Formulation Aspects and Manufacturing Technology – A Review on Fast Disintegrating Tablets

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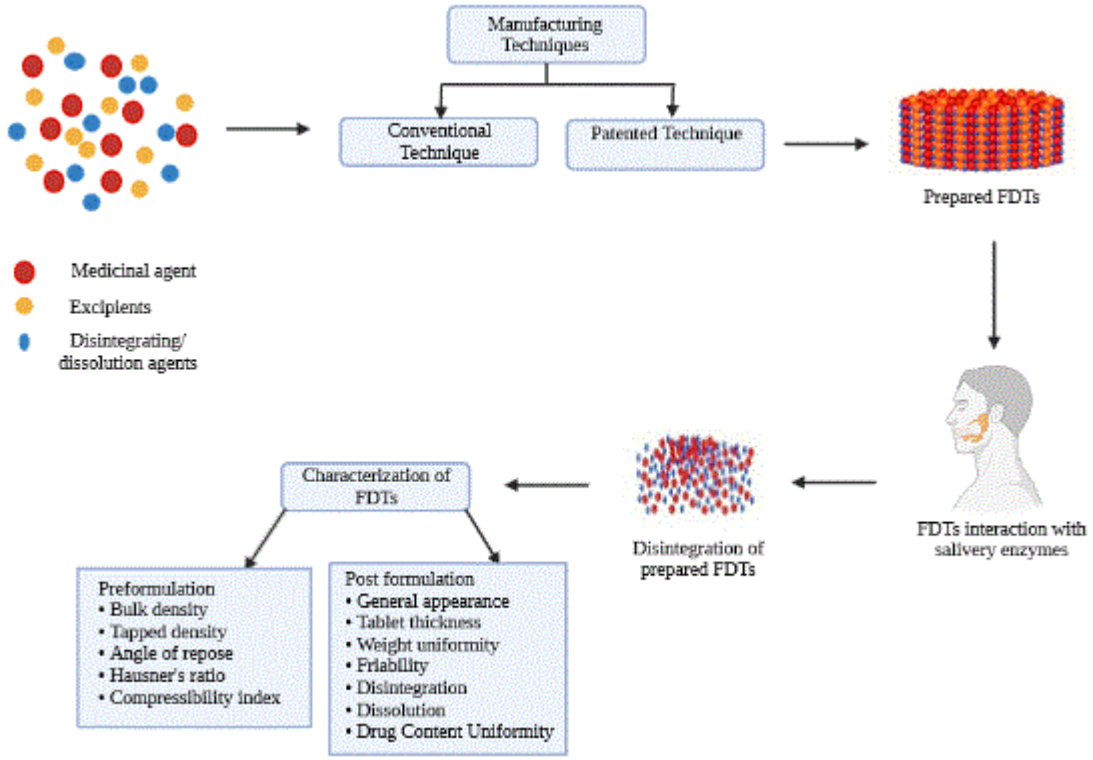
Abstract

Fast disintegrating tablets (FDTs) have piqued the pharmaceutical industry's attention in recent decades, and the demand of this dosage form has risen as well. The oral route is still the favored route for medication. Most of the researchers have been encouraged to produce FDTs due to enhance patient compliance and low convenience. These dosage forms melt or disintegrate in the mouth and release active medicinal components without the need of water. Because of the popularity and utility of such formulations, many FDT technologies have been created. FDTs are particularly useful for pediatric, geriatric, schizophrenic, and other patients with lack of water assessment while travelling, as well as those who have difficulty in swallowing traditional dosage form. This research describes a variety of patent formulas and technology for generating quick dissolution/disintegrating tablets in the mouth. FDT methods such as freezing, tablet molding, mass extrusion and direct compression etc. also ways to improving FDT features like spray drying, masking taste and use of super-disintegrating agent. This study focuses on ideal criteria, the necessity for different FDT technologies to be developed, formulation issues, the applicability of excipient such as super-disintegrants, taste masking, and other excipient, as well as preformulation and post formulation characteristics.

Keywords: Fast disintegrating tablets, super-disintegrants, spray drying, taste masking, mass extrusion.

Graphical Abstract



1. Introduction

Among the different ways studied for the distribution of pharmaceuticals through various products of pharmaceutical goods, drug delivery via orally has been the most extensively utilized mode of administration [1]. Orally delivered medications are accepted around 60.0 % of all dosage form. Solid dosage forms are the most favored type of dosage forms as their route of administration is simplest one, high dose precision, and feasibility of self-medication, patient compliance, and avoidance of pain [2]. For certain patients, one significant disadvantage of this dosage form is the difficulty in swallowing it, especially in the case of motion sickness, rapid coughing, common cold, and hypersensitivity [1,3].

Tablets with quick dissolution or disintegration in the mouth (buccal) cavity have gotten much attention for all the reasons stated above. The fast-dissolving tablet dissolves or disintegrates into the mouth without the need for any dissolving media. Due to the quick dissolution and absorption rate, a tablet's rapid disintegration results in a rapid commencement of action [2]. The difficult parameter in developing medication is to improve oral bioavailability of hydrophobic active medicinal compounds.

Oral bioavailability is determined by the drug's dissolving rate and solubility. Because dissolution is a rate determining stage in the emergence of therapeutic effects, several efforts are made to improve drug dissolution that has low aqueous solubility. Approaches that can elevate the properties of dosage form include size reduction, formation of salt and addition of appropriate solvent or surfactant.

2. Fast disintegrating system (FDS)

FDS is a revolutionary formulation method that involves the combined benefit and provides extra benefit of liquid as well as solid dosage form [1, 2]. The FDS formulation combines the easy swallowing of a liquid preparation with the convenience of easy handling of a tablet formulation. When compared to the primary alternative liquid dosage form, it provides superior dosing accuracy. This type of formulation is intended for dysphasic, elderly, pediatric, bedridden, mobile, and schizophrenic patients having problems ingesting traditional oral preparations [2].

