

FAST DISSOLVING TABLET: THE NEW ERA

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This article is available online at www.ss-journals.com

ABSTRACT

The Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop fast disintegrating tablets (FDTs) with improved patient compliance and convenience. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an opportunity for product line extension in the Many elderly persons will have difficulties in taking conventional oral dosage forms (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Swallowing problems also are common in young individuals because of their underdeveloped muscular and nervous systems. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes the various formulation aspects, disintegrants employed and technologies developed for FDTs, along with various excipients, evaluation tests, marketed formulations, and drugs explored in this field.

Keywords: Disintegration, lyophilization, orodispersible tablets, superdisintegrants, mouth dissolving, fast disintegrating, direct compression, dysphagia

1. INTRODUCTION

“A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the ‘Orange Book’, an FDTs as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”.¹ Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient.” Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance.² The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.³⁻⁵ The advantage of the basic approach in development of

FDTs (Fast Dissolving Tablets) is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrrolidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms.^{6 7 8} Patients for whom chewing is difficult or painful can use these new tablets easily. FDTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth. Recent market studies indicate that more than half of the patient population prefers FDTs to other dosage forms and most consumers would ask their

doctors for FDTs (70%), purchase FDTs (70%), or prefer FDTs to regular tablets or liquids (>80%).⁹

2. SIGNIFICANCE^{10 11 12 13}

Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include:

- 1) As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- 2) No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.
- 3) Easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients) iv. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- 4) Medication as bitter pill has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs. vi. Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased.
- 5) Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.

3. IDEAL PROPERTIES OF FDTs^{14 15}

They should,

- 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 mouth feel.
- 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 equipments at low

4. ADVANTAGES OF FAST DISSOLVING TABLET

- 1) Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should

not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients.^{16,17}

- 2) Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- 3) Good mouth feel property of MDDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients due to improved taste of bitter drugs.
- 4) Convenience of administration and accurate dosing as compared to liquid formulations.
- 5) More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.
- 6) Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing sideeffects.^{18,19}

5. SELECTION OF DRUGS

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the postgastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An ODT may have varying degrees of pregastric absorption and thus, the pharmacokinetic profiles will vary.²⁰ Therefore, the ODT will not be bioequivalent to the conventional oral dosage form. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.^{21,22}

6. FORMULATION ASPECT FOR FDTs

In the formulation of FDT the most important additives are as follows.

1. Superdisintegrants^{23,24}: As FDT require faster disintegration. So, pharmacist needs to formulate Disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an

enormous increase in the volume of granules to promote disintegration.

Mechanism of Superdisintegrants: There are four major mechanisms for tablets disintegration as follows

a). 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.

b). 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 network around the drug particles

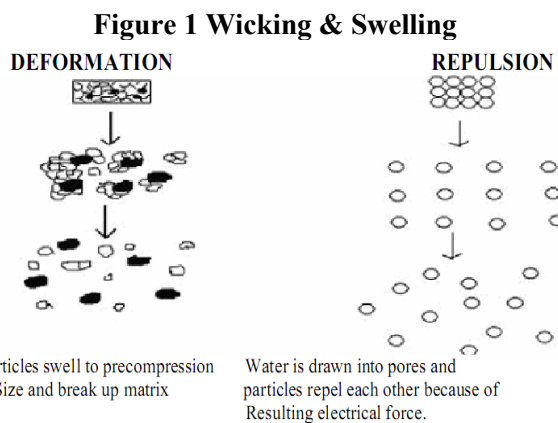
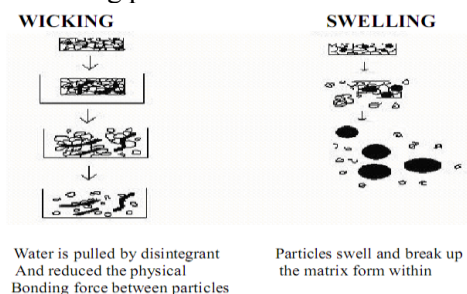


Figure 2: Deformation & Repulsion

c). Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrant 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 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.

d). 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.

Table 1: List of super disintegrants

EXAMPLE	SUPER-DISINTEGRANTS	MECHANISM OF ACTION	SPECIAL COMMENT
Crosslinked cellulose	Crosscarmellose Ac-Di-Sol Primellose Vivasol	Swells 4-8 folds in < 10 seconds. Swelling and wicking both.	Swelling is in two dimensions. -Direct compression or granulation -Starch free
Crosslinked PVP	Crosspovidone	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Crosslinked starch	Sodium starch glycolate	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Crosslinked alginic acid	Alginic acid NF ^{II}	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Natural super Disintegrants	Soy polysaccharides ^{II}	Rapid Dissolving	Does not contain any starch or sugar. Used in nutritional products.

