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FAST DISSOLVING DOSAGES FORM: BOON TO EMERGENCY CONDITIONS

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ABSTRACT

Recent advancements made in oral drug delivery technology prompted researchers and scientists to develop oral disintegrating tablets with improved patient convenience and compliance. FDTs have gained considerable attention especially for those patients who have difficulties in swallowing owing to dysphasia, hand tremors problems and they have additional advantage for unconscious, young patients with underdeveloped muscular systems and nervous system. Novel FDT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing tablet and capsules. Technologies used for manufacturing of FDTs are either conventional technologies or patented technologies. This review describes the various advantages, limitations, desired characteristics, formulation aspects, super-disintegrants employed; technologies developed for FDTs, evaluation tests, and marketed formulations.

Keywords: Fast dissolving Tablets, Superdisintegrants, Formulation of FDTs.

INTRODUCTION

Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage form are being tablets and capsules and important drawback of these dosage forms for some patients however is the difficulty to swallow.[1,2] Difficulty in swallowing (dysphasia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with this group. For these reason, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a lot of attention. Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but are also ideal for active people.[3]

Fast dissolving tablets are solid oral single –unit dosage forms that are placed in mouth, allowed to dispersed/dissolve within 60 second in mouth saliva (ph-6.8) without the need of water and get absorbed through the buccal membrane thereby providing a quick onset of action. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of drug is found significantly greater than those observed from conventional tablet dosage form.[4,5] According to united state food and drug administration (USFDA) defined FDTS as, a solid dosages form containing medicinal substances or active ingredients which disintegrate rapidly within a few seconds when placed up on tongue.[6,7] The use of super disintegrants like croscarmellose, sodiumstarchglycolate, polyvinylpyrollidone, crosspovidone etc, which provide rapid disintegration of tablet and release drug in saliva is the basic approach development of FDTS. [8]

Advantages: [9, 10]

- Ease of administration for those patients who have difficulty in swallowing tablet.
- No need of water to swallow the dosage form.
- Achieve increased bioavailability through pregastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
- Have rapid dissolution and absorption of the

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drug which will produce quick onset of action.

- It combines advantages of solid dosage form in terms of stability and liquid dosage form in term of bioavailability.
- Cost-effective, lower production packaging and distribution costs compared to current commercial available products.
- For superior therapeutic benefit.
- New business opportunity like product differentiation, product promotion patient extension, and life cycle management

Limitations to FD tablets: [10, 11]

1. Careful handling is required because tablets usually have insufficient mechanical strength.
2. If tablets are not formulated properly they may leave unpleasant taste or grittiness in the mouth.
3. Drugs difficult to formulate into FDT with relatively larger doses.
4. Drugs with short half-life and frequent dosing and those whom require controlled or sustained release are unsuitable candidates of FDTs.

Desired Characteristics of Fast Dissolving Tablets: [12]

1. **Fast disintegration**- The disintegrated tablet should become a soft paste or liquid suspension, which can provide smooth swallowing and good mouth feel.

2. **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.

3. **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.

4. **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.

5. **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.

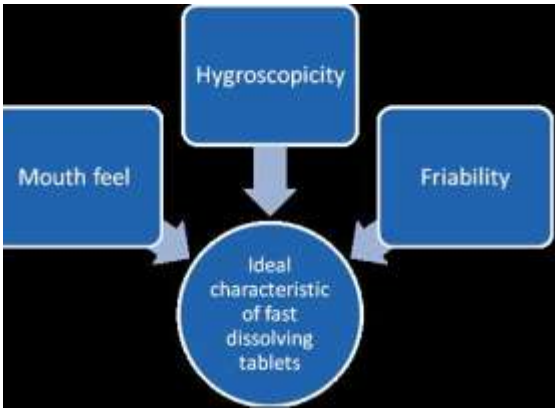

Fig. 2: Showing Ideal characteristic's of Mouth dissolving tablet (Adopted from Ref. 24)

Mechanism:

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of a drug mainly depends on physiochemical properties of the drug. The rate of drug dissolution is greatly influenced by disintegration of the tablet. Disintegrants are important excipient of the tablet formulation, they are always added to tablet to induce breakup of tablet when they are comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as integration process and excipients which induce this process are known as disintegrants. The objectives behind

addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive

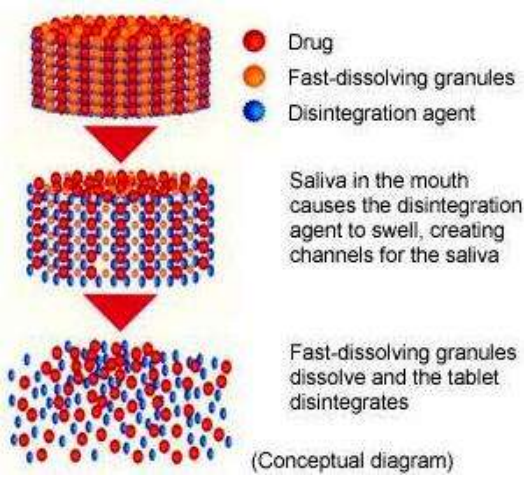

Fig. 1: Showing Disintegration of FDTs after oral intake (Adopted from Ref. 21)

forces that keep particles together. [6, 9]

Drug Selection Criteria for FDTs: [13]

1. Have better solubility.
2. Low dose.
3. Have better availability to permeate oral mucosal tissue.
4. Less or not bitter in taste.
5. Good stability both in water as well as in saliva.