The Fast-disintegrating tablets (FDT) are well-known as rapid or fast melting/ dispersing/ quick dissolving. All FDTs fall within the category of orally disintegrating tablets, according to FDA (Food and Drug Administration). The term Oro-dispersible tablet was recently created by European Pharmacopeia to describe a tablet that may disperse or dissolve in the buccal cavities in less than 3 minutes before being swallowed. This firm hard solid tablet breaks down into small particles and transforms into a gel-like structure, making it simple for patients to swallow. Good FDTs disintegrate in a matter of seconds to a minute [1, 3]. Analgesic, antipsychotics, anti-histaminic, erectile dysfunction, and cardiovascular agents are among the pharmacological possibilities for FDS. When a tablet is put on the tongue without chewing or water, it dissolves or disintegrates instantly, and the tablet is dissolved or destroyed in the presence of salivary fluid. This causes higher medication absorption, and fast onset of action as compared with traditional tablet dosage form [2].

3. Need to formulate fast disintegrating tablets [4]

Because of poor patient acceptability and compliance with invasive drug delivery methods, a restricted market range for drug firms and medication application, and the high cost of illness care, non-invasive drug delivery technologies will continue to be needed. FDT is a solid dosage form that may be effective in a variety of situations:

- Elderly people with tremors and dysphasia, as well as children who are unable to take the traditional dosage form comfortably.
- Patients with diarrhea and motion sickness while travelling.
- Person who is unable to swallow medication due to continuous nausea. For example, people suffering from cancer and experiencing very sickness after receiving chemotherapy are taken H2 blockers to prevent stomach ulcers.
- Patients with mental disabilities, immobile, and schizophrenic patients [5, 6].

3.1 Advantages of fast disintegrating tablets

- Kidney patients, immobile patients, cerebral hemorrhage, and person who deny such as pediatric, geriatric & schizophrenic patients.
- Immediate initiation of pharmacological treatment.

- Suitable for touring and busy individuals, who have a lack of water.
- Increased bioavailability and quick absorption of medication by pre-gastric absorption into the saliva.
- Good mouth feel quality, especially for children, that assists to modify the impression of medicine as a bitter tablet.
- The safety is increased since physical blockage minimizes the danger of sticking or suffocation at the time of administration through oral route.

3.2 Limitations of fast disintegrating tablets

The mechanical power of tablets is inadequate. As a result, extreme caution is essential.

- If there is an issue with the tablet formulation, it might cause disagreeable taste, and even grittiness in the buccal cavity.

4. Key points in the formulation of FDTs

➢ **Palatability**

The FDTs include the medicament with improved taste since most medications are unpleasant. Because these delivery systems breakdown or dissolve, the active components are released into the patient's oral cavity and come into touch with the taste buds, taste masking of the pharmaceuticals becomes crucial to patient compliance.

➢ **Mechanical strength**

FDTs are prepared as tablets by compressing with very low compressing power, which makes them friable or brittle, difficult to handle, and may even need specialist peel-off blister packaging, which adds to the expense while allowing to disintegrate quickly in the buccal cavity. There are few reported technologies that can produce tablets with sufficient hardness and durability, allowing them to pack and stored in multi dose container such as Durasolv by CIMA labs [7] and Wow tab [8] by Yamanouchi.

➢ **Hygroscopicity**

Because of hygroscopicity of number of orally disintegrating dosage forms, they are not able to retain their physicochemical quality under normal ambient conditions, so they need specific product packaging.

➢ **Amount of drug**

When it comes to fast dissolving oral dosage form, this formulation aspect is especially difficult. For insoluble medications, the quantity of drug in lyophilized dosage form should not exceed 400mg, and soluble drugs should not exceed 60 mg.

➢ **Aqueous solubility**

Hydrophilicity of medicines produces eutectic mixture, which causes depression at freezing point. This leads to the generation of a transparent solid that due to the lack of supporting structure may breakdown when subjected to drying phase. The use of matrix forming chemicals like mannitol, which may make it crystalline and so impart stiffness to the

amorphous composite, can avoid this disintegration.

➢ **Tablet size**

The size of the tablets determines how easy they are to be handled. According to research, the simplest tablet to engulf is 7-8 mm in size [2].

5. Manufacturing technologies for FDTs

The manufacturing technologies can be classified and shown in Figure 1.

