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Review Article

## Fast dissolving tablets: waterless patient compliance dosage forms

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### ABSTRACT

Drug delivery by the oral route is the most prescribable and acceptable route in terms of patient's compliance. Improvement of patient's compliance has always a challenge towards the development of oral drug delivery system. In the market different types of oral dosage forms are available in which tablets, capsules, syrups, suspensions are preferred ones. Oral solid drug delivery faces drawback in case of swallowing especially with paediatrics and geriatric psychotic patients. Therefore scientists attracted towards fast mouth dissolving drug delivery systems to encounter existing problems with unique property of palatability and rapid disintegration. The concept of fast dissolving tablet came into existence in late 1970 and further improvements are still going on in connection with its preparation and methodology. Fast dissolving tablets have faster disintegration and dissolution rate and releases within 30 seconds as they come in contact with saliva. These systems also obviate the requirement of carry water during drug administration. This facilitate drug delivery to the patients of dysphasic, psychic, paediatrics, geriatric and bed-ridden, unconscious population. As fast dissolving tablets falls under desired expectation of safer, convenient and economical solid dosage forms, several techniques have been developed to improve disintegration quality in the recent past years. This article mainly focuses on formulation and evaluation technologies with recent advancement made so far in the field of fast dissolving tablets.

**Keywords:** Fast disintegration; Dysphasia; Mouth dissolving; Self-medication.

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### 1. INTRODUCTION

Oral route is the preferred route for drug delivery as per its ease of administration, accurate dosing, self-medication, economic manufacturing, pain avoidance patient's convenience and comfort. Apart from conventional oral solid dosage forms, fast dissolving tablets emerged as a new generation of formulation having added advantages of both solid and liquid dosage systems. It also offers convenience in tablet manufacturing and much more accurate dosing than the liquid orals as a primary alternative. These dosage forms after coming in contact with saliva rapidly disintegrate and thereafter dissolve in order to release the drug.<sup>1,2</sup> We may take this medicament with or without water which makes it more attractive for patients of dysphasic, psychic, paediatrics, geriatric and bed-ridden, unconscious population. These tablets can be swallowed more conveniently than the conventional tablets and capsules among patients of all aged groups and also a miracle for travelling patients who may not have easy access to water. Children and elderly patients who refuse to swallow conventional oral formulations may find comfort in case of fast dissolving tablets as they simply vanish after placing in the mouth upon the tongue. Overall these tablets may take less than 30 seconds to disintegrate completely. Claritin

(loratadine) was the first drug as fast dissolving dosage form which was approved by United States FDA in 1996 manufactured by Schering-Plough Corporation.<sup>3</sup> Fast dissolving tablets are promising approach for the delivery of neuroleptics, analgesic, anti-allergic, cardiovascular agents and delivery of high molecular weight proteins and peptides.<sup>4</sup> Now days these types of tablets become the first choice of medicine among all dosage forms available in the market due to its fast dispensing, melting and dissolving ability. These tablets also have ability to convert into solution, suspension or paste like medicament after keeping on the tongue to avoid the risk of choking and suffocation.

Several new advanced techniques in the recent past years have been introduced for fast dissolving tablet formulations. The techniques concentrating features like taste masking, fast disintegrating, pleasant mouth feel, sugar free and ease fabrication. The formulation technique of fast dissolving tablets include direct compression, molding, extrusion, sublimation, spray -drying, cotton candy, lyophilization, thin film and nanoionization. These techniques works on the principle of pore size enhancement and use of superdisintegrants. Mechanical strength, drug stability, mouth feel, disintegration time, rate of dissolution, taste, absorption rate and drug bioavailability are the few

characterization techniques of fast dissolving tablets.<sup>5</sup> While formulating fast dissolving tablets, it is essential to study their biopharmaceutical factors like pharmacokinetics and pharmacodynamics. Pharmacokinetics includes studies on absorption, distribution, metabolism, and excretion. When a drug undergoes absorption through the oral cavity, i.e., after attending its therapeutic level, it will show a pharmacological effect. So both the rate and extent of absorption affects its response. In conventional tablets, dissolution is slow as their disintegration is slow while in

fast dissolving tablets disintegration and dissolution are rapid. Some factors like tissue permeability, binding of the drug to tissue, disease, the rate of perfusion, drug interaction affect drug distribution. The current review presents a detailed study regarding formulation, evaluation, a silent features and recent research work done over on fast dissolving tablets. Fast dissolving tablets possess advantages of both solid and liquid dosage forms. Figure 1 showing the pictorial representation about its advantages over conventional tablet.



