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Review article

FAST DISSOLVING TABLETS OF POORLY SOLUBLE DRUGS: PREPARATION, CHARACTERIZATION AND EVALUATION: AN OVERVIEW

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ABSTRACT: Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Fast-dissolving drug-delivery systems (FDDS) were first developed in the late 1970s as an alternative to tablets, capsules, and syrups. Products of FDTs technologies entered into the market in the 1980. This has encouraged both academia and industry to generate new orally disintegrating formulations and technological approaches in this field. At present 40% of the drugs in the development stages and approximately 60 % of the drugs are poorly soluble. The poor solubility of drugs is a big challange for industry, for the development of the solid dosage form drugs. Drugs having slow dissolution rate show the incomplete absorption and low bioavailability when orally administered. Various technologies are applied for the enhancement of solubility such as micronization technology, solid dispersion technology, complexation technology etc. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by the pharmaceutical companies. Generic drug manufacturers will also need to employ economically efficient methods for the delivery of poorly soluble drugs in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry.

Keywords: Bioavailability, dissolution rate, fast-dissolving drug-delivery system, poorly soluble drugs.

INTRODUCTION:

1. Fast dissolving Drug Delivery System

For most therapeutic agents used to produce systemic effects, the oral route represents the perfect way of administration and having several advantages and high patient compliance in comparison to many other routes (Valleri *et al.*, 2004)

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of easy self administration, compact in nature, easy to manufacture and it can be deliver in accurate dose. The problem of swallowing is common phenomenon in geriatric patient due to fear of

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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. Difficulties in swallowing of tablet and capsule are also occurs when water is not available. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention (Seager 1998)

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue."European Pharmacopoeia described orally disintegrating tablets as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within 3 min" (Yourong *et al.,* 2004 and Bandari *et al.,* 2008)

Fast dissolving tablets are also define as mouth-dissolving tablets, melt-in mouth tablets, Oral dispersible tablets, rapimelts, porous tablets, quick dissolving tablet.

1.1 Criteria for Fast dissolving Drug Delivery System:

The tablet should (Bhowmik *et al*., 2009):

- Water is not required for swallowing.
- Be compatible with taste masking.
- Have a good mouth feel.
- After administration of drug have either minimum or no residue in mouth.
- Have Low sensitivity for environmental condition such as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

1.2 Advantage of Fast Dissolving Drug Delivery System:

- Ease of administration in swallowing.
- Rapid dissolution rate and absorption of the drug, which will produce quick onset of action.
- Bioavailability can be increased due to pregastric absorption.
- Due to reduction of dose; improve clinical performance through a reduction of unwanted effects.
- The risk of chocking during oral administration is avoided.
- Have benefit when an ultra rapid onset of action required such as in motion sickness, allergic attack and in case of coughing.
- Bioavailability can be increasd, particularly in cases of hydrophobic drugs.
- Ability to provide advantage of liquid medication in the form of solid preparation.
- Due to stability for longer duration of time fast dissolving tablets shows the advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.2 Selection of drugs:

For the selection of drug, there are following criteria (Arya *et al*., 2010):

- No bitter taste.
- Dose lower than 20mg.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially unionized at the oral cavities pH.
- Oral mucosal tissue can be permeated.

2. ENHANCEMENT OF SOLUBILITY

Solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at a specific temperature. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality , volume fraction, mole fraction. The Indian Pharmacopoeia defines solubility in terms of number of millilitres of solvent required to dissolve 1g of solute.

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability and dissolution rate. These factors govern the rate and extent of oral drug absorption from immediate release solid oral-dosage forms. It classifies drugs into four classes. Which are shows into the table 1:

Table 1: Biopharmaceutical classification system

		Low	High
Permeability	High	I	II
	Low	III	IV
	Solubility		

Model list of Essential Medicines of the World Health Organization (WHO) has assigned BCS (Biopharmaceutics Classification System) classification on the basis of data available in the public domain. Out of 130 orally administered drugs on the WHO list, 61drugs could be classified with certainty (chavda *et al.*, 2010).