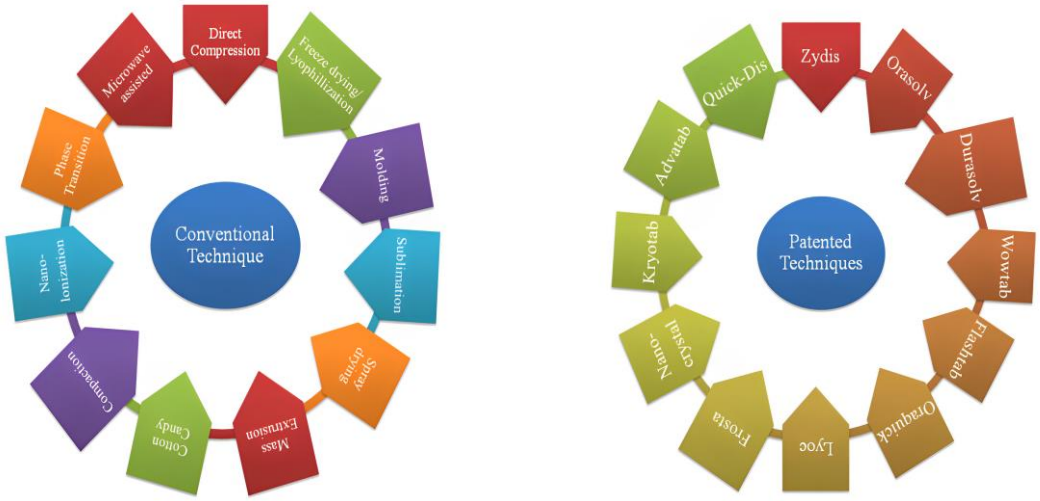


Figure 1. Conventional and patented manufacturing technologies

5.1 Conventional methods for the preparation of FDTs

5.1.1 Super-disintegrants addition

Disintegrants may be defined as a chemical that allows the tablet formulation to break down into little pieces when exposed to gastrointestinal fluids. At the solid dosage form, super-disintegrants are employed in a low concentration, 1.0-10.0 % by wt. compared to the final wt. of the tablet. Croscarmellose (cross linked cellulose), crospovidone (cross linked polymer), and sodium starch glycolate are examples of super-disintegrants. The correct picking of disintegrants and its uniformity of performance are key elements for the formulation creation of tablets. To make quick dissolving tablets, several cellulose derivatives such as micro-crystalline cellulose, and low substituted hydroxyl propyl cellulose may be employed as disintegrants (8:2-9:1 range). To produce fast dissolving tablets, porosity may be increased by treating the water and employed agar powder as a disintegrant. Croscarmellose, Sodium starch glycolate, and crospovidone are some of the most often used super-disintegrants [4] shown in Table 1.

Table 1. Various super-disintegrants of commercial grade

S. no.	Type	Polymer	Description	Brand name
1.	Polyvinyl-pyrrolidone	Crospovidone	Quickly swell and disperses in water.	Kollidon CL, Polyplasdone XL,
2.	Modified cellulose	Croscarmellose Sodium.	Outstanding swelling and water uptake properties.	Ac_di_sol, Primellose, Solutab.
3.	Modified Starch	Sodium starch Glycolate	High swelling ability and fast water uptake.	Primogel, Explotab, Glycolys.

5.1.2 Freeze drying or Lyophilization

Water sublimes from the product after freezing, making it one of the first-generation processes for creating FDT. In contrast to other solid formulations, the substance generated by the freeze-drying method [9, 10] dissolves/disintegrates faster. The improved dissolving properties are due to the emergence of transparent amorphous structure of -insolubility and strong aqueous stability in suspensions are suitable pharmacological qualities for this technique. Water soluble medication produces a drop in freezing point owing to the production of a eutectic mixture, as well as the production of transparent solid which may be broken upon sublimation. Cryoprotectants, such as mannitol, are used to provide amorphous material rigidity by causing crystallinity, which prevents the structure from collapsing and masks the bitter taste. There are several benefits to adopting the freeze-drying method, including the ability to handle medicinal compounds at low temperature, so avoiding thermal impacts. However, this method has the disadvantage of having a high processing and equipment cost. Other drawbacks include the absence of resistance required for conventional blister packing of finished formulation.

5.1.3 Tablet molding

This approach is used for tablet production by molding a solid dispersion including active pharmaceutical agents, water soluble additives, and additional excipient. All of these are first dry mixed before being moistened with a solvent (alcohol) and then compressing of mixture is done using low forces. The solvent within the tablet is air dried to create porous tablets. Different techniques used for tablet molding are:

- **Compression molding**

  Initially the powder mixture is soaked in a solvent such as alcohol/ water and then the wetted mass is pushed into the mould plate.

❖ **Heat molding**

The medication is disseminated in the molten matrix in this manner.

❖ **Lyophilization/freeze-drying**

This technique includes total evaporation of solvent/moisture from the solution/suspension of medicament at room temperature.

Molded tablets are like solid dispersion. Physical appearance is determined by the degree at which the medication dissolves in the molten/wetted mass. Because the dispersion is formed of water-soluble excipient, this approach may achieve a rapid dissolving rate. The mechanical strength of molded tablets, on the other hand, is a key problem. Various binding agents including sugar, and cellulose polymers, may be used as additive solutions to boost mechanical strength. However, the range of flavor masking in molded tablets is quite restricted [11].

❖ **Direct compression**

Previously in formulation of tablets several methods like direct compression, wet, and dry granulation [12, 13] has been accepted for FDTs production. Out of all these techniques, the simplest in manufacturing tablets is direct compression. This approach is popular because of its low production cost, well-known equipment, readily accessible excipient, and reduced number of operational steps. Higher dose may be allowed, and the wt. of final tablet easily surpasses that of conventional manufacturing processes [14]. In the case of compressed tablets, the rate of disintegration and solubilization is determined by the action of excipient such as disintegrants, hydrophilic substance, and an effervescent agent along or in combination. Super-disintegrants are important for disintegration, and dissolution of directly compressed FDTs. It's critical to choose the right kind and quality of disintegrants to provide a high disintegration rate and a pleasant tongue feel.

5.1.4 Spray-Drying

Highly fine powders with high porosity may be prepared by using this process. Allen et al. used this method to make FDTs. Gelatin (supporting matrix), mannitol (bulk forming agent), and croscarmellose or starch glycolate (disintegrant) in FDT's formulations. The disintegration and dissolution rates may be enhanced by the addition of effervescent agents, such as sodium bicarbonate, citric acid, tartaric acid. Spray drying was previously used to turn the mixture into a porous powder [15, 16].

5.1.5 Sublimation

Because traditional tablets are made up of highly hydrophilic chemicals, they dissolve slowly due to their poor porosity. As a result, a porous substance is added to the tablet matrix, which is a crucial aspect in the quick disintegration of fast disintegrating tablets.

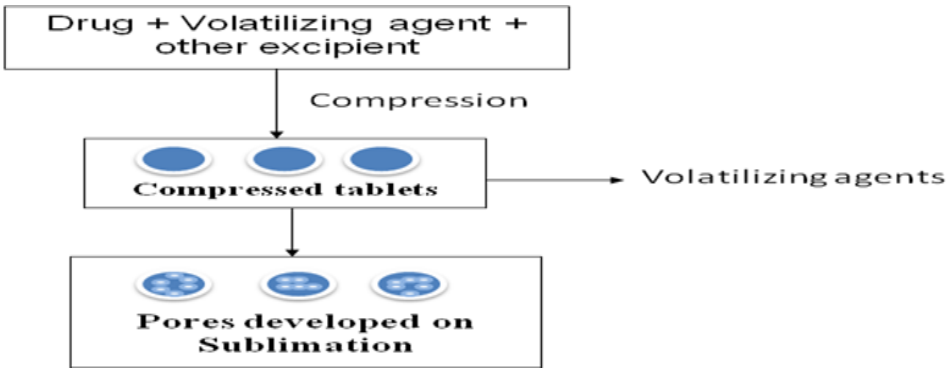


Figure 2. Steps involved in Sublimation

Volatile chemicals such as camphor, which sublimated from the produced tablets, may be utilized in the tableting process to increase porosity. Koizumi et al. [17] formulated FDTs using a mixture of camphor and mannitol. After preparing the tablets, the Camphor was sublimate for 30 minute in a vacuum at 80° as shown in Figure 2.

