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A Review on Fast Dissolving Tablets by Using Co-Processed Superdisintegrants

			
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ABSTRACT

Fast dissolving tablets are the tablet which dissolves rapidly and shows higher bioavailability than conventional tablets. It facilitates water less administration and rapid onset of action. It also helps in improving oral bioavailability. The fast disintegration followed by dissolution leads to quick therapeutic activity makes these tablets superior over available tablets. Disintegration is an important key step for any solid dosage forms to show its pharmacologic effect as any solid dosage forms should disperse into its fine particles from which it is prepared. In fast dissolving tablets, superdisintegrants are incorporated in the right amount for quick disintegration with improved bioavailability. Based on the source various types of super disintegrants are available. They are synthetic, semi-synthetic, natural, and co-processed. In this review, main emphasis is given on different types of superdisintegrants used in fast dissolving tablets, their mechanisms and applications.



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INTRODUCTION

Tablets have remained the most common dosage form by which medicaments are usually administered to patients because of their advantages over the other dosage forms. Tablet dosage forms are the most popular and preferred drug delivery systems in terms of precision of unit dose, low cost, patient compliance, and good physical and chemical stability. Tablets account for 70% - 80% of all pharmaceutical dosage forms¹.

USFDA defined a fast-dissolving tablet (FDT) as "a solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." Fast dissolving tablets are also known as mouth-dissolving tablets, Oro-dispersible tablets, rapid melts, and porous tablets. Hence in the present study, fast dissolving tablets of Famotidine were prepared by super disintegrants and have been utilized for faster disintegration².

Advantages of fast dissolving tablets³:

- Rapid onset of drug therapy.
- Achieve increased bioavailability/rapid absorption through GIT.
- Good mouth feels property helps to change the perception of medication as a bitter pill, particularly in pediatric patients.
- Convenient for administration and shows better patient compliance.
- The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

REQUIREMENTS OF FAST DISINTEGRATING TABLETS

The tablets should follow different requirements⁴:

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

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

IDEAL CHARACTERISTICS ON FAST DISINTEGRATION TABLET

Fast disintegration tablet should following characteristics⁵:

1. They should not require water or other liquid at the time of administration.
2. Should easily disintegrate and dissolve.
3. Mask or overcome unacceptable taste of drug.
4. They should have high drug loading.
5. They should have pleasant feel in mouth.
6. They should have negligible or no residue in oral cavity after administration.
7. They should have low sensitivity against environmental conditions like moisture and temp. etc.
8. Ease of administration for patients who are mentally ill, disable and uncooperative.
9. It should be portable without fragility concerns.
10. They should be manufactured using conventional tablet processing and packing equipment at a low cost.

ADVANTAGES OF FAST DISINTEGRATING TABLETS

Fast disintegration tablet should have the following advantages⁶:

1. Ease to administration to patients who refuse to swallow a tablet such as paediatrics, geriatric patients and psychiatric patients.
2. No need or little water is required to swallow the dosage form which is a highly convenient feature for patients who are traveling and do not have access to water.
3. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
4. Rapid disintegration and absorption of drug which will produce the quick onset of action.
5. Quick absorption from the GIT improves patient compliance.
6. Drug and dosage stability.
7. New business opportunities like differentiation, line extension, and life cycle management. The exclusivity of product promotion although chewable tablets has been on the market for some time.
8. They are not the same as the new fast-dissolving tablets. Patients for whom chewing is difficult or painful can use these new tablets easily.
9. Fast dissolving tablets can be used easily children who have lost their primary teeth but do not have full use of their permanent teeth.

DISADVANTAGES OF FAST DISINTEGRATING TABLET

Fast disintegration tablet should have the following disadvantages⁷:

1. Most fast-dissolving Tablets lack the mechanical strength common to the traditional tablet. Many products are very lightweight and fragile requiring them to be individually packaged. Patients should be advised not to push these tablets through the foil film, but instead. Peel the film back to release the fast dissolving tablet.