- 84% of these drugs belong to class I
- 17% of these drugs belong to class II
- 39% of these drugs belong to class III
- 10% of these drugs belong to class IV

The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility (Lindenberg *et al.*, 2004)

2.1 Techniques for Solubility Enhancement

There are following techniques (Kumar *et al.*, 2013):

2.1 Particle size reduction technology
2.2 Polymorphism technology
2.3 Drug dispersion technology
2.4 Emulsification technology
2.5 Liquid–Solid technology
2.6 Complexation technology
2.7 Adsorption technology
2.8 Ultra-rapid Freezing technology
2.9 pH adjustment technology
2.10 Salt formation technology
2.11 Prodrug technology
2.12 Nano-based technology
2.13 Other techniques:

- Co-solvency
- Co-crystallization
- Hydrotrophy
- Functional polymer technology
- Porous-microparticle technology
- Co-administration with other drugs

2.1 Particle size reduction technology: Particle size is the first choice technique for the enhancement of solubility. As the size reduces, surface area volume ratio increases. Due to large surface area of drug molecule, it allows a greater interaction with the solvent which ultimately cause increase in solubility (Lindenberg *et al.*, 2004). This technique has the various methods which are as follows:

2.1.1 Micronization: It is a conventional technique. Due to decrease in particle size, dissolution rate of drugs is increased by increasing the surface area but it does not increase equilibrium solubility (Dubey., 2006) Micronization of drugs is done by milling technique using jet mill, rotor stator colloid mills etc. This process is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug (Blagden., 2007)

2.1.2 Nanonization: Drug solubility and pharmacokinetics can be improved, while systemic side-effects are decreased in nanonization process. Wet milling, homogenization, emulsification, solvent evaporation technique, Pearl milling, spray drying etc are the different techniques which are used for the nanonization process. (Kumar *et al.*, 2013)

2.1.3 Sonocrystalisation: Sonocrystalisation is the novel approach for particle size reduction on the basis of crystallization by using ultrasound. It enhances solubility and dissolution of hydrophobic drugs and also used to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size (Sharma *et al.,* 2007)

2.1.4 Supercritical fluid process: Supercritical fluid (SCF) is novel nanosizing and solubilizing technology. This process is also defined as a dense non-condensable fluid. The flexibility and precision offered by SCF processes allows micronization of drug particles, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanosuspensions of particles 5-2,000nm in diameter (Vemula *et al*., 2010)

2.2 Polymorphism Technology: Polymorphism is the phenomenone for most of drugs which are exist in more than one crystalline form. These different polymorphs of a drug are chemically similar, but they exhibit different physical properties which play an important role in absorption and ultimately in therapeutic effect. Amorphous form of drug is always more suited than crystalline form because of their higher energy, improved surface area and thus the higher solubility. They require less energy to transfer a molecule into solvent because of greater aqueous solubility than crystalline form. So order of dissolution of different solid forms of a drug is as follows (Bindu *et al.*, 2010)

Amorphous > Metastable polymorph > Stable polymorph.

2.3 Drug dispersion Technology:

2.3.1 Solid dispersions: The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles (kumar *et al*., 2009). The solid dispersions may also be called solid-state dispersions, as first used by Mayersohnand Gibaldi. Once the solid dispersion is exposed to aqueous media and the carrier dissolve, the drug is released as very fine to colloidal particles. Because of greatly enhanced surface area, the dissolution rate and the bioavailability of poorly water-soluble drugs are high. A water soluble carrier results in a fast release of the drug from the matrix, and a poorly soluble or insoluble carrier leads to a slower release of the drug from the matrix (Chiou *et al*., 1971)

Various pharmaceutical approaches are applied for the preparation of solid dispersions, include fusion method, solvent method, melting solvent method, melt agglomeration process, solvent evaporation method, lyophilization method, mass extrusion method, spray drying method and electro-spinning method etc.

2.3.2 Eutectic mixtures: A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. Solid eutectic mixtures are usually prepared by rapid cooling of two compounds to obtain a physical mixture of very fine crystals (Sharma *et al*., 2009) The concept of eutectic mixtures was originally proposed by Sekiguchi and Obi in 1960s (Sekiguchi *et al.,* 1961) The resulting mixture has large surface area, more dissolution rate and improved bioavailability.

2.3.3 Solid solutions: Solid solution is a binary system having solid solute dispersed in a solid solvent. Since the two compartments crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersion or mixed crystals. In solid solution, the particle size is reduced to molecular level. Solid solutions can be classified into two categories:

- Continuous solid solutions.
- Discontinuous solid solution.