5.1.6 Mass extrusion

The combination of PEG and methanol makes softened blend of active drug and concurrently extrusion or syringing of the softened blend to get segments of the product using a hot blade to create tablets. To disguise the bitter taste of blend, coating can be done by using dried cylinder [18].

5.1.7 Cotton Candy Process

The cotton candy process involves both melting as well as spinning to prepare the polysaccharide matrix. The obtained candy floss is then recrystallized and mixed with the active drug and excipient. Finally, the resultant product is milled/grind and compressed to form tablets. A high drug loading capacity and maintenance of the tablet strength can be achieved by preparing ODTs by this process [19].

5.1.8 Nano-ionization

Nano-ionization is based on the principle of wet grinding. In this process the wet powder mix is ground to get nanoparticles. The stabilization of nanoparticles is done with physisorption of the inert substance to keep away from aggregation. In this technique, the surface area and bioavailability enhancement are observed for BCS class II drugs [20].

5.1.9 Compaction

In this method super-disintegrants such as croscarmellose, sodium starch glycolate, acrylates, and polyvinylpolypyrrolidone, and sodium alginate are used. For examples ODTs of baclofen, and carbamazepine have been prepared by using super-disintegrants 2-10% of crospovidone and MCC [21, 22].

5.1.10 Phase-transition Method

This method involves a minimum of 2 sugar alcohols, such as xylitol and erythritol, with different melting points, one of which is elevated melting point than the other. At a temperature between the melting points of both sugar alcohols used, the combination with the

sugar alcohol is reduced to a fine paste and compressed to form tablets. This method gives products which can withstand the transportation, freight, and storage conditions as these have sufficient hardness [23].

5.1.11 Microwave-assisted Method

This technique includes preparation of the ODTs (oral disintegrating tablets) by microwave irradiation and direct compression. The ODTs are prepared according to the direct compression method and then microwave exposure to the ODTs for at least 5 min at 490W. The final product results in the hardness of approx. 3 to 5 kg/cm2 with disintegration time of about less than 60 seconds [24].

6. Patented methods for the preparation of FDTs

The various patented technologies are describe and shown in Table 2

6.1 Zydis technology

The medicinal agent is entrapped in a matrix made up of sugar moiety and polymers in this method [25- 27]. Polymers such as partly hydrolyzed gelatin and dextran, dextrin, alginates, polyvinyl alcohol, and pyrrolidine are often utilized in Zydis technology. The procedure entails preparing a component solution or dispersion, which is then packed into blister cavities and frozen in a liquid nitrogen atmosphere. The porous wafers are made when frozen solvent is removed by the sublimation process. The peelable backing foil is used to bundle the Zydis units. The Zydis formulation is moisture sensitive and may deteriorate at humidity levels over 65% relative humidity (RH) [28] shown in Figure 3.

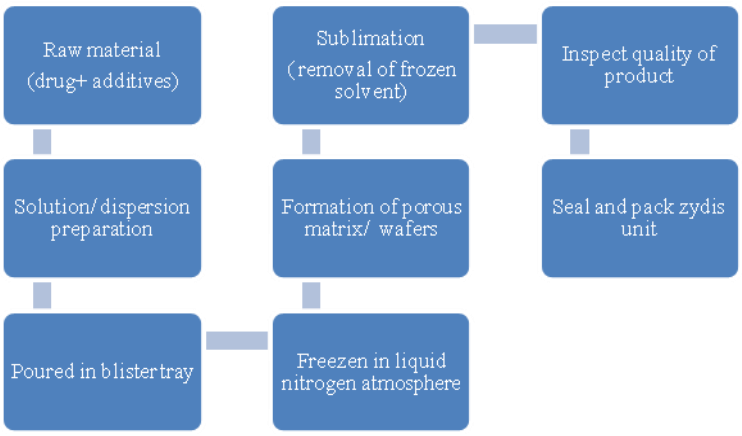


Figure 3. Tablet processing by Zydis technology

6.2 OraSolv technology

Cima's first generation fast-disintegrating/ dissolving formulation was OraSolv. The FDTs dissolves in the saliva and produces effervescence in this technique. After the tablet matrix dissolves in saliva, the medication power is released in less than one minute. Sweeteners and taste aren’t the only way to mask a drug’s disagreeable taste [29, 30]. In OraSolv technology,

both coating the medication power and effervescence are employed to hide the taste. The OraSolv formulation's biggest flaw is its mechanical strength.

6.3 Durasolv technology

Cima's DuraSolv was the company's IInd generation FDT. DuraSolv is made in the way as OraSolv, but due to the high compaction pressure applied in the tablet creation, it has a stronger mechanical strength than OraSolv. DuraSolv tablets were made using traditional tableting machinery and have a friability of less than 2%. As a result, the DuraSolv product is manufactured quicker and at a lower cost. Because of its excellent durability, DuraSolv may be packed in typical blister packing, pouches, or vials. DuraSolv has the problem of subjecting the formulation to high pressure during compaction, which is incompatible with bigger concentration of active medicated substances. In contrast to OraSolv, excessive medication dosage may affect taste masking. Due to the fracture during compaction in the DuraSolv product, the bitter-tasting medicine may be exposed to the taste buds of patient; hence The DuraSolv is best preferred formulation containing comparatively tiny quantities of active components [7, 25].

