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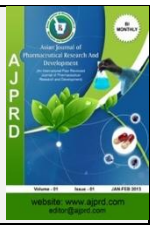

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Review Article

Fast Dissolving Tablets- A Novel Approach

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A B S T R A C T

Fast dissolving tablets emerge as one of the popular and widely accepted dosage forms, especially for pediatric patients because of incomplete development of the muscular and nervous system and a case of geriatric patients suffering from Parkinson's disorder or hand tremors. Few solid dosage forms like capsules and tablets are present days facing the problems like difficulty in swallowing (dysphagia), resulting in many incidences of non-compliance and making the therapy ineffective. Oral dosage form and oral route are the most preferred route of administration for various drugs have limitations like first-pass metabolism, psychiatric patients, bedridden and uncooperative patients. FDTs are disintegrating or dissolve quickly in the saliva without a need of water. Fast dissolving tablets are designed to dissolve in saliva remarkably faster, within a few seconds (less than 60 seconds), and those are real fast-dissolving tablets. FDTs formulations contain super disintegrants to enhance the disintegration rate of a tablet in the buccal cavity. FDTs have advantages such as easy portability and manufacturing, accurate dosing, good chemical and physical stability and an ideal alternative for geriatric and pediatric patients. FDTs have disintegrated quickly, absorb faster so, in vitro drug release time improve and this property of drugs (dosage form) enhanced bioavailability. FDT formulations have the advantage of both conventional tablet formulation and liquid dosage form. There are several technologies that are conventional or patented based on spray drying, cotton candy process, sublimation, melt granulation, direct compression freezes drying/lyophilization, phase transition process, mass extrusion, etc. have been developed for manufacturing of FDTs. In this review contain brief information about FDTs including definition, advantages, needs or requirements of FDTs, salient features of FDTs, limitations, challenges to developing FDT, marketed formulations of fast dissolving tablets, etc

Key words: Fast dissolving tablets, Oral dosage form, Buccal cavity,

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INTRODUCTION:

Fast dissolving Tablets are disintegrating 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. 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 are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething, and to those who cannot swallow intact sustained action tablets/capsules. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. Drinking water plays an

important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. These dosage forms are also used to attain instant a higher concentration of drug in body for immediate actions. Fast dissolving tablets can be prepared by using various conventional methods like direct Compression, wet granulation, molding, spray drying, freeze drying, and sublimation method and by using different type of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmeliose), Sodium starch glycolate, Polyvinylpyrrolidoneetc Natural Polymers increased the drug release rate from the tablet, decrease the dissolution and disintegration time, used as binder superdisintegrant, diluents[1-3].

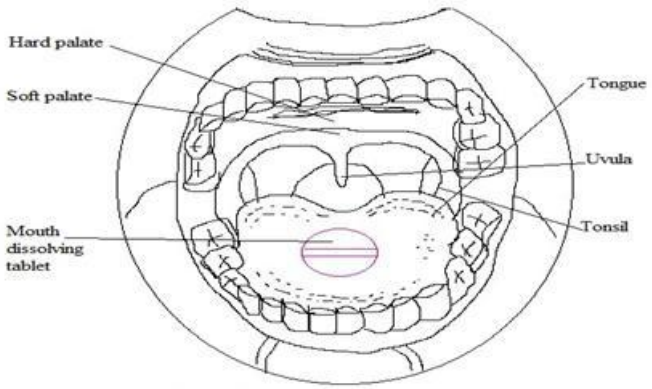

Figure: 1 Administration of Mouth Dissolving Tablets

Advantages

- Convenient and easy to administer as does not require water for oral administration.
- Durable and sufficient strength to withstand the rigors of the manufacturing process and manufacturing handling.
- Pleasant mouth feel.
- Compatible with taste masking.
- Rapid drug therapy intervention.
- Patient having difficulty in swallowing tablet can easily administer this type of dosage form
- Useful for paediatric, geriatric and psychiatric patients.
- Good chemical stability.

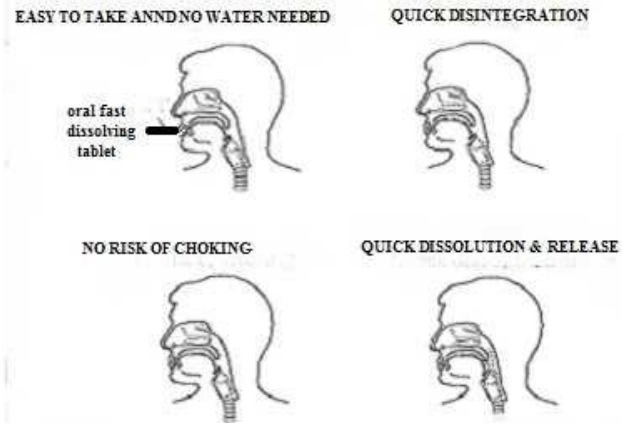

Figure 2: Advantages of FDT [6]

Limitation:

- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.
- It is also showing the fragile, effervesces granules property.
- FDT requires special packaging for properly stabilization & safety of stable product[4].