2. Due to the formation of fast dissolving tablets that are also more susceptible to degradation via temp, and humidity, some of the newest fast dissolving tablet formulations is dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such formulation to ensure they are not exposed to high levels of moisture or humidity excess handling of a tablet can introduce enough moisture to initiate the dissolution of the tablet matrix.
3. The tablet may leave an unpleasant taste and/or grittiness in the mouth if not formulated properly.
4. Drugs with relatively larger doses are difficult to formulate in a fast-dissolving tablet. E.g. Antibiotics, like ciprofloxacin(500 mg).
5. A patient who concurrently takes anticholinergic medications may not be the best candidate for FDT.
6. Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be a good candidate for this tablet formulation.

Superdisintegrants: Disintegrating agents are substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment. They endorse moisture penetration and dispersion of the tablet matrix. The major function of disintegrant is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet. New materials termed as "super disintegrants" have been developed to improve the disintegration processes. Superdisintegrants are another version of super-absorbing materials with tailor-made swelling properties. These materials are not planned to absorb significant amounts of water or aqueous fluids but planned to swell very fast. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10 % by weight relative to the total weight of the dosage unit. Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an objectionable mouth-feel from either large particles or gelling. The particles are also compressible which improves tablet hardness and its friability. Effective

super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high- dose drugs. Generally, one gram of super disintegrants absorbs 10-40 g of water or aqueous medium. After absorption, swelling pressure and isotropic swelling of the superdisintegrants particles create stress concentrated areas where a gradient of mechanical properties will exist due to which whole structure will break apart⁸.

Selection criteria for superdisintegrants⁹:

- Particle size should be small
- Should be non-toxic
- Compatible with other excipients and drugs
- Good hydration capacity
- Good flow property
- Good mouthfeel
- Effective in less quantity



Classification of superdisintegrants

Based on their source of origin, superdisintegrants can be categorized as

- A. Natural
- B. Synthetic
- C. Co-processed

Natural superdisintegrant

Natural superdisintegrants are commonly used in tablet formulation which facilitates the disintegration of the tablet. Examples of natural superdisintegrants are given in the table.

Advantages

- Local accessible
- Eco-friendly and Bio-acceptable
- Low price as compared to synthetic and renewable sources.

Synthetic super disintegrant

Synthetic superdisintegrants are commonly used in tablet formulation which facilitates the disintegration of the tablet. Examples of synthetic superdisintegrants are given in the table.

Advantages of synthetic superdisintegrants

- Effective in low concentration as compared to starch.
- Have a low effect on compressibility and flowability.
- More effective intracranially.

Limitations

- Hygroscopic in nature and may cause problems with water-sensitive drugs.

Co-processed superdisintegrants

Co-processing excipients provide superior property compared to a physical mixture of individual excipient mixture. Examples of commercially available co-processed superdisintegrants are given in table⁹.

Table No. 1: Co-processed superdisintegrants

S.No	Co-processed superdisintegrants	Consists of
1.	Ludipress	Lactose monohydrate, polyvinylpyrrolidone, and crospovidone
2	Starlac	Lactose and maize starch
3.	Starcap 1500	Corn starch and Pregelatinized starch
4.	Ran-Explo-C	Microcrystalline cellulose, silica and crospovidone
5.	Ran-Explo-S	Microcrystalline cellulose, silica and sodium starch glycolate
6.	Pan Excea MH300G	Microcrystalline cellulose, hydroxyl-propyl-methyl cellulose, and crospovidone
7.	Ludiflast	Mannitol, crospovidone and polyvinyl acetate

Advantages of the Co-processed Directly Compressible Excipients¹⁰

- Absence of chemical change
- Improved flow properties
- Improved compressibility
- Better dilution potential
- Less fill weight variation
- Reduced lubricant sensitivity



CHALLENGES IN FORMULATING FDTs:

Palatability: Most orally disintegrating drug delivery systems disintegrate or dissolve in the patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance^{11,12}.

Mechanical strength: To allow FDTs to disintegrate in the mouth, they are made with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and

often requiring specialized peel-off blister packing that may increase the cost. Only a few technologies such as Wowtab® by Yamanouchi Shaklee and Durasolv® by CIMA labs can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles^{13,14}.

Hygroscopicity: Several FDTs are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging¹⁵.

Amount of drug: For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs¹.

Aqueous solubility: Water-soluble drugs form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process¹⁶.

Size of tablet: It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve¹⁷.

EVALUATION:

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

Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation¹⁸. Weight variation specification as per I.P. is shown in table 2.