6.4 Wowtab technology

Yamanouchi Pharmaceutical Co. has patented Wowtab technology. Wow is an acronym for "Without Water". This is soluble compressed tablet made from a blend of less moldability sugars and elevated moldability sugars for excellent bound properties and quick disintegration intra-buccally to create a fast melt, robust tablet. These tablet is made using a traditional manufacturing technique in which the API is blended with saccharide of less moldability, then convert into granules with a saccharide of elevate moldability and lastly compressed to form a tablet. Saccharide of less mouldability includes, Glucose, Lactose, xylitol, and sucrose where as saccharide of extreme mouldability includes oligosaccharides, sorbitol, and maltose. The active component may account for up to 50 % in terms of weight of the tablets [8, 25].

6.5 Flash tab technology

Flash tab has been patented by Prographarm laboratories. The production of a quick dissolving tablet containing an API in the form of microcrystals is part of this technique. Any common process, like size extrusion, co-acervation, pan coating procedures, and microencapsulation, may be used to make drug microcrytals. The microcrystals of the drug's microgranules are mixed with the granulating agent (wet and dry) and compacted into tablets [31-33]. The tablets are made using traditional tableting technique and possess high mechanical strength and a disintegration period not more than a minute.

6.6 Flash dose technology

Fuisz has patented flash dose technology [31, 32]. Biovail Corporation released the first commercial product, Nurofen meltlet. Nurofen meltlet was created as melt-in-mouth tablets with ibuprofen as the active ingredients. Floss is included in the flash dosage tablets (self-binding shearform matrix). Using an inimitable spinning method, this technology

creates floss like structure, similar to “cotton candy”. The sugars are exposed to flash heat and centrifugal force in this process, which elevates the temperature of the bulk and creates an interior flow state. The floss is flung by the spinning head, which collects the flowing mass. Because the floss produced so far is amorphous, it must be recrystallized. The active medicine is then mixed with the crystalline sugar and compacted into a tablet. The dosage form’s ability to hold the medicine is up to 600mg. The tablets are very friable, fragile, and moisture sensitive, which is the major, disadvantages of these dosage forms.

6.7 Oraquick technology

A patented taste masking technique is used in the Oraquick FDTs [25, 32]. Because the taste masking technique does not use any solvents, it allows for more efficient manufacturing. Oraquick is also the preferable technique for heat sensitive pharmaceuticals because to features such as reduce manufacturing heat compared to rival mouth-dissolving/disintegrating technologies. The matrix that surrounds and protect the medication power in micro-encapsulated particles, according to KV pharmaceuticals, is more elastic (tablets can be compressed to achieve significant mechanical strength without disrupting taste masking) Oraquick promises to dissolve in a matter of seconds and to have superior taste masking properties [1].

6.8 Lyoc Technology

Lyoc technology was the first freeze drying based technology which came into existence. In this technology liquid solution or suspension of the drug is prepared by using additives like fillers, thickening agents, surfactants, flavoring agents, or sweeteners. Then the prepared homogenous liquid is filled in blister cavities and allowed to freeze dry [35].

6.9 Advatab

Advatab technology [34] offers combined effect, as it can be combined with Eurand’s technology such as Microcaps® taste masking technology and Diffucaps® (controlled release technology). The Microcaps® offers additive effects, as it can be combined with AdvaTab technology, which gives better mouth feel by masking the bitter of prepared dosage form. The combined technology unit disintegrates within 30s in the mouth.

6.10 KryotabTM

This technology involves formation of unit doses from lyophilized tablet products. Also, the water that must be escaped is introduced as ice particles and then allowed to combine with other excipient, and then subjected to compress at a low temperature. The porosity is reflected by both the size and the number of ice particles. Then to get the rigid tablets with higher tensile strength, binder is added into the formulation. Additionally, the binders in these formulations dissolve, which improves the adhesion property of the drug and additives used [36].

6.10 Nanocrystal technology

This technology provides numerous pharmacokinetic benefits to FDTs which are administered orally with a size smaller than 2µ. In this technology, water soluble additives

are combined with drug dispersion in the form of nanosized crystals before being lyophilized. In this technique, granulation and blending of tablet manufacturing processes are not implimented, so this technology can be a better substitute for potent drug candidate. This technology improves both drug property as well as the properties of the final formulated product [37].

6.11 FrostaT

In this technology, the porous and plastic granules are compressed at low pressure with enhanced water penetration followed by granulation with the addition of binding agent. The final formulation possesses high mechanical strength with quick disintegration time i.e., 15 to 30 s [38].

6.12 Quick-DisTM

In this technology oral film is prepared by solvent casting method using water as solvent followed by drying process. Thin, flexible, and easily dispensed film is produced by this technique. After oral administration, rapid dissolution of film produces local as well as systemic effects. The hot or cool extrusion method can be used as an alternate technique for preparing films [39].

Table 2. Patented technologies used in FDTs

Sr. No.	Technique Name	Mechanism	Owner	Drugs	Patent/ Year
1	Dura-solv	Molding	Cima Labs Inc	Hyoscyamine sulfate, Zolmitriptane	U.S. /1998
2	Flash Dose	Cotton candy process	Fuisz technology ltd. USA	Tramodol HCL	U.S./ 1997
3	Wow tab	Comresssion	Yamanouchi Pharma Technologies, Inc. Japan	Famotidine	U.S./2004
4	Zydis	Lyophilization	R.P. Scherer crop	Loratidine, Olanzapine	U.S./1996
5	Ora solv	Compression	Cima Labs	Paracetamol, Zolmitriptane	U.S./1991
6	Flash-tab	Lyophilization	Prographarm	Ibuprofen	U.S/1995
7	Lyoc	Multiparticulate compression	Cephalon Corporation	Phloroglucinol hydrate	E.U./1985
8	Frosta	Disintegration	Akina	---	U.S./2010
9	Nanocrystal	Dissolution	Elan Corporation	Loratidine	U.S./1996
10	Kryotab	Cryogenic Processing	Biotron labs	-------	U.S./2001

11	Advatab	Microcaps and Diffuscap CR Technology	Eurand International	Adva tab cetirizine, Advatab Paracetamol	WO/1997
12	Quickdis	Dissolution	Lavipharm Laboratories	---	I.P./2003

7. Drugs to be promising in co-operated in fast disintegrating tablets

The various drug candidates used in FDTs [2] are mentioned in Table 3.