Figure 1: Benefits of fast dissolving tablet over conventional tablet

### Advantages of fast dissolving tablets<sup>6,7</sup>

#### ▪ Ease of administration and Patients compliance

These tablets are easy to administer in case of patients who cannot swallow (Bedridden patients, stroke victims, and elder patients), who should not swallow (like renal failure) and who refuse to swallow (Paediatrics, geriatric and psychiatric patients).

These tablets offer patients compliance in case of bedridden disabled patients and for people who are busy or travelling as water is not required for administration.

#### ▪ Rapid onset of action

These tablets are having rapid onset of action as these tablets are getting absorbed through pre-gastric area.

#### ▪ Enhanced bioavailability

Bioavailability of poorly soluble drugs increases by adding hydrophilic disintegrating agents which results in rapid disintegration and dissolution.

Due to pre gastric absorption, these tablets bypass the first pass metabolism which results in reduced dose, less side effect and enhanced bioavailability.

#### ▪ Fast dissolving tablets are palatable

Property of having good feel, it is more accepted among paediatrics patients, as it improves the taste of bitter drugs.

#### ▪ Good alternative to conventional tablet and liquid dosage forms

Mouth dissolving tablets are solid unit dosage forms having accurate dosing, having no risk of choking and suffocation with advantages of both solid and liquid dosage forms.

### Disadvantages of fast dissolving tablets<sup>8,9</sup>

#### ▪ Mechanical strength

These tablets are very brittle, fragile and porous in nature as they are prepared by low compression force. Thus, requires proper packing and handling while transportation.

#### ▪ Unpleasant taste

If not properly prepared, these tablets can leave unpleasant taste or feeling of grittiness in the mouth.

#### ▪ Required dry condition for storage

These tablets are hygroscopic in nature and thus should be stored in dry condition.

## 2. EXCIPIENTS USED IN FAST DISSOLVING SYSTEMS

USFDA defines oral disintegrating tablets as "A solid dosage form containing medicinal substance, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".<sup>10</sup> As per requirement of fast dissolving tablets, it should disintegrate quickly in the oral cavity. Any selected excipient should not have any interaction with the active ingredient or any other excipient. As excipients of fast dissolving tablets mainly consists of at least one disintegrant, a diluent and a lubricant. In addition to that it may contain swelling agent, flavoring agent and sweeteners based on the characteristic of tablet required. While selecting any excipient, we should check its organoleptic property like color, taste, and odor so that final fast dissolving tablet may not get affected. Table 1, shows the listed excipients which are widely used in the formulation of fast dissolving tablets with their role and functions.

Table 1: Excipients widely used in fast dissolving tablets<sup>11, 12, 13, 14</sup>

S. No.	NAME	EXAMPLE	RANGE	ROLE/FUNCTION
1	Superdisintegrants	Croscarmellose Sodium, Crospovidone, Sodium starch glycolate, Pregelatinised starch, Microcrystalline cellulose & Sodium Carboxy methyl cellulose.	1-10%	Helps in quick disintegration of the tablet which results in fast dissolution.
2	Diluent/Bulking agents/Filler	Dextrose, Fructose, Maltose, Mannitol, Sorbitol, Starch hydrolysate, Polydextrose, Xylitol, Lactitol & Directly compressible lactose.	10-90%	Increases the bulk of the tablet.
3	Lubricant	Stearic acid & Magnesium stearate.	1 to 5%	Reduces the friction between the surface of die wall and tablet and thus preventing sticking and picking.
4	Sweeteners and sugar based excipients	Dextrose, Sugar, Fructose, Aspartame, Sodium saccharine, Sucralose and sugar alcohols.	-	Good mouthfeel and pleasant taste hence enhancing patient's compliance.
5	Flavoring agent	Peppermint flavor, Cooling flavor, aromatic flavor oil, vanilla, citrus oils & fruit essences.	-	To impart flavor to the tablet.

### 3. SUPERDISINTEGRANTS

Superdisintegrants can be defined as the substances which help in the faster disintegration in small concentration as compared to disintegrant. They are used in 1-10% by weight relative to the total weight of the solid dosage unit. While formulating fast dissolving tablet, we are using superdisintegrant as an excipient and thus, it has to comply some important criteria other than its swelling property which are mentioned in below section.

