Ten tablets should be taken and their thickness was measured by Vernier calipers.

Uniformity of Weight[29]

Randomly 20 tablets should be selected and to be weighed individually and together in a single pan balance. The average weight should be noted with the standard deviation. United States Pharmacopoeia (USP- 29) limit for weight variation in case of tablets is as follows: for weight 130mg or less, ± 10%, for 130 mg through 324 mg, ± 7.5% and more than 324 mg, ± 5%.

$$\%\ \text{Weight Variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability[27]

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

$$F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}}$$

Compressed tablets should not lose more than 1% of their initial weight**.**

Hardness of Tablet

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. The hardness of prepared tablets can be determined for 10 tablets of each batch by using Monsanto or Pfizer tablet hardness tester.

Wetting Time[28]

Five circular tissue papers of 10 cm diameter should be placed in a petri dish with a 10 cm diameter. Add ten ml of water containing a water soluble dye (eosin) is to be added to the Petri dish. A tablet should be carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet is to be noted as the wetting time. Three trials for each batch and standard deviation should be determined.

$$di/dt = r\Upsilon\cos\theta/(4\eta l)$$

Where

l = length of penetration

r = capillary radii

γ = surface tension

η = liquid viscosity

t = time

θ = contact angle

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

Water Absorption Ratio

The weight of the tablet should be noted before keeping in the petri dish (W_b). The fully wetted tablet should be taken from the petri dish and reweighed (W_a). The water absorption ratio R can be determined according to the following formula.

$$R = (W_a - W_b)/W_a \times 100$$

Disintegration Time[31]

Disintegration time is very important for FDTs which is desired to be less than 60 seconds. This rapid disintegration assists swallowing of the tablet and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. *In vitro* disintegration time can be determined using disintegration test apparatus without disks. The test should be carried on six tablets using distilled water at 37˚ ± 2˚ as disintegration media. Time is noted in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. The test should be carried in triplicate.

***In vitro* Dissolution studies**

The development of dissolution methods for FDTs commensurate with the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with investigation for a bioequivalent FDT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for FDT much in the same way as conventional tablets.

CONCLUSION

As a drug entity approaches near to the end of its patent life, it is common for Pharmaceutical manufacturers to develop the given drug entity into a new and improved dosage form. A new dosage form allows a manufacturer to expand the market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast dissolving/ disintegrating tablet formulations are alternative to many conventional formulations that are now commonly available. Fast disintegrating tablets technology acquired more popularity in last decade. It emerged as a new drug delivery system for treating various patients and diseases. FDT offers advantages of both solid and liquid oral dosage forms. This system allows easy self-administration without the need of water to swallow. It has provided new area for research and development both for industries and academics.

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