2.4 Emulsification Technology: Emulsification technology is based on use of surfactant molecules for their stabilization purpose. The presence of surfactants may lower the surface tension and increase the solubility of the drug.

2.4.1 Microemulsions: The term microemulsion was first used by Shulman in 1959. A microemulsion is defined as a four component system which is composed of external phase, internal phase, surfactant and co-surfactant. Dilution of microemulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug however; the fine particle size of the resulting precipitate would still enhance absorption (Lawrence *et al*., 2000). Concentration of surfactant should be above the critical micelle concentration for the enhancement of solubility.

2.4.2 Micelles: A micelle is an aggregate of surfactant molecules dispersed in a liquid colloid. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They can also be used to stabilize drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration, and the temperature of the system is greater than the critical micelle temperature or Kraft temperature, then formation of micelle occurs, entrapping the drugs within the micelles (Dutt *et al*., 2003). This process is known as micellization and generally results in enhanced solubility of poorly soluble drugs.

2.5 Liquisoild Technology: Liquisoild technique is a novel concept for oral drug delivery of drugs. This approach is suitable for immediate or sustain release formulations. The technique is based upon dissolving the insoluble drug in the suitable nonvolatile solvent, blending the liquid medicament with mixture of carrier and coating material, liquid medicament can be converted into non adhere, dry looking powder with acceptable flow properties and compression behaviour using by direct compression method. Drug release increases due to increase in surface area. This improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability(Houssieny *et al*., 2010 and Khaled *et al*., 2001)

2.6 Complexation Technology:

2.6.1 Physical Mixture: Active drug with suitable polymer in different ratios mixed in a mortar for about one hour with constant trituration. The prepared mixture is passed through the sieve and stored in dessicator over fused calcium chloride.

2.6.2 Kneading method: Active drug with suitable polymer in different ratios is added to the mortar and triturated with small quantity of ethanol to prepare a slurry. Drug is mixed into the slurry with constant trituration. The prepared slurry is then air dried at 25^{o}C for 24hrs. The resultant product is pulverized and passed through the sieve and stored in desiccators over fused calcium chloride (Das *et al*., 2012).

2.6.3 Co-precipitate method: Active drug is dissolved in ethanol at room temperature and suitable polymer is dissolved in distilled water. Active drug and suitable polymers are mixed in to the different molar ratios. The mixture is stirred at room temperature for one hour and the solvent is evaporated. The resultant mass is pulverized and passed through sieve no. 80 and stored in a desiccators (Shah *et al*., 2012).

2.7 Adsorption Technology: In this method the incorporation of the drug into hydrophilic carriers or drug solution deposition onto the adsorbents. The surface area of a drug available for contact with the dissolution medium is increased by the use of particulate adsorbent carriers, whereby the drug is bound to the carrier and thus cannot agglomerate. This is done by dissolving the drug in an organic solvent and adsorbing this solution onto the carrier. The evaporation of organic solvent results in a rapid precipitation of drug either on the surface or within the pores of adsorbent material (Heike et al., 2006).

2.8 Ultra-rapid Freezing Technology: This is a novel, cryogenic technology that is used to reduce the particle size of poorly water soluble drugs and form stable formulation that are readily wetted and have high dissolution rates. In this technology, drug is dissolved in a water miscible or anhydrous solvent along with a stabilizer which acts as a crystal growth inhibitor. Thereafter, drug/stabilizer solution is applied to a cryogenic liquid for ultra-rapid freezing of the drug solution. Liquid nitrogen has been employed as a cryogenic liquid (−196^{0}C). The suspended frozen droplets can then be separated from the cryogen by allowing it to evaporate. The frozen particles are lyophilized to obtain highly porous, dry and free-flowing micronized powders (Evans et al., 2006)

2.9 pH Adjustment Technology: The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. pH adjustment can be used for both oral and parenteral administration (Jain et al., 2004). Solubilised excipients that increase environmental pH within a dosage form (tablet or capsule), to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, and those excipients which act as alkalising agents may increase the solubility of weakly basic drugs (Graham *et al*., 1986). After pH adjustment, ionisable compounds are stable and soluble. It can also be applied to crystalline as well as lipophilic poorly soluble compounds (Tsi *et al*., 2008, Vila *et al*., 2004 and Urrusuno *et al*., 1999).

