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Review Article

FAST DISSOLVING TABLETS: A REVIEW

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ABSTRACT

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

Keywords: Fast dissolving tablets, FDTs, Superdisintegrants, Mouth dissolving tablets, MDTs

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INTRODUCTION

Formulation of drugs into a presentable form is the basic requirement and need of today. The dosage form is a mean of drug delivery system, used for the application of the drug to a living body. Various type of dosage forms are available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having a different type of drug delivery mechanisms. These classical/ modern dosage forms have some advantages and disadvantages. Therefore, the development of an ideal drug delivery system is a big challenge to the pharmacist in the presence scenario. In order to get the desired effect, the drug should be delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected [1].

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. 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. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [2].

The problem of swallowing is a common phenomenon in a geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Approximately one-third of the population (mainly paediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [3].

United States Food and Drug Administration (USFDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue" [3].

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds [5]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets(MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds,without the need to take water.

Recent market studies indicate that more than half of the patient population prefers FDTs to other dosage forms. Mouth dissolving tablets are formulated mainly by two techniques first use of super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone. Another method is maximising pore structure of the tablets by freeze drying and vacuum drying [5]. In all methods, direct compression is preferred because of its effortlessness, quick procedure and cost-effectiveness [1].

The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets [5].

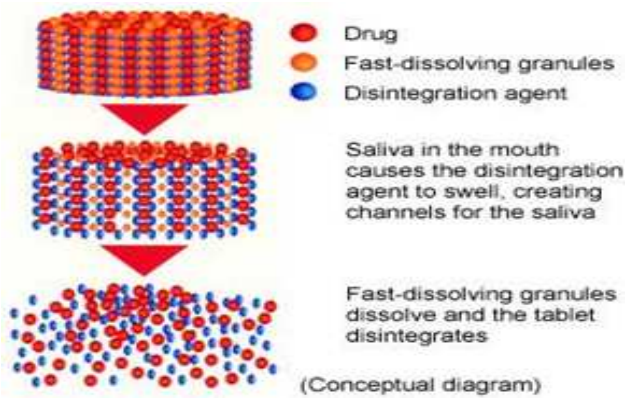

Fig. 1: Conceptual diagram of FDTs. [25]

Requirements of fast dissolving tablets

Patient factors [3]

Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

• Patients who have difficulty in swallowing or chewing solid dosage forms.

• Patients in compliance due to fear of choking.

• Very elderly patients of depression who may not be able to swallow the solid dosage forms

• An eight-year-old patient with allergies desires a more convenient dosage form than antihistamine syrup.

• A middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.

• A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.

• A patient with persistent nausea, who may be a journey, or has little or no access to water.

Effectiveness factor [5]

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulate ions in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fract ion of absorption in the oral cavity and pre-gastric segments of GIT.

Manufacturing and marketing factors [11]

As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation and extend patent protection. For examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U. S. in 2005 in response to a generic challenge filed in the U. S. by Ranbaxy.

Advantages of fast dissolving tablets [6, 7]

• No need of water to swallow the tablet.

• FDTs can be easily administered to pediatric, elderly and mentally disabled patients.

• Accurate dosing as compared to liquids.

• Dissolution and absorption of the drug is fast, offering rapid onset of action.

• Bioavailability of drugs is increased10as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down into the stomach.

• Advantageous over liquid medication in terms of administration as well as transportation.

• First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.

• offering improved safety.

 Suitable for sustained/controlled release actives.

 Allows high drug loading.

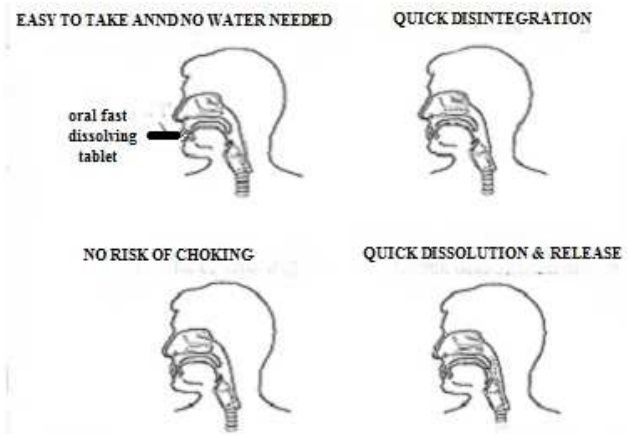

Fig. 2: Advantages of FDT [6]

Limitations of fdts [4, 5]

• The major disadvantages of FDTs is related to the mechanical strength of tablets.