2. Taste-masking agents^{24,25}: Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows:

- 1) Layering the drug onto inert beads using a binder followed by coating with a taste-masking polymer.
- 2) Granulating the drug and coating with a taste masking polymer.
- 3) Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.
- 4) Complexation by the use of inclusion in cyclodextrins.
- 5) Psychological modulation of bitterness.
- 6) Coacervation to form microencapsulated drug within a polymer.
- 7) Formation of pellets by extrusion spherulization.

3. Sweeteners: Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products, although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Therefore, the use of such sweeteners will vary from one country to the next based on national standards. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted. Some commonly used sweeteners are Sorbitol, Mannitol, Hydrogenated starch hydrolysate, Maltitol solution, Maltitol, Xylitol, Erythritol, Glycerin, Sucrose, Fructose.

4 Diluents: Diluent is added to formulation to increase the bulk volume of the active and hence the size of the tablet suitable for handling. The selection of the diluent will depend on the type of processing and plasticity of materials to be used. In general, a direct-compression formulation will require a diluent with good flow and compaction properties. Diluents form a major portion of most of the tablet formulations due to newer high potency APIs. The moisture content, more specifically water activity coefficient of such diluents, may influence API stability since many API are prone to degradation by hydrolysis. In general, moisture content may indicate hydrate form or tightly bound water molecule of crystallization, or surface-bound or surface-absorbed water on the excipient. The bound water

may not cause hydrolysis of sensitive API, but free- or surface- absorbed water may be responsible for hydrolysis of sensitive API. Today pharmaceutical companies increasingly use high speed tablet press for faster and higher productivity. For such high speed tablet press, key process and corresponding diluent knowledge has become important. Use of combination of diluents with synergistic properties or co-processed excipients, such as StarCap 1500®, co- processed starch excipient, are gaining significance in the pharmaceutical industry.

5 Lubricant²⁵: Lubricants are used in formulations to aid in smooth ejection of tablet from die cavity, prevent sticking of powder on punch faces (anti-adherence), reduce interparticle friction during compression and, to improve flow of powder blend on the machine and into the die cavity. For a robust formulation, careful consideration has to be given in selecting right type, concentration, order and duration of mixing of lubricant in the formulation. Lubricants can be further classified into three types based on their detailed functionality: (1) glidant, which enhance flow property of powder blend by overcoming powder cohesiveness, (2) anti- adherent, which reduce the friction between the tablet punch faces and tablet punches, and (3) die wall lubricant, which reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection of the tablet. Die-wall lubricants can be divided into two classes: fluid and boundary lubricants. Fluid lubricants work by separating moving surfaces completely with a layer of lubricant. These are typically mineral oils or vegetable oils, and they may be either added to the mix or applied directly to the die-wall by means of wicked punches. The oily lubricants may give a mottled tablet appearance due to uneven distribution, poor powder flow due to their tacky nature, and reduced tablet strength. Boundary lubricants work by forming a thin solid film at the interface of the die and the tablet. Metallic stearates are the most widely used boundary lubricants.

7. VARIOUS MANUFACTURING TECHNIQUES FOR FDTs

1. Lyophilization
2. Moulding
3. Direct Compression
4. Cotton Candy Process
5. Spray Drying
6. Sublimation
7. Mass Extrusion
8. Nanonization
9. Fast Dissolving Films

(1) Freeze-Drying or Lyophilization: In freeze-drying process, the water is sublimed from the product after it is frozen. This technique forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture MDTs. Jaccard and Leyder used lyophilization to develop an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability of several drugs such as spironolactone and trolendomyacin.¹⁹ Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug^{26,27}. Zydis technology (ZT) is a patented technique, which had been used for drugs like famotidine, loperamide, piroxicam, oxazepam, lorazepam, domperidone, brompheniramine, olanzepine, ondansetron and rizatriptan. Thirteen products are currently available in the market, which had been manufactured using this technology. In the worldwide market, Zydis formulations are also available for oxazepam, lorazepam, loperamide, and enalapril. ZT utilizes a unique freeze-drying process to manufacture finished dosage units which significantly differ from conventional oral systems.^{28,29} The process involves the following steps:

Stage 1: Bulk preparation of an aqueous drug solution or suspension and its subsequent precise dosing into pre-formed blisters. It is the blister that actually forms the tablet shape and is, therefore, an integral component of the total product package.