#### Properties of a superdisintegrant<sup>15</sup>

- Poor gel formation
- Hydration capacity should be good
- Molding and flow property should be good
- Should not form complex with drugs
- Should be compatible with other excipients

- Should not be toxic
- Should be inert

These agents act by the swelling mechanism. Because of swelling, either there is an increase of swelling pressure in the outer direction of tablet leading to tablet burst or more absorption of water increases granules volume facilitating disintegration. With the modern developments in drug delivery system, there is an increase in demand for superdisintegrant. So we need to prepare superdisintegrant that should be effective at low concentration and have more efficacy of disintegration. As we all know, superdisintegrants affects the disintegration rate of the tablet, but at high concentration they are affecting tablet hardness, friability, and mouth feel. Therefore, we have to consider various factors before selecting a superdisintegrants for the formulation as shown in figure 2.

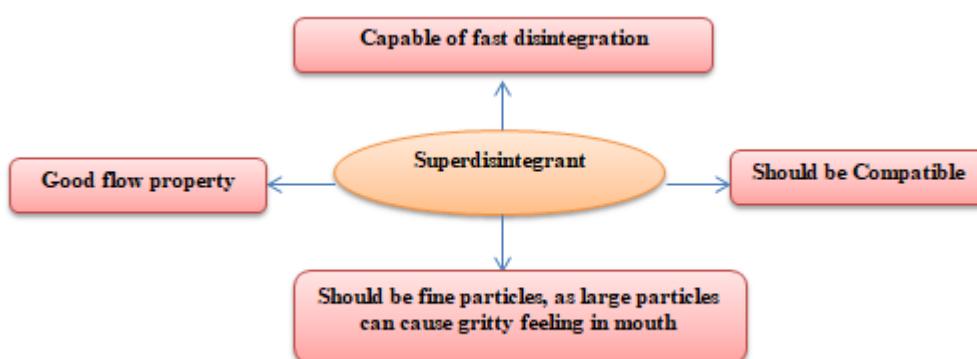


Figure 2: Selection criteria for superdisintegrants

There are two types of superdisintegrants available one is natural and the other is synthetic depending on their source. The selection of a correct superdisintegrant and its constant performance are important parameter during formulation of any solid tablets or capsules. Swelling, wicking, deformation, heat of wetting, release of gases, enzymatic action and

combination action are the different mechanisms through which they acts in order to disintegrate tablets into its fine particles in an aqueous environment. In table 2 and 3, different superdisintegrants are listed down based on their source and type of origin.

Table 2: List of synthetic superdisintegrants<sup>16, 17</sup>

S. No.	NAME	BRAND NAME	COMPOSED OF	MECHANISM OF ACTION
1	Croscarmellose Sodium	Cel-Ca-Dissol, Sudisom, or Ac-Di-Sol	cross-linked polymer of carboxymethylcellulose sodium	Wicking due to fibrous structure, swelling with minimum gelling, effective concentration 1 to 3 %
2	Crospovidone	Kollidon® CL	cross linked homopolymers of N-vinyl-2- pyrrolidone	Water wicking, Swelling and Deformation, effective concentration between 2 to 4%
3	Sodium starch glycolate	Explotab, Primogel	cross linked polymer of carboxymethyl starch	Fast Swelling with less gelling property, effective concentration between 4 to 6%
4	Pregelatinised starch	Starch 1500)	Compressed form of starch, mainly composed of intact and partially hydrolyzed starch grains	Swelling As disintegrant it is used in between 5 to 10 % concentration