• FDT are very porous and soft molded metrics or compressed in a tablet with low compression, which makes tablet friable and brittle which difficult to handle.

• Bad tastes drugs are difficult to formulate as FDT; special precaution should have to be taken before formulate such kind of drug.

• Several FDT are hygroscopic cannot maintain physical integrity under normal condition from humidity which requires specialized package.

• Dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

• Rate of absorption from the saliva solution and overall bioavailability.

•Drug and dosage form stability.

Salient features of fast dissolving tablets or fast dissolving drug delivery system [3, 4, 11]

• Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, a patient affected by renal failure and patient who refuse to swallow such as paediatric, geriatric and psychiatric patients.

• No need of water to swallow the dosage form, which is a highly convenient feature for patients who are travelling and do not have immediate access to water.

• Rapid dissolution and absorption of the drug, which will produce the quick onset of action.

• Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is increased.

• Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage;

Improve clinical performance through a reduction of unwanted effects.

• Good mouth feels property helps to change the perception of medication as a bitter pill particularly in the pediatric patient.

• The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

• New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.

• Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required.

• An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets. Stability for a longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines the advantage of the solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

• Adaptable and amenable to existing processing and packaging machineries.

• Allow high drug loading, Cost effective.

Challenges to develop FDTs [3, 10]

Palatability

As most drugs are unpalatable, FDTs usually contain the medicament in a taste-masked form. FDTs after administration, it disintegrates or dissolves in 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 [3, 11].

Mechanical strength and disintegration time

In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrix or compressed into tablets 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 add to the cost. [3, 11] Only wow tab and durasolv technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi-dose bottles [3].

Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity [3, 11] Hence, they need protection from humidity which calls for specialized product packaging [3].

Amount of drug

The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be less than 400 mg for insoluble drugs and 60 mg for soluble drugs [3, 11] this parameter is particularly challenging when formulating a fast-dissolving oral films or wafers [3].

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they 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 process [3, 5, 11] Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol that can induce crystallinity and hence, impart rigidity to the amorphous composite [3].

Size of tablet

The ease of administration of a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve [3, 5].

Mouth feel

FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible. Moreover addition of flavours and cooling agents like menthol improve the mouth feel [5].

Sensitivity to environmental conditions

FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water [5].

Criteria for excipient used in formulation of FDTs [5, 10-13]

- Their individual properties should not affect the FDTs.
- It must be able to disintegrate quickly.
- It should not have any interaction with drug and other excipients.
- When selecting binder (a single or combination of binders) care must be taken in the final integrity and stability of the product.
- The melting point of the excipients used should be in the range of 30-35 °C.
- It should not interfere in the efficacy and organoleptic properties of the product.
- The binder may be in liquid, semi-solid, solid or polymeric in nature.

Excipients used in FDT preparation [5, 13-20]

Excipients used in FDTs contain at least one super disintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavouring agents.

Table 1: Name and weight percentage of various excipients in FDTs [1, 15]

S. No.	Name of the excipients	% used
1.	Superdisintegrants	1-15%
2.	Binders	5-10%
3.	Antistatic agent	0-10%
4.	Diluents	0-85%

- **Superdisintegrants [13, 14, 17]**

As day's passes, demand for the faster disintegrating formulation is increased. So, the pharmacist needs to formulate disintegrants i.e. super disintegrants which are effective at low concentration and have greater disintegrating efficiency, and they are more effective intragranular. These super disintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes the tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

• Factors to be considered for selection of super disintegrants [5, 16, 23]

Disintegration

The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressure necessary to provide rapid disintegration in the mouth.

Compactibility

It is desirable to have FDT with acceptable hardness and less friability at a given compression force to produce robust tablets that avoid the need to use specialised packaging while maximising production speed.

Mouthfeel

Large particles can result in a gritty feeling in the mouth.

Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water, however, it produces a gummy texture that many consumers find objectionable.

Flow

In typical tablet formulation, super disintegrants are used at 2-5 wt % of the tablet formulation. With FDT formulation, disintegrant level can be significantly higher [16].