Table 3. Various promising drug candidate for FDTs

Sr. No.	Technique Name	Mechanism
1	Alprazolam, Baritones, Bromazepam, Bentazepam	Sedative, Anxiolytic, Hypnotics, and Neuroleptics
2	Omeprazole, Ranitidine, Famotidine	Gastro intestinal agents
3	Quinidine sulphate, Amiodarone, Disopyramide	Anti arrhythmic agents
4	Carbamazepine, Methsuximide, Clonazepam, Methoin	Anti-epileptic agents
5	Carvedilol, Benidipine, Felodipine, Darodipine, Amlodipine, Dilitazem	Anti hypertensive agents
6	Clioquinol, Benzimidazole, Diiodohydroxyquinoline,	Anti protozoal agents
7	Indomethacin, Auranofin, Azapropazone, Benorylate, Etodolac, Ketoprofen, Ibuprofen	Analgesics and anti inflammatory agents
8	Nimuslide	Antipyretics
9	Vitamin A, B and D	Nutritional agents
10	Influenza, Hepatitis, Polio, Tuberculosis	Oral vaxccines
11	Glipzide, Tolbutamide	Anticoagulant
12	Chloroquine, Amodiaquine	Antimalarial
13	Allopurinol, Probencid	Anti-gout
14	Erythromycin, Tetracycline, Doxycycline, Rifampicin	Anti bacterial
15	Digitoxin, Digoxin	Cardiac inotropic agents
16	Albendazole, Cambendazole, Bephenium hydroxynaphthoate	Anthelmintics
17	Ondansetron	Gastroentritis
18	Olanzapine	Antipsychotic agents
19	Piroxicam, Rofecoxib	Non Steroidal Anti-inflammatory drugs
20	Prednisolone	Corticosteroid

8. Formulation aspects for FDTs

The important additives for FDTs are as follows:

8.1 Super-disintegrants

FDTs necessitate a quicker disintegration/ dissolution. As a result, researchers must discover super-disintegrants, or disintegrants that are effective even at low concentrations and have high disintegration efficiency. However, since super-disintegrating agents are hygroscopic, they are not utilized with moisture-sensitive medicines. Although super-disintegrants work by inflating the tablet, they cause it to rupture or create a significant increase in the surface area of granules, which facilitates disintegration/ dissolution owing to pressure applied in the outside or radial direction shown in Figure 4.

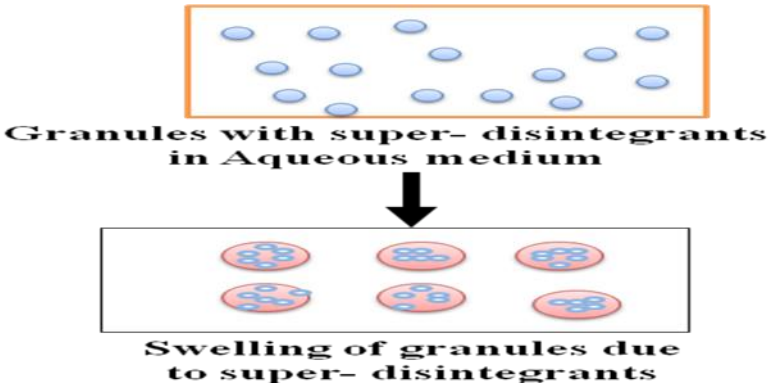


Figure 4. Mechanism of super-disintegrants

8.2 Taste-masking agents

Taste masking can be accomplished by restricting medication exposure to the buccal cavity by the inclusion of flavor masking compounds encapsulated in the polymer system or through complexation. The approaches are as follows:

- Using a binding agent, and a taste masking polymer as coating material, from a layer of medication onto inert beads.
- Granulating the medicine and covering it with a polymer that masks the taste.
- To get taste-masked drug particles, the medication dissolved in a polymer solution is spray dried.
- Inclusion in cyclodextrins for complexation.
- Bitterness in psychologically modulated.
- Microencapsulation into a polymer for coacervation.
- Extrusion spheronization for pellets formation.

- **Sweetener**

In effervescent goods, natural sweeteners like Sucrose and Sorbitol may be employed. Artificial sweeteners, on the other hand, are restricted by health administration. As a result, the usage of sweetening agents varies by country, depending on national norms. Sweeteners such as saccharin (sodium or calcium salts) are employed. In effervescent tablets, aspartame,

an artificial sweetener, is used as a sweetener. Previously, the artificial sweeteners of preference where cyclamates are cyclamic acid, but now-a-days their use is prohibited. Some commonly used sweeteners includes [3, 40].

- **Taste Masking**

  The tongue has around ten thousand taste buds, palate, cheeks, neck region and each taste bud contain around 60–100 types of receptor cells. These receptor cells interact with salivary chemicals to provide a positive and negative taste impression. In their natural condition, many medications are distasteful and unsatisfactory. To prevent interaction of medicine with taste buds and they're by eliminating or reducing the unpleasant response, physiological and physicochemical approaches have been used. FDTs stay in the oral cavity after disintegration into the saliva until they are ingested. If the medicine or formulation has a bitter taste, taste masking of medicine becomes a vital component in the formulation to ensure patient acceptance. FDTs now used sweet tasting chemicals as diluting agent, add flavours, or encapsulate the undesirable tasting medicine into tiny granules to disguise the taste.