Table 3: List of Natural Superdisintegrants available<sup>18</sup>

S. No.	NAME	SOURCE	MECHANISM
1	Plantago ovata seed mucilage (Psyllium or Ispaghula mucilage)	Dried seeds of the plant plantago ovata.	Due to high swelling capacity of the Psyllium husk powder.
2	Lepidium sativum seed Mucilage	Extracted from seeds Natural Lepidium sativum.	Swelling
3	Fanugreek Seed Mucilage	Seeds of plant Trigonella Foenum-graceum.	Swelling
4	Gellan Gum	Obtained from Pseudomonas elodea.	Swelling
5	Locust Bean gum	Extracted from the endosperm of the seeds of the carob tree.	Swelling
6	Gum Karaya	Isolated from the trees of the genus Sterculia. It is a vegetable gum.	Swelling
7	Mango peel pectin	Extracted from mango peel which constitutes 20-25% of the mango processing waste.	Good solubility and high swelling index, swelling mechanism.
8	Agar and treated agar	Dried gelatinous substance obtained from Gelidium amansii (Gelidaceae) and several other species of red algae.	Because of its high strength gelling property makes it as a candidate for superdisintegrant.
9	Guar gum	Isolated from the endosperm seed of the guar plant, Cyamopsis tetragonoloba.	Swelling
10	Gellan gum	Water-soluble polysaccharide produced by Pseudomonas elodea, a bacterium.	Swelling property due to its hydrophilic nature.
11	Soy polysaccharide	High molecular weight polysaccharides obtained from soy beans.	Swelling
12	Chitin and chitosan	Chitin obtained from natural polysaccharide obtained from crab and shrimp shells. Chitosan structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi.	Swelling

#### 4. TECHNOLOGY

On the basis of fast disintegrating principles, different methods are available for preparation of fast dissolving tablets and they differ from conventional tablets in terms of mechanical strength, stability, mouth feel, rate of dissolution

and bioavailability. Three main approaches used in formulation of fast dissolving tablets. They are:

1. By increasing the tablet matrix porous structure
2. By using water soluble excipients
3. By adding superdisintegrant

## 4.1 Conventional technology

### 4.1.1 Lyophilization or Freeze drying

A process, in which water is removed or sublimed from a product, after it is frozen, is lyophilization or freeze drying. The tablets obtained by this technique can dissolve or disintegrate more rapidly than any other solid dosage forms because it will form an amorphous porous structure. Drugs which are water-insoluble with fine particle size, drugs with low aqueous solubility and drugs having low stability in suspension forms are best ideal candidates for this technique. Procedure involved in the preparation of oral dispersible tablet using this technique is given in figure 4. This technique has shown improved absorption and bioavailability. For manufacturing of fast dissolving tablets through lyophilization process, excipients include polymers (gelatin, alginates and dextrin) in order to provide strength and rigidity to tablets, Polysaccharides (sorbitol and mannitol) is used to improve palatability and to impart crystallinity and hardness. Collapse protectants(glycine) is used to prevent shrinking, flocculating agents (Xanthum gum and acacia) to make uniform dispersion of drug particles, preservatives (parabens) to prevent microbial growth, pH adjuster (citric acid), flavors and sweeteners to improve patients compliance.<sup>19</sup>

#### Advantages:

- Lyophilization is useful for heat sensitive drugs.
- Tablets obtained by this technique dissolve more rapidly than any other solid dosage forms because it will form an amorphous porous structure.
- As it melts fast, provides good mouth feel.
- Improved absorption and increased bioavailability

#### Disadvantages:

- Expensive and time consuming process
- Required special packaging as obtained tablets are poorly stable and fragile.

#### Research carried out by this method<sup>20</sup>

Vivek Dave et.al (2017), Bulletin of Faculty of Pharmacy, Cairo University has prepared novel fast dissolving tablet of Chlorpheniramine maleate by using lyophilization technique. For preparation of aqueous solution of gelation, gelatin was soaked in water and hydrated gelatin was stirred on a magnetic stirrer until get a clear solution. To prevent shrinkage of gelatin, equal portion of glycine and mannitol was added. Chlorpheniramine maleate was accurately weighed and dispersed in the aqueous solution prepared, stirred on a magnetic stirrer until to get homogeneous phase having required dose. Above drug dispersion was poured in polyvinyl chloride (PVC) blister pack and kept in deep freezer condition of -20°C for 24 hours and pre freeze tablet mixture was kept in lyophilizer.