Table 2: List of super disintegrants [5, 23]

S. No.	Superdisintegrant	Mechanism of action	Specific properties
1.	Croscarmellose Sodium	Swells 4–8 folds in<10 s. Swelling and wicking action	Effective in low concentration (0.5–2.0%), high swelling capacity, cross-linking of the carboxyl ester groups.
2.	Crospovidone	Combination of swelling and wicking action. Swells 7–12 folds in<30 s.	The effective concentration is 1–3%. Rapidly disperses and swells in water, available in micronized grades.
3.	Cross-linked alginic acid	Hydrophilic colloidal subs-tance which has high sorption capacity.	The combination of swelling and wicking action causes disintegration.
4.	Gellan gum	Strong swelling properties upon contact with water.	Anionic polysaccharide of linear tetrasaccharides, good superdisinte -grants property similar to the modified starch and celluloses.
5.	Sodium starch glycolate	Strong swelling properties upon contact with water. Swells 7–12 folds in<30s.	Rapid absorption of water results in swelling up to 6%, high concentration causes gelling.
6.	Soy polysaccharide	Rapid dissolving	Does not contain starch or sugar so can be used in products meant for diabetics.
7.	Xanthan gum	Extensive swelling prop- erties for faster disintegration.	High hydrophilicity and low gelling tendency, low water solubility.

- **Bulking materials [7, 23]**

Bulking materials are important in the development of fast dissolving tablets. They contribute the functions of a diluent, filler and cost reducer. Bulking agents improve the texture of the tablets that consequently enhances the disintegration in the mouth, besides adding volume and reducing the concentration of the active in the formulation. The bulking agents for this dosage form should be more sugar-based such as mannitol, polydextrose, lactose derivatives such as directly compressible lactose (DCL) and starch hydrolysate for higher aqueous solubility and good sensory perception. Mannitol especially has high aqueous solubility and good sensory perception, as it provides a cooling effect due to its negative heat of solution. Bulking agents are added in the range of 10% to about 90% by weight of the final composition.

The descending order of brittleness of excipients is ranked as microcrystalline cellulose>alpha lactose monohydrate>spray-dried lactose>anhydrous beta lactose>anhydrous alpha lactose>> dicalcium phosphate dihydrate.

The commonly used sugar-based excipients are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which exhibit high aqueous solubility and sweetness thereby contribute taste masking property and provide pleasant mouth feel.

Sugar based excipients can be of types on the basis of moulding and dissolution rate:

Type 1 saccharides: (lactose and mannitol) which exhibit low moldability but high dissolution rate.

Type 2 saccharides: (maltose and maltitol) which exhibit high moldability but low dissolution rate.

- **Emulsifying agents [5, 23]**

Emulsifying agents are significant for formulating fast dissolving tablets as they help in quick disintegration and drug release without the need for chewing, swallowing or drinking water. Also, emulsifying agents stabilize the immiscible blends and increase bioavailability. A variety of emulsifying agents for fast dissolving tablet formulations include alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These can be added in the range of 0.05% to about 15% by weight of the final formulation.

- **Lubricants [5, 12]**

Though not essential excipients, these can aid in making the tablets more palatable after they disintegrate in the mouth. Lubricants reduce grittiness and help in the drug transit process from the oral to the stomach.

- **Flavours (taste masking agents) and Sweeteners [5, 23]**

Flavours and taste masking agents make the products more palatable and pleasing for patients. The incorporation of these ingredients assists in overcoming bitterness and undesirable tastes of some actives. Natural as well as synthetic flavours can be used to enhance the organoleptic characteristic of fast dissolving tablets. A wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose are available. The addition of sweeteners imparts a pleasant taste as well as bulk to the formulation.

Techniques for preparing fast dissolving tablets

Conventional technologies

Various conventional manufacturing techniques for FDDDS

Freeze-drying or lyophilization [2]

It is a pharmaceutical process that allows the drying of heat sensitive drugs and biological under low temperature by the application of vacuum to remove water by sublimation. Drugs are dissolved or dispersed in aqueous solution of a carrier, transferred to preformed blister packs and subjected to nitrogen flush to freeze out, then placed in the refrigerator to complete the process. Characteristics of lyophilization techniques are, they possess high porosity and specific surface area, and gets dissolve rapidly in mouth presenting high drug bioavailability. The major drawback of this system is high cost, time-consuming procedure and fragility, making conventional packing inappropriate for packing this dosage form and stability issues under stress condition.

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.

Moulding method [19]

Tablets are designed using hydrophilic ingredients, with the aim to get maximum drug dissolution. Powder mass is wetted with hydroalcoholic solvent and compressed into a dosage form. The solvent system is then allowed to evaporate. Taste of drug particles is developed by spray congealing the molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethene glycol with an active ingredient into lactose based tablet triturate. Characteristics of moulding method are, very porous as solvents are removed by drying leaving porous mass which promotes rapid dissolution.

