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A REVIEW ON FAST DISSOLVING TABLET

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ABSTRACT

Fast dissolving drug delivery system (FDDS) is now gaining the popularity in pharmaceutical companies as they are the novel drug delivery technique in order to provide the patient with medicines without obstacles in swallowing. The main route of administrating a drug is the oral route which is the oldest and most commonly used because of its ease of administration, self medication and avoidance of pain as compared to parental route. Oral drug delivery remains the preferred route of drug delivery. Novel technologies with improved performance, patient compliance, and enhanced quality have emerged in the recent past. Fast dissolving drug delivery system can be obtained by the various techniques i.e. direct compression, tablet molding, freeze drying, spray drying nanonization. The review describes the various formulation aspects, Super disintegrates employed and technologies developed for FDTs, along with various excipients, evaluation tests, marketed formulation and drugs used in this research area.

KEYPOINT: Fast Dissolving Tablet, Super Disintegration, Drug Delivery System, Patented Technologies, Methodology.

INTRODUCTION

Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self medication, pain avoidance and the most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules.[1,2] A fast-dissolving drug delivery system (FDDS) in most cases is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. Most fast dissolving delivery system films must

include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. The conventional dosage forms like tablet and capsule have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration, easy to manufacture and it can be deliver in accurate dose. One important drawback of such dosage form is the difficulty in swallowing. Therefore, tablet must be rapidly dissolve or disintegrate in the oral cavity[1,5] Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.[3,4]

DEFINITION

The Centre For Drug Evaluation And Research (Cder), Usfda

Defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter seconds, when placed up on the tongue". FDTs 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.[6]

CRITERIA FOR FAST DISSOLVING DRUG DELIVERY SYSTEM

The tablets should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.[7]

Advantages of Fast Dissolving Tablets

- Improved patient's compliance
- No water needed
- No chewing needed
- Improved stability
- Suitable for controlled as well as fast release active.[8,9]
- Cost- effective

Significance of Fast Dissolving Tablet

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

a. Accurate dosing

Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

b. Enhanced bioavailability

Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.

c. Rapid action

Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

d. Patient compliance

No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.

e. Ease of administration

Convenient to administer specially for geriatric, pediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

f. Obstruction free

No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

g. Enhanced palatability

Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.

h. Simple packaging

No specific packaging required. It can be packaged in push through blisters.

i. Business avenue

Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

j. Cost effective

Conventional processing and packaging equipment's allow the manufacturing of tablets at low cost,[10]

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.[11]

Characteristics of Fast Dissolving Delivery System

1. Ease of administration: Fast Dissolving 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.

2. Taste of the medicament

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

3. Hygroscopicity

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

4. Friability

In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft-molded 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

5. 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.[12]

Different Methodology Used For Fast Dissolving Formulations

a) Lyophilization or Freeze-drying

Formation of porous product in freeze-drying process is exploited in formulating FDT. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has Rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug. However, the FDT formed by lyophilization have low mechanical strength, poor stability at higher temperature, and humidity.[13]

b) Tablet Molding

Molding process is of two types 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 300C 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 lyophilisation technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.[14]

c) Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or cross carmellose or cross providence are used as super disintegrate. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & cross carmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.[15]

d) 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 10 involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDT.[16]

e) Disintegrant Addition

This technique involves the addition of superdisintegrants in optimum concentration to achieve rapid disintegration. For example, Crosspovidone (3%w/w) and crosscarmellose (5%w/w) used in prochlorperazine maleate formulation. FDT prepared by this technique are similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friabilty.

Superdisintegrants Example

Crosscarmellose (Ac-Di-Sol) Crosslinked Cellulose

Crosspovidone M (Kollidon) Crosslinked PVP

Sodium starch glycolate

(Primogel) Crosslinked Starch

Soy polysaccharides (Emcosoy) Natural super Disintegrant.[17]

f) Sublimation

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like Ammonium bicarbonate, Ammonium carbonate, Benzoic acid, Camphor, Naphthalene, Urea, Urethane and Phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec.[17]

g) Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of FDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(1) Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(2) Sugar based excipients