- **Sweetening and flavouring agents**

  Additives derived from sugar have a negative heat of dissolution, disintegrate rapidly in the mouth, and gives the finished product a pleasant tongue feel while disguising the flavor. These additives or excipients are often utilized to provide a pleasant tongue sensation. WOWTAB employed carbohydrate and carbohydrate like (mannitol) excipient with “smooth melt action”. Sweeteners and flavors are also included in the Zydis dose form to hide an unpleasant taste. DuraSolv tablet was appropriately taste masked by the addition of sweetening and flavouring agent. Flosses and small spherical particles of sugars contain unpleasant drugs that are mixed with sweeteners and flavours to mask the taste.

8.3 Adjustment of pH values

Because the pH of many medicines differs from the pH of the mouth [25], which is about 5.9, many pharmaceuticals have poorer solubility in the mouth. The medications are not adequately solubilized to be tasted if the concentration is beneath the limits of the threshold pH. Therefore, drugs are not sufficiently solubilized to be available to taste. Adjustment of the pH of granules containing sildenafil was raised by dissolving them in aqueous medium with a dissolution inhibitor (calcium carbonate, sodium carbonate/bicarbonate/hydroxide). After that, a sweetener was added to conceal the bitter taste of medicine.

8.4 Encapsulation of unpleasant drugs

Sweetening and flavouring agents may not be enough to hide the taste of bitter medications in certain cases, thus other taste masking strategies must be used. The unpleasant medicine is often coated to prevent or delay the drug’s disintegration and solubilization. This gives the particles enough time to dissolve in the mouth before being ingested. To avoid exposure to the taste buds when utilizing a coating or encapsulation for taste masking, the bitter tasting

medicine must be completely coated. It is critical that the coating stays intact when in the mouth. Microcaps (Eurand) also use microencapsulation technology, which entails coating medication particles with a polymeric membrane. The procedure known as phase separation or coacervation is used to deposit this material in a liquid phase. This procedure may be useful for generating delayed or controlled release microcapsules with better flavor.

Microcapsules are typically 0.2-0.8 mm in size. Arrangement of microencapsulation with the help of coacervation technique, and subsequently coating of microcapsule with functional membrane with Eudragit L30D disguised the harsh taste of Linezolid. Taste masking of tiny particles like small crystals, granule, and pellets was done before compression of FDTs by coating them with dispersion of methacrylic acid, and ester copolymer (Eudragit RL 30 D, Eudragit RS 30 D, Eudragit L 30 D, and Eudragit NE 30 D).

The FDTs contain the taste-masking tiny granules of drug/API were made by extruding the medicines coated with copolymer amino alkyl methacrylate (e.g., Eudragit E100). Spray drying the medicine and cationic copolymer resulted in taste-masked quick release micromatrix powders. Taste-masking Cima's technology also involves covering the active component with a substance that prevents medication with an unpleasant taste from dissolving in the tongue. A Phase separation method was used to create taste-masked microcapsule. At a temperature where both polymers dissolve, a polymeric substance which is water insoluble is used to encapsulate medication which is dispersed in a non-polar solution and next polymeric substance that facilitates the quick phase separation of the primarily polymeric substance. When the temperature is decreased, phase separation forms the first polymeric layer, and the microencapsulated medication is generated. Removal of solvent and the next polymer substance from the solution produces microcapsule with masked taste. Because Orasolv tablets include an effervescent couple substance, they have a different mouth feel than typical orally dissolving tablets.

Drugs were simply combined with cyclodextrin, in addition to covering bitter-tasting drug particles. Then, formation of blend of drug with cyclodextrin without forming a traditional complex reported beneficial in distinguishing the unpleasant-tasting active components in FDTs [41].

9. Evaluation parameters of FDTs

9.1 Preformulation studies

9.1.1 Swelling index of superdisintegrants

The volume in milliliters filled by 1 g of medicine or other adherent mucilage, after the swelling of medicine in an aqueous solvent about 4 hours is known as swelling index (B.P. Vol. II, 1988). The swelling index was determined by using various polymers. The swelling index was derived using an average of three measurements.

9.1.2 Physical appearance

Organoleptic properties including color, state, aroma, and taste were used to evaluate the

physical appearance of pure drug.

9.1.3 Melting point determination

The pure drug's melting point was established using the capillary fusion technique. One end of the capillary is shut, while the other is filled with a little quantity of medicine. The capillary's sealed end was then inserted into the melting point device. With the thermometer given, the temperature at which the solid medication transforms into a liquid was recorded.

9.1.4 Determination of absorption maxima (λ max)

A 10 μg ml^{-1} drug solution using methanol as solvent was scanned on the UV spectrophotometer between 200-400nm in order to determine absorption maxima (λ_{max}) of the pure drug.

9.1.5 Preparation of calibration curve in different solvent

The required mg of medicine was dissolved in various solvents (100ml) like methanol, water, phosphate buffer etc. (Primary stock solution), and then take 50 ml of freshly prepared primary stock solution in volumetric flask (100 ml) and diluted with solvent up to 100 ml (secondary stock solution) of strength 250 go per ml. Aliquots were withdrawn from this secondary stock solution (0.1, 0.2, ……to 1 ml), and volume makeup was done up to 10 ml with solvents. Solvent was used to create concentrations of 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5 and 25.0 μg per ml, and the absorbance was determined using different solvents as blank.

9.1.6 Infrared spectral assignment

The qualitative identification of sample was carried out by IR analysis. A Fourier transformed infrared spectrophotometer was used to measure the drug's infrared spectra. The drug and KBr pellet were mounted on IR section and scanning was done at wavelength 4000 – 400 cm-1. The IR spectra was then compared with reference to pharmacopoeia.

9.1.7 Drug polymer interaction studies

When creating a rapid disintegrating tablet, it was critical to examine the drug's compatibility with the polymers utilized in the system. Under experimental circumstance, (40 ± 2˚ C and 75 ± 5 % RH) for one month, it is important to establish that there is no interaction between the polymers. The infrared spectra of medicine, and mixture of polymer and medicine were obtained between 4000 – 400 cm^{1}.

10. Characterization of Blends

The mixing procedure involves several formulations and process factors, all of which might alter the physicochemical quantities of the resulting blend, which determines the tablet quality. The fflow properties of blend were determined and mentioned in Table 4.