Melt granulation [24, 25]

Melt granulation technique is a process by which the pharmaceutical powders are capably agglomerated by a meltable binder. The benefit of this technique compared to a conventional granulation is that no water or organic solvents is required. Since there is no drying step, the process is less time consuming and requires less energy than wet granulation. It is a technique useful to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

Mass-extrusion [24, 25]

In this the mixed ingredients are softened by water soluble ingredient i.e. polyethene glycol, using methanol as solvent, passing through an extruder to form thin cylinders. Which further get sliced with a heated blade to form small tablets. Characteristics of this method is these products can be used to mask bitter tasting drugs making small granules thus enhancing oral bioavailability.

Sublimation [18]

Rapid disintegration and dissolution is acquired by formulating into porous mass by incorporating inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate and hexamethylene-tetramine. They were mixed with other ingredients and compressed. The volatile material is evolved by reduced pressure and applying slight temperature leaving the mass in porous form. Characteristics of sublimation method are, they are porous in nature, solvents like cyclohexane and benzene can be used.

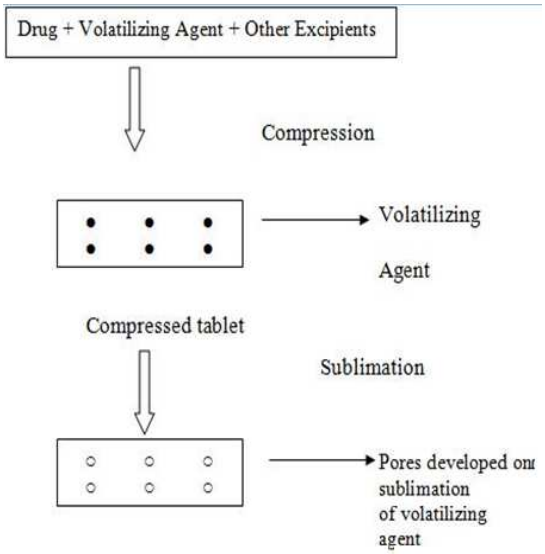

Fig. 3: Schematic diagram of sublimation techniques for preparing fast dissolving tablets [24]

Direct compression [4]

The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets due to certain advantages:

- High doses can be accommodated and final weight of the tablet can exceed that of other methods.
- The easiest way to manufacture the tablets.
- Conventional equipment and commonly available excipients are used.
- A limited no. of processing steps are involved.
- Cost effectiveness.

Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration and high dissolution rates. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

MILLING → SIEVING → MIXING → COMPRESSION

Fig. 4: Process of direct compression [25]

Table 3: Ideal requirements, advantages and limitations of direct compression [25]

S. No.	Ideal requirements	Advantages	Limitations
1.	Flowability	Cost effective production	Segregation
2.	Compressibility	Better stability of API	Variation in functionality
3.	Dilution Potential	Faster dissolution	Low dilution potential
4.	Reworkability	Less wear and tear of punches	Reworkability
5.	Stability	Simple validation	Poor compressibility of API
6.	Controlled Particle Size	Low microbial contamination	Lubricant sensitivity

Cotton candy process [5]

This process is so named as it utilises a unique spinning mechanism to produce a floss-like crystalline structure, which mimics cotton candy. Cotton candy process involves the formation of Matrix of polysaccharides or saccharides by the simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDTs.

However, other polysaccharides such as poly maltodextrins 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 mouth feel due to fast solubilization of sugars in the presence of saliva.

Spray-drying [21]

By this method, ingredients are integrated by hydrolyzed and nonhydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e. g. citric acid) and or alkali material (e. g. sodium bicarbonate) to enhance disintegration and dissolution. Characteristics of the spray-drying method is this method gives rapid dissolution (within 20 seconds) when dosage form gets in contact with the aqueous medium.

Phase transition process [25]

This processes for the disintegration of FDTs by phase transition of sugar alcohols using erythritol (melting point 122 °C), xylitol (93-95 °C), trehalose (97 °C), and mannitol (166 °C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before the heating process, the tablets do not have sufficient hardness because of low compatibility.