Table No. 2: Weight variation and accepted % deviation

Average Weight of Tablet	% Deviation
80 mg or less	10.0
More than 80 mg but less than 250 mg	7.5
250 mg or more	5.0

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 (Monsanto tablet hardness tester). It is expressed in kg or pound¹⁹. 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 measured in "Electro lab friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min or a total of 100 revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation²⁰.

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$$F = \frac{(W_{\text{initial}} - W_{\text{final}})}{W_{\text{initial}}} \times 100$$

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 the following equation,

$$\epsilon = 1 - m / (\rho t V)$$

Where ρt is the true density, and m and V are the weight and volume of the tablet, respectively²¹.

Wetting time and water absorption ratio: Wetting time of dosage form is related to 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 Petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully placed in the center of the Petri dish and the time for the tablet to completely disintegrate into fine particles was noted. The water absorption ratio, R can be determined according to the following equation;

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

W_b; The weight of the tablet before keeping in the Petri dish

W_a; The wetted tablet from the Petri dish is taken and reweighed²²

Moisture uptake studies: Moisture uptake studies for FDT should be conducted to assess the stability of the dosage form. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37°C for 24h. The tablets were weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping a saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrants) was kept to check the moisture uptake by the other excipients. Tablets were weighed and the percentage increase in the weight was recorded.

In-vitro dispersion time: Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C. The time required for complete dispersion of a tablet was measured.

Disintegration test: The time for the disintegration of FDTs is generally less than 1 min and actual disintegration time that patients can experience ranges from 5 to 30s. The disintegration test for FDT should mimic disintegration in the mouth within saliva²³.

Modified disintegration test: A Petri dish (10cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the Petri dish and the time for the tablet to completely disintegrate into fine particles was noted.

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

Dissolution test: The dissolution methods for FDT are practically identical to the 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 the most suitable and common choice for the dissolution test of FDT tablets as compared to USP1 (basket) apparatus due to specific physical properties of tablets. In the 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. Large tablets (≥ 1 gram) may produce a mound in the dissolution vessel which can be prevented by using higher paddle speeds²⁴.

Clinical studies: *In-vivo* studies show the actual action of FDT in the oral–esophageal tract, their pharmacokinetics and therapeutic efficacy, and acceptability. The investigation using gamma-scintigraphy showed that the dissolution and buccal clearance of fast disintegrating dosage forms was rapid²⁵. The esophageal transit time and stomach emptying time were comparable to those of traditional dosage forms i.e. tablets, capsules, or liquid forms²⁶.

Stability study (Temperature dependent): The fast dissolving tablets stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) $40 \pm 1^\circ\text{C}$

(ii) $50 \pm 1^\circ\text{C}$

(iii) $37 \pm 1^\circ\text{C}$ and RH $75\% \pm 5\%$

The tablets were withdrawn after 15 days and analyzed for physical characteristics such as visual defects, Hardness, Friability, Disintegrations, and Dissolution, etc. The data obtained is fitted into first-order equations to determine the kinetics of degradation. Accelerated stability data are plotting according to the Arrhenius equation to determine the shelf life at 25°C .

VARIOUS TECHNIQUES FOR “FDT” PREPARATION:

Many techniques are used for the preparation of fast dissolving tablets which are shown in table.^{27,28,29-31}

Table No. 3: Techniques for FDT preparation

Techniques	Method and characteristics of prepared FD
1-Disintegrant addition	-involves the addition of super disintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. E.g. MCC and sodium starch glycolate are used in the formulation of efavirenz, Crystalline cellulose(AvicelPH-102)and low substituted HPEC used in oxybutynin and pirenzepine formulation. Crospovidone used in galanthamine HBr. Crospovidone (3%w/w) and croscarmellose Na (5%w/w) used in prochlorperazine maleate formulation. Characteristics: similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.