Super-Disintegrants: [14, 15, 16]

Superdisintegrants are the agents that are added to tablet formulations to advance the breakup of the tablets into smaller fragments in an aqueous environment, thereby increasing the available surface area and promoting a more rapid release of the drug substance.

Mechanism of superdisintegrants:

There are four major mechanisms for tablet disintegration as follows:

1. Swelling
2. Porosity and Capillary Action (Wicking
3. Disintegrating particle/particle repulsive forces
4. Deformation

1. **Swelling:** The general mechanism of action for tablet disintegration, which is most widely accepted, is swelling. Tablets with high porosity due to lack of adequate swelling force show poor disintegration. Sufficient swelling force with low porosity is exerted in the tablet. If the packing fraction is very high, fluid is unable to penetrate in the tablet & disintegration is again slows down.

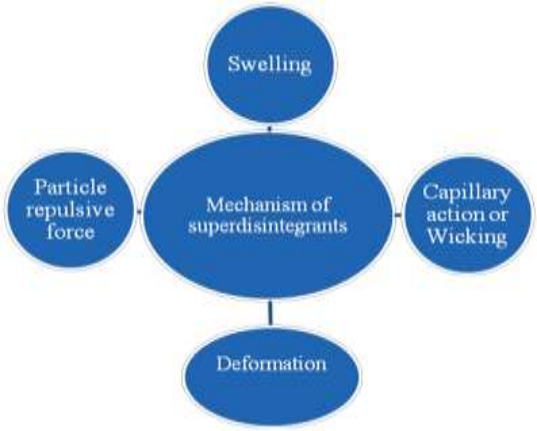

Fig. 3: Mechanism of Super-Disintegrant for tablet disintegration (Adopted from Ref. 24)

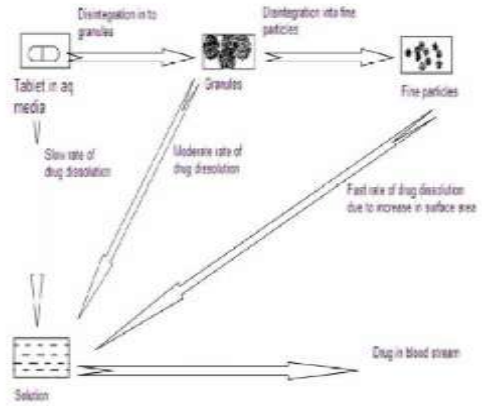

Fig. 4: shows comparative Tablet disintegration Mechanisms (Adopted from Ref. 24)

2. **Porosity and Capillary Action (Wicking):** Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the preparation of fluid into tablets. The disintegrant particles themselves act to enhance porosity and provide pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart.

3. **Disintegrating particle/particle repulsive forces:** Another mechanism of disintegrating attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-

Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

4. **Deformation:** Disintegrated particles get deformed, during tablets compression and when these deformed particles come in contact with aqueous media or water they get into their normal structure. Swelling capacity of starch was improved during compression. Due to this increase in size of the deformed particles produces a breakup of the tablet.

List of Superdisintegrants:

Table 1: List of Superdisintegrants and their mechanism of action.

Superdisintegrants	Example	Mechanism of action
Crosspovidone Crosspovidone M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little ndreturns to original size after compression but act by capillary action
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol®L-HPC	Crosslinked Cellulose	-Swells 4-8 folds in < 10 seconds. Swelling and wicking both.
Sodium starch glycolate Explotab® Primogel®	Crosslinked Starch	-Swells 7-12 folds in < 30 seconds
Calcium silicate		-Wicking action
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action
Soy polysac-charides Emcosoy®	Natural super Disintegrant	

Techniques for Machinating Fast dissolving Tablets:

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

Conventional Techniques Used For Preparation of FDTs: [9, 17]

1. **Disintegration Addition:** Disintegration addition technique is one popular techniques for formulating FDTs because of its easy implementation and cost- effectiveness. The basic principle involved in formulating FDTs by disintegrant addition technique is addition of superdisintegrants in optimum concentration so as to achieve rapid disintegration along with the good mouth feel.
2. **Freeze drying:** A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under condition that allow removal of water by sublimation. Lyophilization results in preparations which are highly porous, with a very high specific surface area, which dissolve rapidly show improved absorption and bioavailability.
3. **Moulding:** In this method, molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression.