The tablet hardness was increased after heating, due to the increase of interparticle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

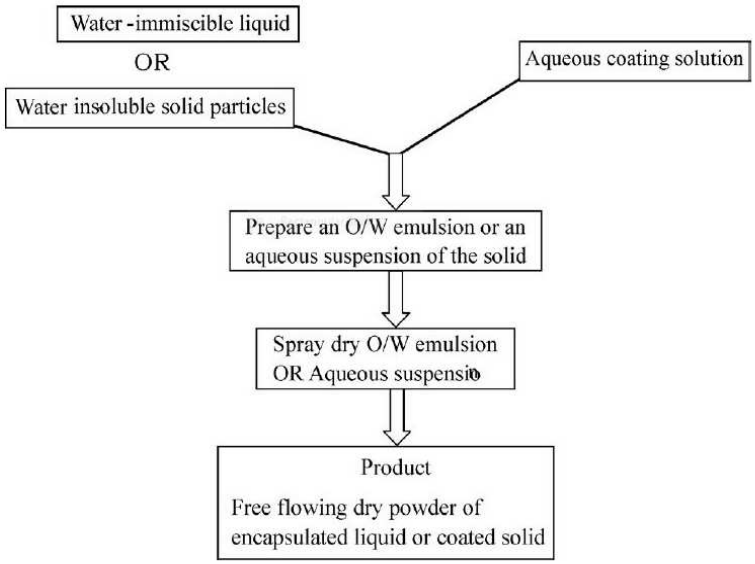

Fig. 5: Flow chart for coating liquid and solid particles using spray-drying process [24]

Nanoionization [25, 27-29]

A recently developed nanomelt technology involves a reduction in the particle size of the drug to nano size 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 MDTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and a wide range of doses (up to 200 mg drug per unit).

Oral disintegrating or fast dissolving thin films [25-29]

It is a new frontier in immediate release tablet that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethylcellulose, hydroxypropyl methyl cellulose, hydroxyl ethyl cellulose, hydroxyl propyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In the case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in the mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper-thin films of size less than 2×2 inches, dissolution in 5 sec, instant drug delivery and flavoured aftertaste.

Patented technologies for fast dissolving tablets

Rapid-dissolving characteristic of FDTs is generally attributed to fast penetration of water into tablet matrix resulting in its fast disintegration. Several technologies have been developed on the basis of formulation aspects and different processes and patented by several pharmaceutical companies. Patented technology is described below: [30]

Zydis technology [30]

Zydis formulation is a unique freeze-dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength.

Limitations

•The amount of drug could be incorporated should generally be less than 400 mg for insoluble drugs and less that 60 mg for soluble drugs.

• The particle size of the insoluble drugs should not be less than 50 µm and not more than 200 µm to prevent sedimentation during processing.

Advantages

• Buccal pharyngeal and gastric regions are all areas of absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism.

• The Zydis formulation self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

• Patients who have difficulty swallowing oral medication due to dysphagia, stroke or medical conditions such as gastroesophageal reflux disease, multiple sclerosis or Parkinson's disease.

Disadvantages

• The process of freeze-drying is a relatively expensive manufacturing process.

• The formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses.

• It has poor stability at higher temperatures and humidities.

• A water insoluble drug can be incorporated only up to 400 mg per tablet or less. On the other hand water, the soluble drug can be incorporated only up to 60 mg.

Orasolv technology [5, 10]

Orasolv technology has been developed by CIMA labs. In this system, the active medicament is taste masked. It also contains the effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimise oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

Advantages [30]

Taste-masking is two-fold, quick dissolution. This technology has been used for drug strengths in the range of 1 mg to 750 mg. Depending on formulation and tablet size, the disintegration time of the tablet can be designed in the range of 10 to 40 seconds.

Disadvantages [30]

They are sensitive to moisture due to the presence of the effervescent system and must be packaged appropriately. Low mechanical strength.

Durasolv technology [4, 5]

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

Advantages [30]

DuraSolv technology is good for tablets having a low amount (125 mcg to 500 mg) of active ingredients and tablets are compressed to a greater hardness of 15-100 N, resulting in a more durable ODT. As a result, this technology enables packaging flexibility; tablets can be bottled and blistered.

Disadvantages [30]

The technology is not compatible with larger doses of active ingredients because the formulation is subjected to high pressure during compaction. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter tasting drugs to the patient taste buds.

Wow tab technology [4, 5, 30-31]

Wow, tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". In this process, a combination of low moldability saccharides and high moldability saccharides is used to obtain a rapidly melting strong tablet. The combination of high and low moldability is used to produce tablets of adequate hardness.