2.10 Salt Formation Technology: Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. It can lead to changes in solubility and permeability of the parent molecule, which can lead to improved bioavailability. Salts of acidic and basic drugs have, in general, higher solubilities than their corresponding acid or base forms. The use of salt forms is a well-known technique to enhance dissolution rates. This may be attributed to the higher dissolution rate of a salt to its higher solubility (relative to the free acid form) in the aqueous diffusion layer surrounding the solid. Generally, an alkaloidal base is slightly soluble in water, but if the pH of medium is reduced by addition of acid, the solubility of the base is increased as the pH continues to be reduced. The solubility of slightly soluble acid increases as the pH is increased by addition of alkali, the reason being that a salt is formed (Kumar *et al.,* 2013)

2.11 Prodrug Formation Technology: Prodrug technology is applied to increase the chemical or metabolic stability, higher water solubility or higher solubility in lipid membranes, improved oral or local absorption, enhanced brain penetration, reduced toxicity, and reduction of local irritation.

2.12 Nano-based Technology: Nanotechnology has emerged as a tremendous field in the medicine. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level i.e approximately 100 nm or less (Keck *et al*., 2006). Nano-based formulations can be produced by two methods:

- Bottom up techniques (precipitation methods)
- Top down techniques (size reduction by milling or high pressure homogenization).

2.13 Other Techniques:

2.13.1 Use of co-solvent: The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co-solvents (Strickley *et al*., 2004). Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds (Vemula *et al*., 2010). This technique is simple to produce and evaluate.

2.13.2 Co-crystallization: This approach is also referred as molecular complexes. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces (Almarsson *et al.*, 2004). Co-crystals are alternative option to salt formation, for neutral compounds to modify the chemical and/or physical properties of a drug without making or breaking covalent bonds. Co-crystals are prepared by evaporation of a heteromeric solution or by grinding the components together.

2.13.3 Hydrotrophy: Hydrotrophy is a molecular phenomenon. Hydrotropy is defining as the enhancement in the solubility of insoluble or slightly soluble drugs in water by the addition of additives. Hydrotrophes are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. Along with solubilisation hydrotrophs serve many functions. The mechanism by which it increases solubility is more closely associated to complexation involving a weak interaction between the hydrotrophic agents and the solute. Solute consists of alkali metal salts of various organic acids (Vemula *et al.*, 2010). They are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersion and conductance percolation, clouding of surfactants and polymers, etc (Bindu *et al.*, 2010)

2.13.4 Functional polymer technology: Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. This can also be applied to heat sensitive materials and oils.

2.13.5 Porous microparticles technology: In this technology, the poorly water soluble drug is entrapped in a microparticle having a porous, water soluble, sponge-like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles. This is the core technology which is called as HDDSTM (Hydrophobic Drug Delivery System). These drug particles provide large surface area for increased dissolution rate.

2.13.6 Co-administration with another drug: Combining of two or more drugs has an effect on the improvement in the solubility as well as synergetic therapeutic effect.

3. METHODS OF PREPERATION OF FAST DISSOLVING TABLET:

For the preparation of fast dissolving tablet there are two types of technologies are included:

- Heating technology
- Non-heating technology

3.1 Heating technology

3.1.1 Cotton candy process: This process is also known as the "candy floss" process and forms the basis of Flash Dose technology (Kumar *et al.*, 2013). The Flash dose technology is a fast dissolving drug delievery system, manufactured using Shearform technology in association with Ceform technology to eliminate the bitter taste of the medicament (Myers *et al.*, 1995 and Cherukuri *et al.*, 1995). The shearform technology uses a unique spinning mechanism to produce floss like crystalline structure, much like cotton candy. This process involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT (Siddiqui *et al.*, 2010). This process is applicable only for thermostable compound.

Characteristics: It can accommodate high doses of drug and offers improved mechanical strength. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva (Gupta *et al.*, 2010).

3.1.2 Tablet molding process: It is of two types:

3.1.2.1 Solvent method: This process is also known as compression molding. The major components for this process are water-soluble ingredients (Yourong *et al.*, 2004). This process involves the moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass. The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution (Kumar *et al.*, 2013). Because moulded tablets are usually compressed at a low pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen.

3.1.2.2 Heat molding: This process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum (Bhowmik *et al.*, 2013). The mechanical strength of moulded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated (Kumar *et al.*, 2013). Another process used is called no-vacuum lyophilization, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure (Gupta *et al.*, 2010).