Table 4. Characterization of blend

S. No	Parameters	Description	Formula	Apparatus/ Equipment	Permissible range
01	Bulk Density	It is the wt. of powder divided by the bulk volume.	$\rho_b = Wt/V_t$ ρ_b - bulk density Wt -Weight of powder V_b - bulk volume	Measuring cylinder	-------
02	Tapped density	It is wt. of powder divided by the tapped volume.	$\rho_t = Wt/V_t$ ρ_t= bulk density V_t= tapped volume	Tapped density apparatus	--------
03	Angle of repose	It is the $\tan^{-1}$ of height of cone divided by radius of heap.	$\theta = \tan^{-1}(h/r)$	Funnel	≤ 25-40
04	Hausner's ratio	It is the indirect index of ease of blend flow.	$H_r = \rho_t / \rho_b$ Hr= hausner's ratio	Measuring cylinder	< 1.25 excellent
05	Compressibi-lity Index	It is the indication of the ease with which material can be induced to flow.	$I = \frac{\rho t - \rho b}{\rho t} X100$ I= compressibility index	Measuring cylinder	≤ 12-21

11. Characterization of Fast Disintegrating Tablets

The tablets were examined for physiochemical characteristics like general appearance, tablet thickness, weight uniformity, tablet hardness, friability, wetting time, disintegration, and dissolution tests after compression of tablets. These parameters are discussed in Table 5.

Table 5. Characterization of fast disintegrating tablets

S. No	Parameters	Description	Procedure	Apparatus/ Equipment
01	General appearance	This includes size, shape, color, odor taste and overall elegance of tablet.	These parameters are evaluated by visual recognition.	------
02	Tablet thickness	It is a significant parameter in both appearance and counting with filling equipment	Take 10 tablets and evaluate thickness using micrometer.	Micrometer, (Mityato Japan)
03	Weight uniformity	It is used for assessing the drug content homogeneity.	Separately and collective weight of 20 tablets were measured using digital balance.	Digital balance

04	Tablet hardness	Force needed to break a tablet per unit area.	10 tablets were taken and placed into hardness tester to check the hardness.	Monsanto hardness tester
05	Friability	This parameter works by combining the effect of abrasion and shock on the tablet during spinning of apparatus.	Place 10 tablets in the friabilator which were previously weighed and friabilator was rotated at rate of 25 rpm for 4 min. Then tablets were cleaned and their weight was noted again.	Roche Friabilator
06	Wetting time	It is the time taken by the tablet to get wetted completely.	A sheet of tissue paper folded twice was placed in small petri dish containing 10 ml of phosphate buffer at pH 6.8.	Petri dish
07	Disintegration	It is the time required by the tablet to break into tiny particle in a given set of conditions like temperature and pH.	6 tablets were placed in a cylindrical jar with a 10-mesh screen and filled with 6 ml phosphate buffer. Disintegration of tablets starts with the shaking of whole assembly.	Disintegration apparatus
08	*In-vitro* dissolution studies	It is used to measure the drug release rate from rapidly disintegrating tablet.	This test was performed at temp 37±0.5 ° C with phosphate buffer (900ml). Collection of sample (5ml) from the dissolving device was done at various time intervals. Then the collected sample solution were filtered through Whatmann filter paper and absorbance was check by using UV-Visible spectrophotometer	USP dissolution apparatus type II/ IP dissolution apparatus type-I. UV-Visible spectrophotometer
10	Drug content uniformity	It is used to measure the drug concentration by measuring absorbance in UV-Visible spectrophotometer.	10 tablets were crushed in to a fine powder after taking their weight, then quantity of powder equal to the weight of tablet was extracted in to phosphate buffer and filtered using Whatmann filter paper and absorbance was checked after suitable dilution with phosphate buffer.	UV-Visible spectrophotometer

12. Stability Studies [39-45]

The drug's optimized rapid disintegrating tablets were packaged in a wide mouth airtight glass container and kept at (40 ±2 Oc and 75 ±5% RH) for three months.

After 15 days, the tablets were extracted and spectrophotometrically examined for physical characteristics and drug concentration at standard nm. Among the several approaches tested for dissolution profile comparison, f2 was found to be most appropriate [43-44].

$$f2 = 50 \bullet \log [1+1/n^{2]-0.5} x\, 100$$

Here Rt= the cumulative percentage of drug dissolved at specific time 'n' points of reference.
Tt = the cumulative percentage of drug dissolved at specific time 'n' points of the test.
If the test and reference are similar that means f2 =100. All recorded time points yield a value of f2 =50 with a 10% mean difference. The FDA has proposed a standard f2 values from 50 - 100 to show similarity between two dissolution profiles [44].

13. Conclusion

The finding of this study reveals that quick disintegration tablets are the most palatable and precise oral dosage form, by passing first pass metabolism and demonstrating grater pharmacological response. Due to both patient compliance (pediatric, geriatric, psychotic, and travelling patients) and industrial acceptance, this dosage form is the most popular. Oral disintegrating tablets may be able to displace traditional tablets from the market due to decreased cost and customer desire. When immediate action is required, FDTs are the finest drug delivery strategy. When put in the buccal cavity FDTs dissolve or disintegrate within two minutes and do not need water for ingestion. Patients who need simple dosage anywhere any time and without water have been added to the target group. The tendency to give the benefits of a liquid drug in the shape of a solid dosage form is a significant advantage of FDTs dosage forms. Because innovative technologies are paired with significant market acceptability and patient demand, the prospect for such dosage forms is excellent.

Abbreviations

FDT: fast disintegrating tablet

FDS: fast disintegrating system

ODT: oral disintegrating tablets

RH: Relative humidity

UV: Ultra violet

API: Active pharmaceutical ingredients

KBr: Potassium bromide

Wt. Weight

IR: Infrared

USP: United state pharmacopoeia

Declaration

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Conflict of interest

The authors declared no conflict of interests.

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