Advantages

Adequate dissolution rate and hardness. Wow, tab product can be packed in both into the conventional bottle and blister packs.

Disadvantages

No significant change in bioavailability.

Flash dose technology [4, 23, 30]

Flash dose technology has been patented by Fuisz. Nurofen melt let, a new form of Ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as floss. Shearform matrices are prepared by flash heat processing.

Advantages

High surface area for dissolution

Disadvantage

• High temperature required to melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity.

• The dosage form can accommodate only up to 600 mg of drug.

• Tablets produced are highly friable, soft and moisture sensitive. Therefore specialised packing is required.

Flashtab technology [38, 39]

The flashtab technology is yet another fast-dissolving/disintegrating tablet formulation.

Prographarm laboratories have patented the flashtab technology. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute.

Oraquick technology [30-33]

K. V. S. Pharmaceuticals have a patent over this technology. It utilizes taste masking microsphere technology called as micromask, which provides superior mouth feel over taste masking alternatives, significant mechanical strength, and quick disintegration/ dissolution of the product. Any kind of solvents are not utilized by taste masking process. Therefore it leads to superior and fast efficient production.

Advantages

Faster and efficient production, appropriate for heat-sensitive drugs

Dispersible tablet technology [5]

Lek in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methanesulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of organic acids. One of the essential excipients in the cimetidine formulate ion a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross–linked sodium carboxymethylcellulose, and cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.

Advatab technology [39]

Advatab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. Advatab is distinct from other FDT technologies as it can be combined with Eurand's complimentary particle technologies like its

world leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

Nanocrystal technology [5, 12, 30]

For fast dissolving tablets, elan's proprietary nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using nanocrystal technology. Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

Nanocrystal fast dissolving technology provides for

• Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix.

• Product differentiation based upon a combination of proprietary and patent protected technology elements.

• Cost-effective manufacturing processes that utilize conventional, scalable unit operations.

Pharmabust technology [5, 12]

Pharmaburst technology is being patented by SPI pharma. The tablet manufactured by this process involves a dry blend of a drug, flavors, and lubricant then followed by compression into tablets which then dissolve within 30-40 seconds. Tablets manufactured by this methodology have sufficient strength can be packed in blister packs and bottles.

Frosta technology (Akina) [5, 12, 13]

This technology is patented by Akina. Frosta technology utilizes the core concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. The process involves mixing the porous plastic material with water penetration enhancer and followed by granulating with a binder.

Table 4: Patents on fast dissolving drug delivery system or FDTs. [4, 6, 7, 40]

S. No.	Author	Drug	Method/polymer	Inference
1.	Lee *et al.* (2013)	Megestrol	Spray drying	Quicker dissolve and mask the bitter taste of drugs.
2.	Szamosi *et al.* (2013)	Phenyl Propano-Lamine HCl	Direct compression	Melt at 37. c and low compression force.
3.	Constantine (2011)	Ondasetron	Polyethylene glycol	Used of the bioactive agent and in the treatment of dysphagia.
4.	Singh *et al.* (2006)	Nimesulide	Sodium starch glycolate	Dissolve or disintegrate in digestive organs.
5.	Aggarwal *et al.* (2005)	Galanthamine	Direct compression	Used in Alzheimer's disease.
6.	Callihan *et al.* (2005)	Aspirin	Direct compression	Mannose provide rapid dis-integration anddissolution.
7.	Szamosi *et al.* (2005)	Ibuprofen	Direct compression	Provide excellent mouth feel.
8.	Khawla *et al.* (2004)	Ibuprofen	Melt extrusion	Very low compression force.
9.	Callihan *et al.* (2004)	Caffeine	Direct compression	Rapid dissolution.
10.	John *et al.* (2003)	Active Substance	Freeze drying	Rapid disintegration.
11.	Abu-lzzakawla *et al.* (2005)	Ibuprofen	Direct compression	Low melting point of compound use.
12.	William *et al.* (2001)	Efavirenz	Wet granulation	Used in HIV.
13.	Gilis *et al.*(2000)	Galanthamine HBr	Direct compression	Used in treatment of Alzheimer's dementia.
14.	Warner Lambert Co. *et al.* (1998)	Active substance	Direct compression	Use low density granules.
15.	Makino *et al.* (1996)	Active substance	Compression molding	High adequate strength disintegration and dissolving rate.