Characteristics: Molded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased.

3.1.3 Mass extrusion: This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets (Bhaskaran *et al.*, 2002, Yu *et al.*, 2008).

Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby mask their bitter taste.

3.1.4 Sublimation: In this process substance directly gets converted to the gas phase without passing through an intermediate liquid phase. It involves formation of a porous matrix, by incorporating volatile ingredients in the formulation that is later subjected to a process of sublimation (Kumar *et al.*, 2013). The presence of a highly porous structure in the tablet Matrix is the key factor for rapid disintegration of FDTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet (Koizumi *et al.*, 1997). Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, menthol, camphor, naphthalene, urea, urethane or phthalic anhydride could be compressed along with other excipients into a tablet (Kumar *et al.*, 2013).

Characteristics: Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc. Disintegration time for these types of tablets is 10-20secs.

3.1.5 Granulation method:

3.1.5.1 Wet granulation method: Bonadeo et al. described the process of producing wet granulation in a fluidized bed (Bonadeo *et al.*, 1998). They found that the tablet disintegrate within 3 to 30 seconds in to saliva due to the acid component of the effervescent agent. This is because the tablet disintegrates by surface erosion and is not amenable to rapid dispersion or disintegration in water prior to oral administration to swallowing- compromised patients. The mixture for wet granulated is prepared with an aqueous solution of a water-soluble or water-dispersible polymer (e.g., polyethylene glycols), carrageenan, and ethylcellulose), which consisted of 1–10% of the final weight of the granule in a fluid bed. Granules with high porosity and low apparent density were obtained and then granules were made into tablets.

Characteristics: Due to porus structure of tablet complete disintegrate with in the 3 minutes.

3.1.5.2 Dry granulation: Eoga and Valia described the method of dry granulation (Eoga *et al*., 1999). Higher density alkali earth metal salts and water-soluble carbohydrates usually do not provide quick disintegration and a smooth mouth feel. Low-density alkali earth metal salts and water soluble carbohydrates are also difficult to compress and caused inadequate content uniformity. For these reasons, low-density alkali earth metal salts or water-soluble carbohydrates are pre-compacted, and then resulting granules are compressed into tablets that dissolve fast. In this process, required density for the powder material is of 0.2–0.55 g/mL.

3.1.5.3 Phase-transition process: Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol (Kuno *et al*., 2005).

Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.

3.2 Non-heating process:

3.2.1 Lyophillization or Freeze drying: Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation (Nail *et al*., 2005)· The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying and packaged.

Characteristics: The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.

3.2.2 Direct compression: It is the easiest way for the manufacturing of tablets. This technique can now be applied to preparation of FDT because of the availability of improved excipients especially superdisintegrants (crosscarmelose, microcrystalline cellulose etc.) and sugar based excipients (dextrose, maltose, lactose etc.). This process has the limited number of steps.

Characteristics: It is most cost effective tablet manufacturing technique.

3.2.3 Spray drying: This technology produces highly porous and fine powders as the processing solvent is evaporated during the process (Allen *et al*., 2001). In this process hydrolyzed or non-hydrolyzed gelatine used as a supporting material and mannitol as a bulking agent and crosscarmellose as disintegrating agent and an acidic or alkali materials are used to enhance the dissolution or disintegration.

Characteristics: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.

3.2.4 Nanonization: A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. This process involves the size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs.

Characteristics: It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

3.2.5 Compaction:

3.2.5.1 Melt granulation: Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet.

Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue.

3.2.6 Three-dimensional Printing (3DP): Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system (Yu *et al.*, 2008). It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume (Ito *et al.*, 1996).

4. Excipients

4.1 Super disintegrants: Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch.

4.2 Flavours: Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptos oil thyme oil, oil of bitter almonds. Flavoring agnets are also included such as vanilla, citus oils, fruit essences etc.

4.3 **Sweetners:** Aspartame, Sugars derivatives

4.4 **Fillers:** Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

4.5 **Surface active agents:** sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.

4.6 **Lubircants:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

5. Characterization of fast dissolving tablet:

5.1 Drug excipient compatibility test:

Detection of any changes in chemical constituent of the drug when combined with the other excipient is determined. This test can be performed by differential scanning calorimeter and fourier transform infrared spectroscopy.