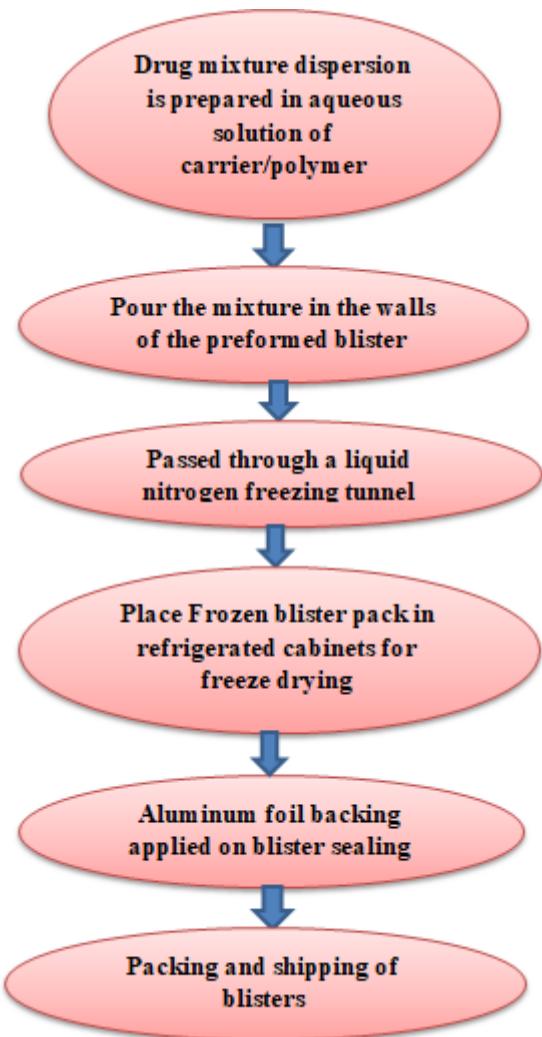


Figure 4: Schematic flowchart of the Lyophilization process

### 4.1.2 Tablet Molding

Water soluble ingredients are used in molding technique which makes tablets dissolves rapidly and completely. Compression molding and heat molding are the two types of molding technique. In figure 5 and 6 compression and heat molding processes are elucidated.

#### 4.1.2.1 Compression Molding (Solvent method)

Powder blend gets moistened with hydroalcoholic solvent and then compressed to form a wetted mass at low pressure in molded plates. By air drying, solvent is removed and tablets produced by this technique are less compact having a porous structure which helps in fast dissolution.

#### 4.1.2.2 Heat method

In this technique, a drug suspension having agar and sugar (mannitol or lactose) is prepared and it is poured in the blister packaging walls which solidify at room temperature to form jelly and further kept for drying under vacuum at 30°C. The mechanical strength of molded tablets is a matter of great concern. Binding agents (likes sucrose, polyvinylpyrrolidone, cellulose) which help in increasing the mechanical strength of the tablets need to be incorporated. The scope of taste masking is limited in this technology.<sup>21</sup>

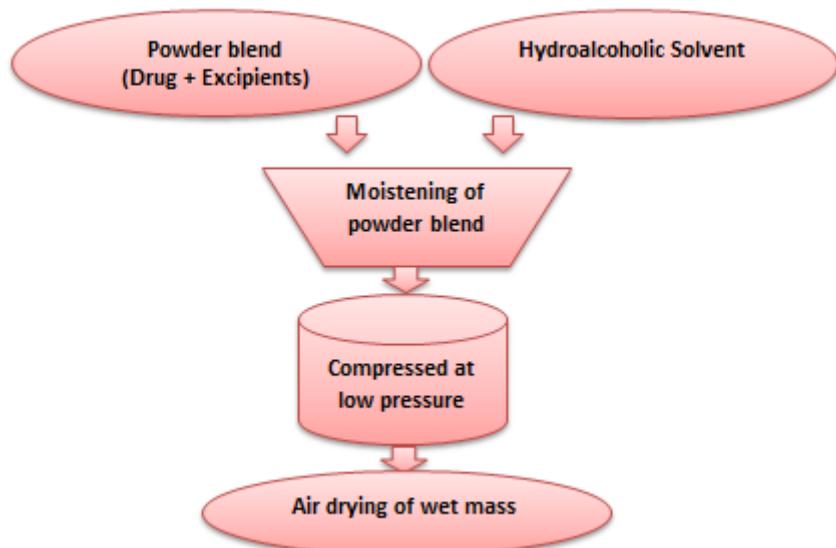


Figure 5: Schematic flowchart of the Solvent Method

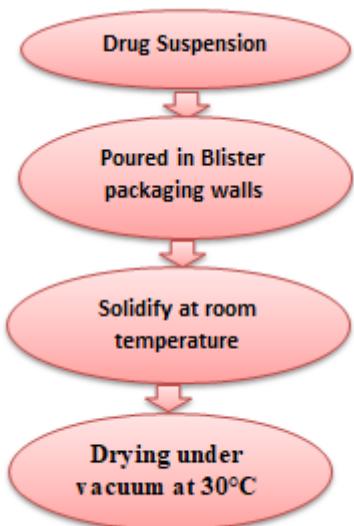


Figure 6: Schematic flowchart of the Heat Method

#### Advantages:

- This technique is easy and feasible to scale up for industrial manufacture.
- As it composed of water soluble sugars, have good mouth taste and disintegrates more rapidly.