This is another approach to manufacture FDT by direct compression. The use of sugar based excipients especially bulking agents like Dextrose, Fructose, Isomalt, Lactilol, Maltilol, Maltose, Mannitol, Sorbitol, Starch hydrolysate, Polydextrose and Xylitol, which display high aqueous solubility and sweetness and hence impart taste masking property and a pleasing mouthfeel. Mizumito *et al* have 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 and low dissolution rate.18

h) Mass Extrusion

This technique involves the softening of active blend by using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of these softened mass through the

extruder or syringe to get a cylindrical shape into even segments to form tablets. Can be used to coat granules of bitter tasting drugs and there by masking their bitter taste.[18]

Important Patented Technologies For Fast Dissolving Tablets

1) 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. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aids wallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength[19] To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are In corporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protect ants such as glycine prevent the shrinkage of zydis units during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.[20]

2) Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment at high mouldability and low These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.[21]

3) Ora Quick

KV Pharmaceutical claims its microsphere technology, known as Micro Mask, 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 taste-masking. 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, psychotropic, and anti-infective.[22]

4) Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.[22]

5) Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first n 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.[23]

6) Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". Inthis process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.[23]

7) Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion spheronisation. All the processing utilized conventional tableting technology.[23]

Excipients Used In The Formulation of Fdt[24,25,26]

Excipients balance the properties of the actives in fast-melting tablets. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets.

These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

1) Bulking agents

Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

2) Emulsifying Agents

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast- tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

3) Lubricants

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

4) Flavors and Sweeteners

Flavors and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose 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 pleasant taste as well as bulk to the composition.

5) Gas producing disintegrates

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Care should be taken during tab letting, particularly on moisture level. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates. In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide.

Fdt Release Mechanism of Superdisintegrants

There are four major mechanisms for tablets disintegration as follows:

 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.[27]

 Porosity and 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 net work around the drug particles.[27]

 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.[27]

Due to deformation

During tablet compression, disintegrated 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.[27]

Evaluation of fast dissolving tablet[28,29,30]

1) General appearance

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

2. Size and Shape

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

3. Tablet thickness

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

4) Weight variation

20 tablets were selected randomly from the lot and weighed individually to check for weight variation. Weight variation is given by the formula.

(% weight variation; Individual weight – average weight / Average weight)

5) Hardness

The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers. It is expressed in kg or pound.

6) Disintegration Test

The time for disintegration of FDTs is generally less than 1 min and actual disintegration time that patient can experience ranges from 5 to 30s. The disintegration test for FDT should mimic disintegration in mouth within saliva.

7) Friability

To achieve % friability within limits (0.1-0.9%) for an FDT is a challenge for a formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Friability of each batch was measure in "Electro lab friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation.

8) Measurement of Tablet Porosity

The mercury penetration porosimeter can be used to measure the tablet porosity. The tablet porosity (ε) can be calculated by using following equation, $\varepsilon = 1\text{-}m / (\rho t V)$ Where ρt is the true density, m and V are the weight and volume of the tablet, respectively.

9) Wetting Time and Water Absorption Ratio

Wetting time of dosage form is related with the contact angle. Lower wetting time implies a quicker disintegration of the tablet. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully placed in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted. The water absorption ratio, *R* can be the determined according to the following equation;

$$R = 100\ (Wa\text{-}Wb) / Wb$$

Wa; The wetted tablet from the petridish is taken and reweighed.

Wb; The weight of the tablet before keeping in the petridish

10) Disintegration in Oral Cavity

The time required for complete disintegration of tablets in mouth was obtained from six healthy volunteers, who were given tablets from the optimum formulation.

11) Dissolution Test

The dissolution methods for FDT are practically identical to conventional tablet when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1N HCl, pH 4.5 and Ph 6.8 buffers should be used for evaluation of FDT in the same way as their ordinary tablet counterparts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 25-75 rpm is commonly used. Since the dissolution of FDTs is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile.

CONCLUSION[31]

Now days there are wide range of products available commercially in market, which are produced by the same technologies as employed in the manufacturing of fast dissolving tablets. Still there is broad area for research on this technology. (Virely et al., 1990) Some of the major challenges like formulating a drug of bitter taste and moisture absorbing nature create problems for formulation scientist. When the dose of drug is large, it creates problem of enhanced disintegration time. The two points to be considered in case of FDTs are shortening the disintegration time and at the same time keeping other parameters in mind like friability, taste and mouth feel and tablet strength within the accepted range. These problems may be solved by using taste masking and super-disintegrating agents without significant increasing the weight and volume of final dosage forms. There is also a scope to develop better packaging system to formulate FDTs more stable during handling.

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