Stage 2: Passing the filled blisters through a specially designed cryogenic freezing process to control the ultimate size of the ice crystals which ensures that the tablets possess a porous matrix to facilitate the rapid disintegration property. These frozen units are then transferred to large-scale freeze dryers for the sublimation process, where the majority of the remaining moisture is removed from the tablets.

Stage 3: Sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions. Lyoc is a porous and solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus.

Advantages: The major advantage of using this technique is that the tablets produced by this technology have very low disintegration time and have great mouthfeel due to fast melting effect.

Disadvantages: Although being a fairly routine process, lyophilization has some disadvantages like it is a relatively expensive and time consuming process. Furthermore, the product obtained is poorly stable and fragile, rendering conventional packaging unsuitable.^{19,30}

(2) Tablet Moulding: Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly. Following are the different tablet moulding techniques: This manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

i) Heat-Moulding Process: Heat-moulding process involves setting the molten mass containing a dispersed drug.

This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C under vacuum.

ii) Moulding by Vacuum Evaporation without Lyophilization: This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process.. Tablets produced by moulding are solid dispersions. The drug, depending on its solubility in the carrier, exists either as discrete particles or microparticles dispersed in the matrix and is dissolved totally/partially to form a solid solution/dispersion in the carrier matrix.

Advantages: As the dispersion matrix is made from water-soluble sugars, moulded tablets disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the moulding process are used. In comparison to lyophilization process, tablets produced by moulding technique are easier to adapt to the industrial scale.

Disadvantage: As the moulded tablets have poor mechanical strength, they may undergo erosion and breaking during handling. Though hardening can increase the strength of the tablets but it would be at the cost of their disintegration time.^{31,32}

(3) Direct Compression (DC): DC is the simplest and most cost effective tablet manufacturing technique for MDTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tableting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugarbased. The present technology uses the concept of effervescence to achieve fast-disintegration. In this technology, the microparticles are prepared by dispersing the drug into a suitable polymer (ethyl cellulose, methyl cellulose, acrylate or methacrylic acid resins) along with other excipients (mannitol and magnesium oxide). The drug and mannitol are added to the polymeric dispersion under stirring, followed by addition of magnesium oxide. Here, mannitol and magnesium oxide are known as release promoters as they aid in drug release from the polymeric coating. This mixture is then dried for one hour at 50 °C, delumped and dried for another hour at the same temperature. The material is then screened (8-mesh) and dried for one hour at 60 °C.^{33,34,35}

(4) Cotton Candy Process: The FLASHDOSE® is FDTs manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

I. Floss Blend: In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in

maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

II. Floss Processing: The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

III. Floss Chopping and Conditioning: This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.^{36,37}

IV. Blending and Compression: Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.³⁸

(5) Spray-Drying: Allen et al.³⁹ have used spray-drying for the production of FDTs. The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscarmellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.

(6) Sublimation: Sublimation has been used to produce FDTs with high porosity. A porous

matrix is formed by compressing the volatile ingredients alongwith other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose.^{40,41}

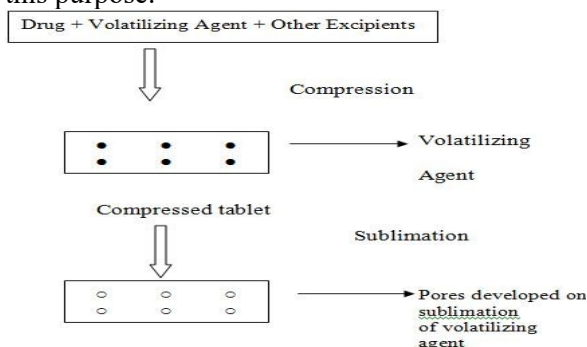


Figure 3: Steps Involved in sublimation

8. EVALUATION OF BLENDS^{42,43}

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics-of blends produced.

The various characteristics of blends tested are as given below:

1. Angle of Repose: The frictional force in a loose powder can be measured by the angle of repose θ . It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ , is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\tan \theta = h/r$$

Therefore $\theta = \tan^{-1} h/r$

Where θ = Angle of repose

h = height of the cone

r= Radius of the cone base

Angle of Repose less than 30 ° shows the free flowing of the material.