#### Disadvantages:

- They may break while handling due to poor mechanical strength.

#### 4.1.3 Direct compression

Direct compression is the easiest method with advantage of low manufacturing cost, conventional equipment, commonly

available excipients and less number of processing steps. By direct compression method, it can accommodate high dose and also possible to exceed the final weight of the tablet as compared with another method. Superdisintegrants, water-soluble excipients and effervescent agents are used in tablet formulations which determine the disintegration property of tablet. Disintegration of fast dissolving tablet prepared by direct compression method mainly depends on superdisintegrants used. Thus superdisintegrants selection plays a significant role in the disintegration, and pleasant mouth feel of the tablet. Availability of good superdisintegrants and sugar based excipients makes direct compression method suitable for the production of fast dissolving tablets.<sup>22</sup> Figure 7 is showing the schematic flow of the direct compression process comprising superdisintegrants.

#### (a) Superdisintegrants

Selection and addition of proper superdisintegrants affects the disintegration and dissolution of fast dissolving tablets prepared by direct compression method. Other excipient such as water soluble excipients and effervescent agents help in fastens the disintegration process of fast dissolving tablets.

#### Research carried out by this method<sup>23</sup>

Deepak Sharma (2013), Hindawi Publishing Corporation, has prepared fast dissolving tablets of salbutamol sulphate by direct compression method. Superdisintegrant and binder were optimized to get desired hardness and friability of the tablet is the main critical step. Salbutamol sulphate accurately weighed and optimized concentration of superdisintegrant and binder along with other excipients were blended together and tablets are punched by direct compression method.

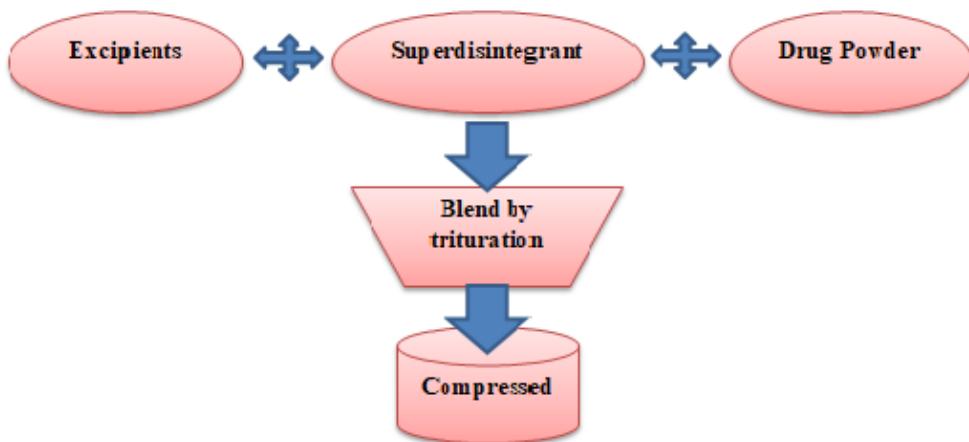


Figure 7: Schematic flowchart of direct compression method

#### 4.1.3 Spray Drying

This process was used by Allen et al. for the preparation of fast dissolving tablets. It consists of bulking agent mannitol and sodium starch glycolate or croscarmellose sodium as a disintegrating agent. Addition of effervescent agent's citric acid and sodium bicarbonate results in improved dissolution and disintegration. Fast dissolving tablets obtained by this method disintegrates less than 20 seconds in an aqueous medium. In this method, aqueous solution containing matrix (Gelatin either hydrolyzed or unhydrolyzed) and other components are sprayed in spray dryer resulting in the formation of a free flowing support matrix.<sup>24</sup> This free flowing support matrix then mixed with the active ingredient and finally compressed to form fast dissolving tablet which is schematically given in figure 8.