Table 5: (A) Work done on fast dissolving drug delivery system or FDTs: [3, 4, 40]

S. No.	Author	Drug	Method	Inference
1.	Durgabhavani *et al.* (2016)	Valsartan	Vaccum drying technique	Improved disintegration time.
2	Karia *et al.* (2015)	Olmesartan medoxomil	Co-processed excipients technique	Better *in vitro* drug release.
3	Subbaiah *et al.* (2015)	Amoxicillin Trihydrate and Potassium clavunate	Direct compression	Improved disintegration time and *in vitro* drug release.
4	Munde *et al.* (2015)	Lansoprazole	Direct compression	Improved *in vitro* drug release
5.	Metkari *et al.* (2014)	Carbamazepine	Direct comp. using solid dispersion	Good Dissolution Profile with short disintegration time.
6.	Babu *et al.* (2014)	Carbamazepine	Direct compression	*In vitro* drug release increased.
7	Arunachalam et. al (2013)	Levofloxacin	Direct compression	Improved disintegration time.
8	Valera et. al (2013	Amoxicillin Trihydrate and Potassium clavunate	Dry granulation method	Improved *in vitro* drug release
9.	Rawat et. al (2013)	Pioglitazone hydrochloride	Direct compression	Improved patient compliance.
10.	Saroha et. al (2013)	Amoxicillin Trihydrate	Direct compression	Better disintegration rate.
11.	Bhati et. al (2013)	Metoclopramide hydrochloride	Direct compression	Improved patient compliance in pediatricand geriatric.
12.	Layer *et al.* (2013)	Risperidone	Solvent evaporation method	Enhanced dissolution andincrease bioavailability.
13	Singh et. al (2013)	Amoxicillin Trihydrate and Potassium clavunate	Wet granulation method	Improved *in vitro* drug release.
14.	Rao *et al.* (2012)	Fosinopril	Sublimation method	Increase rate of dissolution and bioavailability.
15.	Rao *et al.* (2012)	Fosinopril	Direct compression	Used in treatment of various cardiovascular disorder.
16.	Bhupati *et al.*(2012)	Terbutaline Sulphate	Direct compression	Maintain Therapeutic concentration and enhance and improve bioavailability.

The technology can be used for almost any drugs including market place and extension of patent term of innovator. The clinical studies show FDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. Considering the many benefits of FDTs, it is only a matter of time until a majority of oral formulations are prepared in FDT forms.

Table 5: (B) Work done on fast dissolving drug delivery system or FDTs [3, 4, 7, 40]

S. No.	Author	Drug	Method	Inference
17.	Dewalkar *et al.* (2012)	Ziprasidone	Direct compression	Show better parameter by using crospovidone as super disintegrant.
18.	Swamy *et al.* (2012)	Enalapril maleate	Direct compression	Improved disintegration time.
19.	Rao *et al.* (2012)	Baclofen	Direct compression	Enhanced bioavailability.
20.	Sharma *et al.* (2011)	Aceclofenac	Direct compression	Intended benefits.
21.	Pandey *et al.* (2011)	Ampicillin and Cloxacillin	Direct compression	Faster disintegration and drug release
22.	Daram *et al.* (2011)	Ketorolac Tromethamine	Direct compression	Faster disintegration anddrug release.
23.	Gaur *et al.* (2011)	Aceclofenac	Sublimation method	Enhance patient compliance and using a sublimating agent.
24.	Rizwanulla *et al.* (2011)	Oxcarbazepine	Direct compression	Better patient compliance and Maximum dissolution rate.
25.	Panwar *et al.* (2011)	Piroxicam	Direct compression	Prolonged therapeutic action.
26.	Rao *et al.* (2010)	Carbamazepine	Direct compression	Improved bioavailability and effectiveness.
27.	Ravikiran *et al.* (2010)	Piroxicam	Direct compression	Improved dissolution.
28.	Tiwari *et al.* (2010)	Celecoxib	Holt melt extrusion	Enhanced bioavailability.
29.	Narmada *et al.* (2009)	Amlodipine Besylate	Sublimation method	Acceptable Friability by design full factorial method.
30.	Singh *et al.* (2009)	Combination of Omeprazole and Domperidone	Direct compression	Enhance patient compliance.
31.	Patel *et al.* (2009)	Glipizide	Direct compression	Enhance patient compliance.
32.	Patel *et al.* (2008)	Etoricoxib	Sublimation method	Improved dissolution.

Lyo (Pharmalyoc) [5, 12, 13]

Oil in watr emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. A high proportion of filler reduces the porosity of tablets due to which disintegration is lowered.