Sr. no	Angle of Repose	Type of Flow
1	< 20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very poor

2. Bulk Density: Density is defined as weight per unit volume. Bulk density, p_b , is defined as the

mass of the powder divided by the bulk volume and is expressed as gm/ cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. There are two types of bulk density. The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density. Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. A standard procedure used for obtaining bulk density or its reciprocal bulkiness is given, below. A sample of about 50 cm³ (blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm³.

$$Pb = M/V_p$$

Where

p_b =Bulk Density "

M = Weight of sample in gm

V = Final volume of blend

in cm³

3. Bulkiness: Specific bulk volume or reciprocal of bulk density is called bulkiness or bulk. Bulkiness increases with a decrease in particle size. In mixture of material of different sizes, however the smaller particle shifts between the larger particles and tends to reduce the bulkiness. The bulkiness can be calculated by the following formula

Bulkiness = $1/p_b$, where, p_b = Bulk Density.

Loose bulk density.

It is defined as the ratio of weight of blend in gms to the loose bulk volume (untapped volume) in cm³ Loose bulk density is given by Loose bulk density $p_u = \text{Weight in gms} / V_b$ Where V_b = Bulk volume (untapped volume)

4. Void Volume: The volume of the spaces is known as the void volume "v" and is given by the formula

$$V = V_b - V_p$$

Where V_b = Bulk volume (volume before tapping) V = True volume (volume after tapping)

5. Porosity: The porosity ϵ of powder is defined as the ratio of void volume to the bulk volume of the packaging.

The porosity of the powder is given by

$$\epsilon = (V_b - V_p) / V_p = 1 - V_p/V_b$$

Porosity is frequently expressed in percentage and is given as

$$\% \epsilon = (1 - V_p/ V_b) \times 100$$

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

6. Percent Compressibility: It is an important measure obtained from bulk density and is defined as,

$$C = \frac{Pb - Pu}{Pb} \times 100$$

If the bed of particles is more compressible the blend will be less flowable and flowing materials.

9. EVALUATION OF TABLETS^{44,45,46,47}

1. General Appearance: The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, 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. Uniformity of weight: I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Average weight of	Maximum percentage
Average Wt. of Tablet	% Deviation
80 mg or Less	± 10
More then 80 mg but less then 250 mg	± 7.5
250 mg or more	± 5

5. Tablet hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

6. Friability: It is measured of mechanical strength of tablets. Roche fribaiator was used to

determine the friability by following procedure. A preweighed tablet was placed in the fribaiator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{Friability} = \frac{\text{loss in weight}}{\text{Initial weight}} \times 100$$

7. In Vivo Dsintegration test: The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

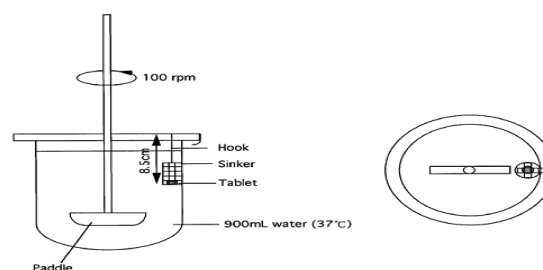


Figure 4: Schematic view of modified dissolution apparatus for disintegration test⁴

8. Wetting time⁴⁷: The method reported by Yunxia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation was also determined.

9. In vitro dispersion time: In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

10. Stability testing of drug (temperature dependent stability studies): The fast dissolving tablets are packed in suitable packaging and 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 a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability,

Disintegrations, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25° C.

11. Dissolution Testing of Mouth Dissolving Tablets^{49,50:} The conventional method of dissolution could be extended to in-vitro evaluation of MDT⁴⁹ The dissolution conditions for the reference listed drugs available in USP can be utilized for preliminary in-vitro studies to mimic better in-vivo conditions. Apart from the above, multimedia dissolution studies in various buffer solutions of different pH viz. 0.1 N HCl; pH 4.5 and 6.8 buffers should be carried out for interpretation of their in-vivo performance and pharmaceutical equivalence. USP apparatus II (paddle) with a speed of 50 rpm seems to be most suitable and common choice with appropriate dissolution media volume to maintain sink condition. Typically, the dissolution of MDTs is very fast when using USP monograph conditions and therefore, under such conditions the dosage forms behave almost equally. Hence, slower paddle speeds may be employed to obtain a profile and better discrimination among various batches prepared during the developmental stage. In case of tablets approaching or exceeding one gram weight and containing relatively dense insoluble particles, there are the chances of heap formation at the bottom of the dissolution vessel. Under such a condition, although the tablet disintegrates completely, there is a significant reduction in the apparent dissolution rate. However, this issue can be resolved by using higher paddle speed of 75 rpm⁵⁰