Table 1: Ideal properties of FDT19

S. No.	Properties	Yes/No
1	Suitable for Conventional tablet processing and packaging	Yes
2	Portable	Yes
3	Fragility Concern	No
4	Good Mouth Feel	Yes
5	Sensitive to Environmental factors (humidity, temperature)	No
6	Water required for swallowing	No
7	Economic	Yes
9	Patient Compliance	Yes
10	Leave Residue in oral cavity/Grittiness	No
11	Compatible with Taste Masking	Yes

Table: 2 Potential Drug Candidates for Mouth Dissolving Tablets.

S. No.	Category	Drug candidates
1	Non-steroidal Anti-Inflammatory Drugs:	Ketoprofen, Piroxicam, Paracetamol, Rofecoxib, Nimesulide, Ibuprofen.
2	Anti-ulcer Drugs:	Famotidine, Lansoprazole.
3	Antidepressants Drugs:	Mitraxepine, Fluoxetine.
4	Antiparkinsonian Drugs:	Selegiline.
5	Antimigrane Drugs:	Sumatriptan, Rizatriptan benzoate, Zolmitriptan
6	Anti-histaminic Drugs:	Loratadine, Diphenhydramine, Meclizine
7	Antiemetic Drugs:	Ramosetoron HCl, Ondansetron, Baclofen [15, 16, 17]

Basic Principle of Fast Dissolving Tablets: -

There are four major mechanisms for tablets disintegration as follows

- Swelling
- Wicking
- Particle Repulsive Forces
- Due to Deformation.

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.

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 /excipients and on tablet conditions. For these types of disintegrates maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

Particle Repulsive Forces

Another mechanism of disintegrant 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 andwater is required for it. Researchers found that repulsion is secondary to wicking.

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[5].

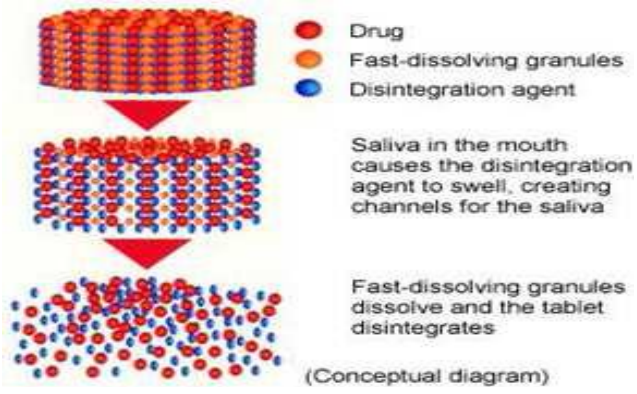

Figure 1: Conceptual diagram of FDTs.

Characteristics of Fast Dissolving Tablets

Fast Disintegration

These tablets should disintegrate in the mouth without additional water or with a very small amount 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 smooth swallowing and good mouth feel

Drug Properties

Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, bioavailability, flow property and bulk density of a drug can significantly affect the final tablets characteristics, such as disintegration and tablet strength.

Taste of Active Ingredients

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. An ideal taste-masking technology should provide drugs with good mouth feel and without grittiness.

Moisture Sensitivity

These tablets 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.

Tablet strength and porosity

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 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.

Techniques for Preparing Fast dissolving Tablets.

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

1. Freeze drying / lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

Freeze-Drying or Lyophilization

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[6].

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 possess 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.

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 crosscarmellose or crospovidone are used as superdisintegrants. 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&croscarmellose 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.

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. Even solvents like cyclohexane; benzene can be used as pore forming agents.

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.

Mass-Extrusion

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

Important Patented Technologies for Fast Dissolving Tablets

ZydisTechnology:

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 aid swallowing. The zydis matrix is composed of many materials 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. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. 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 protectants 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.

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 and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

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.

Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofenmeltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by biovail corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water”. In this 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 (eg. lactose, glucose, and mannitol) and granulatedwith a high mouldability saccharide (eg. Maltose, oligosaccharides) and compressed into table

Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists 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[7].

Evaluation of Fast Dissolving Tablets

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness:

A significant strength of FDT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. 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.

Friability:

To achieve % friability within limits for an FDT is a challenge for a formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Thus, it is necessary that this parameter

should be evaluated and the results are within bound limits (0.1-0.9%).

Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Wetting time of the FDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet.The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio

R can be the determined according to the following equation.

$R = 100 (Wa-Wb) / Wb$

Moisture uptake studies:

Moisture uptake studies for FDT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a dessicator over calcium chloride at 370C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks.Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Disintegration test:

The time for disintegration of FDTs is generally <1min and actual disintegration time that patience can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for FDT should mimic disintegration in mouth with in salivary contents.

Dissolution test:

The development of dissolution methods for FDT is comparable to approach taken for conventional tablets and is practically identical when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N 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. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of FDTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for FDT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile[8-9].

Industrial Applications

- To develop an orally disintegrating dosage forms and to work with existing disintegrants.
- To further improvise upon the existing technology of FDTs.
- To optimize the blend of disintegrants or excipients to achieve FDTs.
- To select and develop proper packaging material and system for enhanced stability of the product and also develop a cost-effective product.
- To arrive at various taste-masking agents and prepare palatable dosage forms thereby increasing patient compliance.
- To develop disintegrants from different polymers which are used as coating materials by certain modifications and use them for formulating FDTs.

Future Prospects:

These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Should next generation drugs are predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by FDTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide[10-11].

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