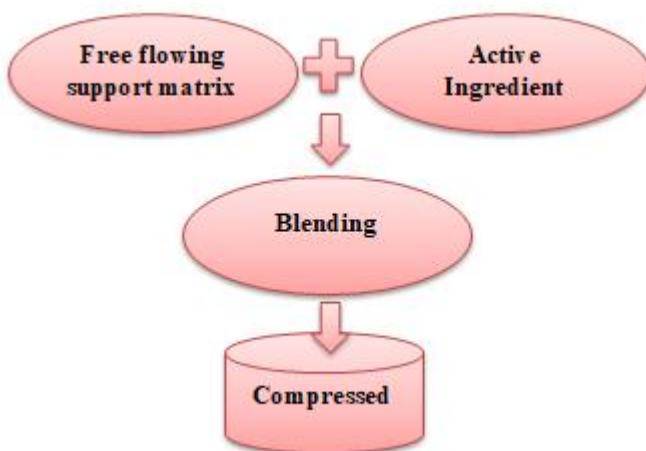


Figure 8: Schematic flowchart of the spray drying method

#### Advantages:

- Helpful in the formation of highly porous and fine powder. Hence, tablet formed are capable of

disintegrate within 20 sec after dispersed in aqueous medium.

#### Research carried out by this method:<sup>25</sup>

Balagani Pavan Kumar, G. Archana, Yaddalapudi Swarupa, and Katamreddy Jyothshna Devi (2015), World Journal of Pharmaceutical Research, has prepared fast dissolving tablet of Nizatidine using Spray drying technique. Drug solid dispersion was prepared using Carrier Eudragit E100 and then tablets were compressed using superdisintegrants and prepared solid dispersion by direct compression method.

#### 4.1.4 Sublimation

This technique is used to produce fast dissolving tablets with high porosity. To form a porous matrix, volatile ingredients are added along with other excipients and compressed to form tablet and then compressed tablets are subjected to sublimation process. A schematic flow of the procedure involved in the preparation of fast dissolving tablet using sublimation technique given in figure 9. By utilizing a mixture of camphor and mannitol, Koizumi et al. developed a fast dissolving tablet. In vacuum at 80 °C for 30 minutes, camphor was sublimated after preparation of tablets. Highly volatile inert solid ingredient like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane have used for this purpose.<sup>26</sup>

#### Research carried out by this method<sup>27</sup>

S. B. Shirasand, Sarasija Suresh, V. Kusumdevi and P. V. Swamy (2011) Indian J Pharm Sci. has prepared fast dissolving tablets of Clonazepam using 3<sup>2</sup> factorial design to find out the combined effect of croscarmellose sodium and camphor. Here, camphor was used as a sublimating agent, mannitol as diluent and to impart hardness aerosol was added. All the ingredients were mixed after sieving separately followed by addition of lubricant and glidant then mixed again and compressed to tablets by direct compression. After that tablets were kept in hot air oven at 60°C for 6 hours for sublimation.

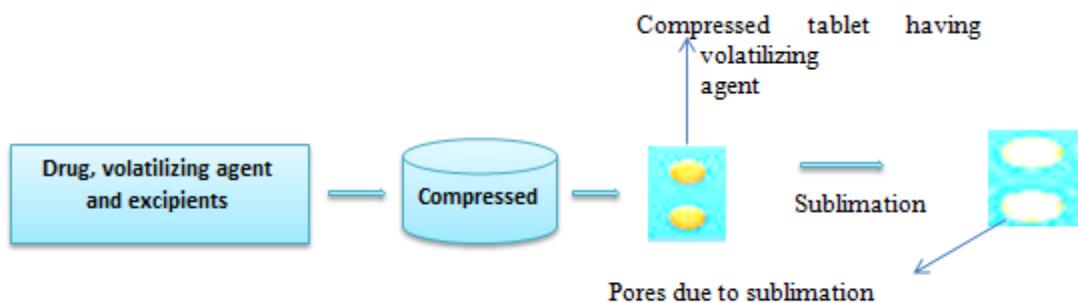


Figure 9: Schematic flowchart of the Sublimation method

#### Advantages:

- Tablets produced with good mechanical strength.
- High porosity tablets obtained and thus dissolve in saliva within 15 seconds.