<p>2- Freeze Drying or Lyophilization</p>	<p>-the drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through a liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. Finally, the blisters are packaged and shipped. Characteristics: The preparations are highly porous, have a high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.</p>
<p>3- Moulding</p>	<p>-water-soluble ingredients with a hydro-alcoholic solvent are used and are molded into tablets under pressure lower than that used in conventional tablet compression. Characteristics: Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased.</p>
<p>4- Sublimation</p>	<p>- inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethylenetetramine) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates a porous structure. Characteristics: porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.</p>
<p>5-Spray-Drying</p>	<p>-by hydrolyzed and not hydrolyzed gelatins as supporting agents, mannitol as a bulking agent, sodium starch glycolate or croscarmellose sodium as a disintegrating agent and an acidic material (e.g. citric acid) and/or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution. Characteristics: prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.</p>
<p>6-Mass-Extrusion</p>	<p>-involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using the heated blade to form tablets. Characteristics: The dried product can be used to coat granules of bitter-tasting drugs and thereby masking their bitter taste.</p>
<p>7- Direct Compression</p>	<p>- conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Characteristics: It is the most cost-effective tablet manufacturing technique.</p>
<p>8-Cotton candy process</p>	<p>- involves the formation of a matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT. Characteristics: It can accommodate high doses of the drug and offers improved mechanical strength</p>
<p>9- Compaction; a) Melt granulation</p>	<p>a)prepared by incorporating a hydrophilic waxy binder (super polystrate) PEG-6-stearate. Super polystrate not only acts as a</p>

<p>b) Phase-transition process</p>	<p>binder and increase physical resistance of tablet but also helps the disintegration of the tablet. Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue. b) - prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after the heating process due to the increase of interparticle bond induced by the phase transition of lower melting point sugar alcohol. Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.</p>
<p>10-Nanonization</p>	<p>- involves the size reduction of a drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. Characteristics: It is used for poorly water-soluble drugs. It leads to higher bioavailability and reduction in dose, cost-effective manufacturing process, conventional packaging due to the exceptional durability and a wide range of doses (up to 200 mg of drug per unit).</p>
<p>11- Fast Dissolving Films</p>	<p>-a non-aqueous solution is prepared to contain water-soluble film-forming a polymer (pullulan, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste-masking ingredients are used to form a film after evaporation of the solvent. In the case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. Characteristics: The thin films size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste</p>

PATENTED TECHNOLOGIES: 32-36

Rapid-dissolving characteristic of FDTs is generally attributed to fast penetration of water into a tablet matrix resulting in its fast disintegration. Several technologies have been developed based on formulation aspects and different processes and patented by several pharmaceutical companies. Table of patented technology is given below;

Table No. 4: Patented technologies

S. No.	Technology	Process involved	Patent owner	Drugs Used (Brand name)
1	Zydis	Lyophilization	R.P.Scherer Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
2	Quicksolv	Lyophilization	Jansen Pharmaceutical	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-tab)
3	Flashtab	Lyophilization	Ethypharm	Ibuprofen (Nurofen Flashtab)
4	Lyoc	Multiparticulate Compressed tablets	Farmlyoc	Phloroglucinol Hydrate (Spasfon Lyoc)
5	Orasolv	Compressed Tablets	Cima Labs Inc	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt)
6	Durasolv	Molding	Cima Labs Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)
7	RapiTab	Compressed Tablet	Schwarz Pharma	--
8	Wow tab	Compressed Molded Tablets	Yamanouchi Pharma Technologies, Inc.	Famotidine (Gaster D)
9	Fast melt	Molding	Élan Corp.	--
10	Ziplets	Molding	Eurand	Ibuprofen (Cibalgina Due Fast)
11	Flash does	Cotton-candy process	Fuisz Technology Ltd.	Tramadol HCl (Relivia Flash dose)
12	Oraquick	Micromask taste Masking	KV Pharm. Co., Inc.	Hyoscyamine Sulfate ODT
13	Advatab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetrixine, AdvaTab Paracetamol

CONCLUSION:

Superdisintegrants play a critical role in the formulation of fast dissolving tablets. These agents help and facilitate tablets to disperse into their smaller fragments. The selection criteria, methodology, and mechanism of different types of super disintegrants have to be studied and incorporated. It has been found that super disintegrants addition method by direct compression gained popularity among researchers. The ease of availability and compatibility makes the formulation of fast dissolving tablets less complex than other patented technologies. fast-dissolving tablets were prepared by direct compression method by using co-processed superdisintegrants like Crospovidone, Sodium Starch Glycolate, Mannitol, Microcrystalline Cellulose as a diluent, Sodium saccharin as a sweetening agent, Mint as a flavor, Magnesium Stearate, Talc used as a lubricant and glidant. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of a drug (Famotidine) as well as other components and can be compressed into tablets.

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