Sublimation:

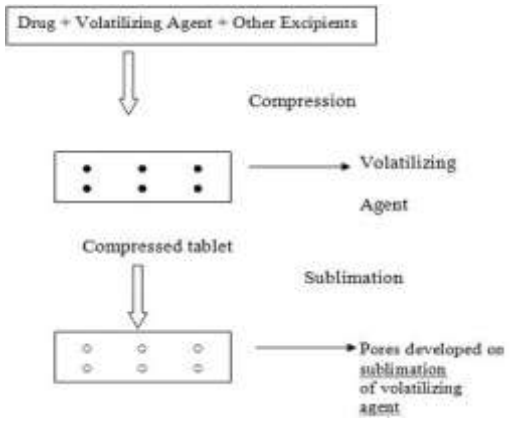

Figure 5: Steps Involved in Sublimation process (Adopted from Ref. 20)

4. **Spray- Drying:** Spray drying can produce highly porous and fine powders that dissolve rapidly.

The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material(e.g. citric acid) and/or alkali material(e.g. sodium bicarbonate)to enhance disintegration and dissolution.

5. **Mass- Extrusion:** This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blades to form tablets.

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

   This method complete within 3 steps i.e.

   I. Milling of drug and excipients
   II. Mixing of drug and excipients
   III. Tablet compression

Fig. 6: Steps Involved In Direct Compression Process (Adopted from Ref. 21)

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

8. **Phase transition process:** It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus

Patented Technologies for Fast Dissolving Tablets: [9, 18]

1. Zydis technology.
2. Durasolv technology.
3. Orasolv technology.
4. Wowtab technology.
5. Flashtab technology.
6. Ziplets/Advatab technology.
7. Pharmaburst
8. Nanocrystals technology.

Table 2: Few Examples of Marketed Fast Dissolving Tablets In India

NAME OF THE PRODUCT	ACTIVE INGREDIENTS
Imodium lingual	Imodium
Pepcidin rapitab	Pepcid
Mosid-MT	Mosapride citrate
Calritin reditabs	Claritin
Nimulid-MD	Nimesulide
Zyrof-meltab	Rofecoxib
Claritin Reditab	Micronized loratadine
Feldene melt	Piroxicam
Maxalt-MLT	Rizatriptan
Pepcid RPD	Famotidine
Zyprexa Zydis	Olanzapine

Evaluation of tablets:

1. **Hardness:** The strength of tablet is expressed as tensile strength (kg/cm^2). It is measured using a tablet Hardness tester (Pfizer Hardness Tester). [3,19]

2. **Weight variation:** 20 tablets are selected randomly from the batch and the average weight of the tablets is calculated. The tablets are weighted individually to check for weight

variation from the average. Weight variation specification as per I.P. is shown in table.[19,20]

Table 3: Showing Weight variation specification as per IP

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250mg	±7.5
250 mg or more	±5

3. **Friability:** Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator is generally used for the purpose. Reweighed sample of ten tablets is placed in the friabilator, which is then operated for 100 revolutions. After 100 revolutions the tablets are de-dusted and reweighed. Compressed tablets should not lose more than 1% of their initial weigh. [18,21]

   Percentage friability = (initial weight-final weight/initial weight) × 100

4. **Disintegration Time:** The time for disintegration of FDTs is generally less than one minute and actual disintegration time that patient can experience ranges from 5-30 seconds. The test is carried out on six tablets using distilled water at 37 ^{0}C ± 2 ^{0}C is used as disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured in seconds. Various scientists have developed new *in-vitro* methods that allow an accurate determination of disintegration test. The disintegration test is performed using a texture analyzer instrument. In this test, a flat-ended cylindrical probe penetrates into the disintegrating tablet immersed in water. As the tablet disintegrates, the instrument is set to maintain a small force for a determined period of time. The plots of some distance traveled by the probe generated with the instrument's software provide disintegration profile of the tablets as a function of time. The plot facilitates calculation of the start and end-point of the tablet disintegration. [12,22]

5. **Wetting time:** Five circular tissue paper of 10cm diameter are placed in a petridish with a 10cm diameter. 10 ml of simulated saliva pH (phosphate buffer pH 6.8) was poured into the tissue paper placed in the petridish. Few drops of eosin solution is added to the petridish. A tablet is placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet is noted as the wetting time.[20, 21,23]

6. **Water absorption ratio:** The weight of the tablet before keeping in the petridish is noted (Wb). Fully wetted tablet from the petridish was taken and reweighed (Wa). The water absorption ratio R can be determined according to the following formula. [21,24]

   R= (Wa – Wb)/Wa x 100

7. **Estimation of drug content:** 10 tablets are taken randomly and weighed. The average weight is calculated and the tablets are then crushed in the mortar. The weight equivalent to the label claim is weighted accurately and is dissolved in 100 ml of the solvent being used for the dissolution study. The solution thus prepared is analyzed spectro-photometrically and the concentration is determined.[21,25,26]

CONCLUSION

Orally disintegrating tablets have potential advantages over conventional dosage forms, with improved patient compliance, convenience, bioavailability and rapid onset of action. They might be a very good alternative for drug delivery to geriatric and pediatric patients. They have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aids in stability of dosage forms and transform into liquid form within few seconds after its administration. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus FDT has tremendous scope for being the delivery system for most of the drugs in near future.

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