5.2 Pre-compression evaluation (Lachmann et al., 1998**):**

5.2.1 Bulk density: Weigh the 10 g of powder (presieved 40-mesh) and poured into the 100ml measuring cylinder and note volume occupied by the powder via a large funnel. It is expressed in g/ml and is given by,

$$\mathbf{D_b = M / V_b}$$

Where, M is the mass of powder
V_b is the bulk volume of the powder.

5.2.2 Tapped density: Weigh the 10 g of powder (presieved 40-mesh) and poured into the 100ml measuring cylinder and note volume occupied by the powder via a large funnel or in mechanical tapper apparatus, which is operated for a fixed number of taps (~1000 times) until the powder bed volume has reached a minimum. It is expressed in g/ml and is given by,

$$\mathbf{D_t = M / V_t}$$

Where, M is the mass of powder
V_t is the tapped volume of the powder.

5.2.3 Angle of repose: The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

$$\tan(q) = h / r$$

$$q = \tan^{-1}(h / r)$$

Where, q is the angle of repose.
h is the height in cm
r is the radius in cm.

Table 2: Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	**Angle of Repose (°)**	**Type of Flow**
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

5.2.4 Carr's index (or) % compressibility:

Table 3: Relationship between % compressibility and flowability

Sr. No.	**% Compressibility**	**Flow ability**
1	5 – 12	Excellent
2	12 – 16	Good
3	18 – 21	Fair Passable
4	23 – 35	Poor
5	33 – 38	Very Poor
6	< 40	Very Very Poor

5.2.5 Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\textbf{Hausner ratio} = D_t / D_b$$

Where, D_t is the tapped density.
D_b is the bulk density.
Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

5.3 Evaluation of fast dissolving tablet:

5.3.1 General appearance: The general appearance of a tablet is its visual identity and overall elegance including size and shape, tablet thickness and unique identification marking.

5.3.2 Uniformity of weight: Take twenty tablets and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content.

Table 4: Weight Variation Specification as per IP

Sr. No.	**Average Weight of Tablet**	**Maximum % difference allowed**
1	130 or less	10
2	130-324	7.5
3	More than 324	5

5.3.3 Hardness: It is also termed as tablet crushing strength. The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Monsanto tablet hardness tester, Pfizer hardness tester). It is expressed in kg or pound **(**Lachmann et al., 1998**)**.

5.3.4 Friability: Tablet friability is measured by ROCHE friabilator (USP). A pre weighed tablet sample is placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed at 25 rpm for 4 min. and calculated by the following formula:

Percentage friability= [initial weight-final weight)/initial weight] ×100

5.3.5 Wetting time and water absorption ratio: Wetting time of dosage form is related to with the contact angle. Lower wetting time implies a quicker disintegration of the tablet. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully placed in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted. The water absorption ratio, *R* can be the determined according to the following equation;

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

W_b; weight of the tablet before keeping in the petridish

W_a; wetted tablet from the petridish is taken and reweighed (Morita *et al.*, 2002) .

5.3.6 Moisture uptake study: Ten tablets from each formulation will be kept in desiccators over calcium chloride at 37ºC for 24h. The tablets will be weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity will be achieved by keeping saturated calcium chloride solution at the bottom of the desecrator for 3 days. One tablet as control (without super disintegrant) will be keep to check the moisture uptake by the other excipients. Tablets will be weighed and the percentage increase in the weight will be recorded.

5.3.7 *In-vitro* dissolution studies: Release of drug from bilayer matrix tablet will be determined by USP Paddle method. The dissolution rate will be studied using 900 ml appropriate dissolution medium. 0.1N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of fast dissolving tablet. (paddle speed of 25-75 rpm is commonly used.

5.3.8 Modified disintegration test: A 10cm petridish is filled with 10 ml of water. The tablet is carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles will be noted.

5.3.9 *In-vitro* dispersion time: Tablet will be added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°c. Time required for complete dispersion of a tablet will be measured.

5.3.10 Drug content uniformity: Drug content of fast dissolving tablets will be calculated by weighing ten tablets of each formulation, pulverizing to a fine powder. A quantity of powder equivalent to 10 mg of drug dissolved in methanol and solution will be filtered through a 0.45 µm whatmann filter paper. Drug content will be determined by measuring the absorbance UV visible spectrophotometer after appropriate dilution with methanol. The drug content will be determined using calibration curve. The mean percent drug content will be calculated as an average of three dimensions.

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