Sheaform technology [5]

The technology is based on the preparation of floss that is also known as, shear from matrix, which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass.

The floss so produced is amorphous in nature, so it is further chopped and recrystallized by various techniques.

Marketed products of fast dissolving tablets

The commercialised products of FDT which are available in the market are given in table no. 6 and 7.

Table 6: Fast dissolving tablets products available in Indian market [2-8]

Brand (Trade) name	Active drug	Manufacturer/Company
Acepod-O	Cefpodoxime	ABL Lifecare, India
Acufix DT-TAB	Cefixime	Macleods, India
Alepam	Amoxycillin trihydrate and Potassium clavulanate	Scoshia Remedy, India
Bigcef DT-TAB	Cefuroxime	Bestochem, India
Clonazepam ODT	Clonazepam	Par Pharmaceutical
Dompan	Pantoprazole and Domperidone	Medley pharmaceuticals, India
Mosid-MT	Mosapride citrate	Torrent Pharmaceuticals, Ahmedabad, India
Minoclav DT-TAB	Amoxycillin trihydrate and Potassium clavulanate	Minova life Sciences, India
Nulev	Hyoscyamine sulfate	Schwarz Pharma, India
Nimulid MDT	Nimesulide	Panacea Biotech, New delhi, India
Numoxylin CV DT	Amoxycillin trihydrate and Potassium clavulanate	Gepach international, India
Zyrof Meltab	Rofecoxib	Zydus, Cadila, India
Romilast	Montelukast	Ranbaxy Labs Ltd., New Delhi, India
Torrox MT	Rofecoxib	Torrent Pharmaceuticals, Ahmedabad, India
Olanex Instab	Olanzapine	Ranbaxy Labs Ltd., New Delhi, India
Kemstro	Baclofen	Schwarz Pharma, India
Romilast	Montelukast	Ranbaxy Lab. Ltd. Delhi, India
Rofaday MT	Rofecoxib	Lupin,, India
Valus	Valdecoxib	Glenmark, India
Zinase-Clav	Amoxycillin trihydrate and Potassium clavulanate	Rapross Pharmaceuticals Pvt Ltd, India

Table 7: Fast dissolving tablets products available in international market [2-6]

Brand (Trade) name	Active drug	Manufacturer/company
Benadryl Fastmelt	Diphenhydramine and Pseudoephedrine	Warner-Lambert, NY, USA
Claritin redi Tab	Loratidine	Schering-Plough Corp.,USA
Domperidon Ebb	Domperidon	Ebb medical, Sweden
Domperon	Domperidon	Astra Pharma, Bangladesh
Feldene Fast Melt	Piroxicam	Pfizer Inc., NY, U. S. A
Febrectol	Paracetamo	Prographarm, Chateauneuf, France
Gaster D	Famotidine	Yamanouchi
Imodium Istant Melts	Loperamide HCL	Janssen, UK
Maxalt MLT	Rizatriptan	Merck and Co., NJ, U. S. A
Nasea OD	Ramosetoron HCl	Yamanouchi
Klonopin Wafers	Clonaxepam	Roche Laboratories
Pepcid RPD	Famotidine	Merck and Co., NJ, U. S. A
TempraQuiclets	Acetaminophen	Bristol-Myers Squibb NY, USA
Zelapar TM	Selegiline	Amarin Corp., London, UK
Zyprexia	Olanzapine	Eli Lilly, Indianapolis, USA
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK

CONCLUSION

Fast dissolving tablets are innovative dosage forms developed and specially designed to overcome some of the problems that seen in conventional solid dosage form i.e. difficulty in swallowing of the tablet in geriatric and pediatric patients. Fast dissolving tablets are designed to dissolve or disintegrate quickly in the saliva generally within less than 60 seconds (range of 5-60 seconds). Fast dissolving tablets have better patient compliance and acceptance may improve biopharmaceutical properties, bioavailability improved efficacy, convenience, and better safety compared with conventional oral dosage forms. The popularity of FDTs has increased fabulously over the last decade. FDTs need to be formulated for psychotic patients, bedridden, geriatric, pediatric patients, for those patients who may not have access to water, patients who are busy in traveling. FDTs formulations formulated by some of these convetional and patent technologies and FDTs have sufficient mechanical strength, quick disintegration/dissolution in the buccal cavity without water. The newer technologies utilized for the formulation of the FDTs that provide more effective dosage forms with more advantages and minimal disadvantages.

CONFLICT OF INTERESTS

Declare none

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