10. THE EFFECT OF RECENT FDA GUIDANCE ON ODT TECHNOLOGIES AND APPLICATIONS^{51,52}

The 2008 FDA industry guidance on ODTs (2) provides recommendations that clarify the expectations of the ODT dosage form. ODTs were originally developed for, and are mostly associated with, good patient acceptance and compliance. Compressed ODT formulations provide the convenience of using standard tableting technology and taste-masked APIs. Specialty companies can apply this technology, but the availability of super-disintegrants also make this technology accessible for in-house pharmaceutical development. Products made via compressed tableting and with sugar-floss systems can also meet the FDA guidance by going through some further product optimization with respect to

disintegration time The first ODTs to market and have been successful in terms of sales value, sales volume, and number of worldwide product approvals. Different ODTs have proven to be versatile, by spanning a range of clinical applications (e.g., bioequivalence, buccal uptake, and stable formulations of macromolecules.) Having set the original standard for ODTs, the products provide the additional assurance of compliance with the FDA guidance. The FDA guidance reinforces such thinking by focusing on disintegration time and unit size in the context of what does and does not constitute an ODT because these two parameters heavily influence ODT patient acceptance and compliance. In addition to meeting the FDA guidance recommendations, palatability remains a factor that may influence the choice of ODT technology for a specific API.

11. FUTURE RESEARCH TRENDS IN FDTs⁵³

Although the FDT area has passed its infancy, as shown by a large number of commercial products on the market (as listed in Table 2), there are still many aspects to improve in the FDT formulations. Despite advances in the FDT technologies, formulation of hydrophobic drugs is still a challenge, especially when the amount of drug is high. The low dose drugs, such as Loratadine with 10 mg dose, pose little problem, but as the dose increases, the formulation sacrifices its fast disintegrating property. A new technology is being developed to incorporate higher doses of hydrophobic drugs without affecting the fast disintegrating property too severely. The disintegration times of most FDTs on the market are acceptable—i.e., less than 60 seconds—but certainly there is a room for improvement. Because the disintegration time is related to other formulation variables, a balance has to be maintained between shortening the disintegration time and other tablet properties. The tablet hardness, friability, and stability can be further improved to such a level that multi-tablet packaging in conventional bottles becomes a norm. The future of FDTs lies in the development of FDTs with controlled release properties. If one FDT can deliver drugs with short half-lives for 12–24 hours, it would be a quantum improvement in the FDT technology. In addition, the ability to formulate drugs in large doses will bring another important technological advance. In general, the FDT formulations require large amounts of excipients, and having large doses of drug will only make the final formulation too big to handle.

12. CONCLUSION

Fast dissolving tablets constitute an innovative dosage form, which overcomes the problem of swallowing and provides a quick onset of action. The paediatric and geriatric populations are the primary. Targets, as both the groups found it difficult to swallow conventional tablets. The basic approach followed by all the currently available technologies engaged in the formulation of Fast dissolving tablets is to maximize the porous

structure of the tablet matrix and incorporate super disintegrating agents in optimum concentration so as to achieve rapid disintegration and instantaneous dissolution of the tablet along with good taste masking properties and excellent mechanical strength. The availability of the various technologies and manifold advantages of Fast dissolving tablets will surely increase its popularity in the near future.

MARKETED FAST DISSOLVING TABLETS IN INDIA

Table 2: Marketed Fast Dissolving Tablets in India

Name of the Product	Active Ingredients
Imodium Lingual	Imodium
Pepcidin Rapitab	Quick releasing antiulcer preparation of pepcid
Mosid – MT	Mouth melt tablet of Mosapride citrate.
Calritin Reditabs	Immediate Dissolving formulation of Calritin
Nimulid – MD	Nimesulide
Zyrof Meltab	Rofecoxib
Claritin Reditab	micronized loratadine
Feldene Melt	piroxicam (10 or 20 mg),
Maxalt-MLT	rizatriptan (5 or 10 mg), peppermint flavor
Pepcid RPD	famotidine (20 or 40 mg),
Zyprexa Zydis	olanzapine (5, 10, 15 or 20 mg),
Zofran ODT	ondansetron (4 or 8 mg), strawberry flavor
Remeron Soltab	mirtazepine (15, 30, or 45 mg), orange flavor

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