#### 4.1.5 Mass Extrusion

Taste masking of bitter drug granules using mass extrusion technique is main step of this process and then tablets are compressed using taste masked granules and excipients including superdisintegrant. Procedure for preparation of fast dissolving tablets by this technique is given in figure 10. For taste masking, softening of active blend is done by utilizing mixture of polyethylene glycol and methanol. Expulsion of this soft mass done through the extruder or syringe to get cylinder of the products into even segments by using heated blade to

form tablet. For taste masking of dried granules of bitter drugs, these dried cylinders are used.<sup>28</sup>

#### Research carried out by this method<sup>29</sup>

P. S. Zade et.al, has prepared fast dissolving tablets of Tizanidine HCl using mass extrusion method. Drug Eudragit e 100 taste masked granules were prepared by using mass extrusion method. Drug and eudragit were mixed in different ratios in mortar pestle and then 10% ethanol was added to each mixture and gel was prepared. Manually prepared gel was extruded via a syringe. Then kept overnight for evaporation of ethanol and the resulted solidified gel was crushed into granules in a mortar. Then fast dissolving tablets of Tizanidine HCl was punched by direct compression method using taste masked granules, different superdisintegrants (like sodium starch glycolate, crospovidone, Croscarmellose sodium), Mannitol and Avicel as direct compressible diluents.

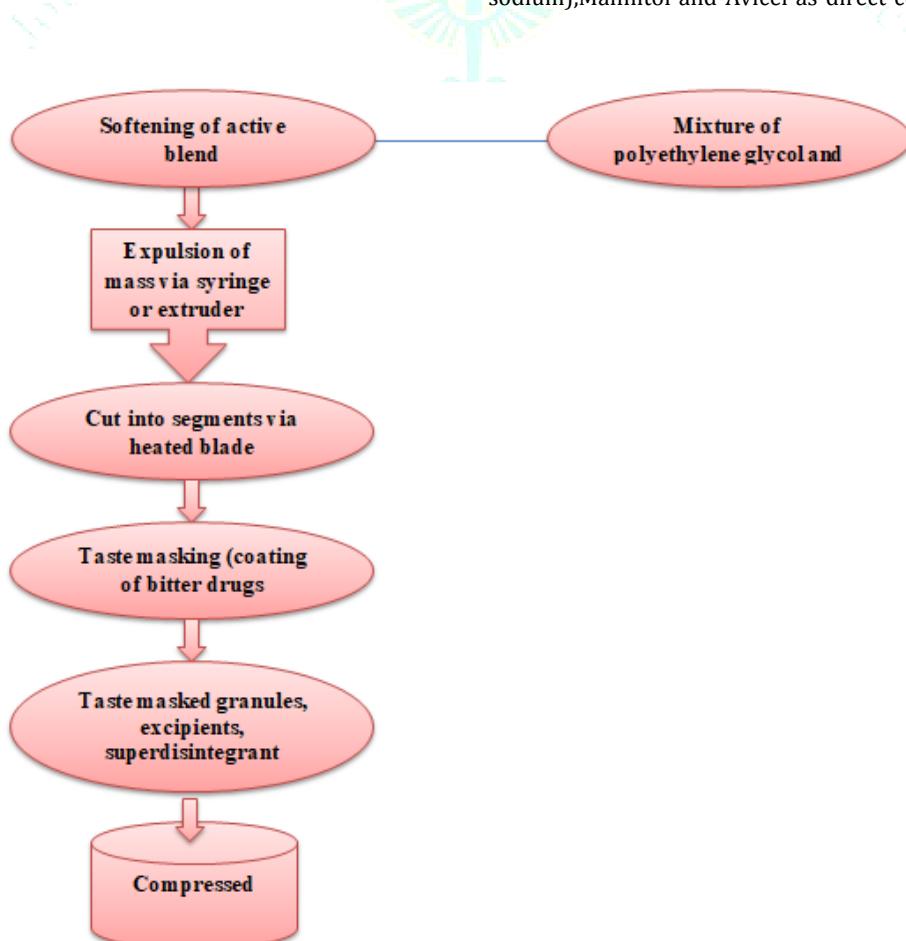


Figure 10: Schematic flowchart of the Mass extrusion method

## 4.2 Patented technology

### 4.2.1 Zydis technology

Catalent Pharma has the patent for Zydis technology. This is a unique technology which involves entrapping or dissolving of drug within the fast dissolving matrix carrier. These tablets disintegrate instantaneously as we keep in the mouth. It is composed of different excipients with an objective for imparting strength and rigidity. For hardness and crystallinity, saccharides such as mannitol and sorbitol are added and to achieve fast disintegration water is added

during manufacturing to achieve porous units. Addition to that, gums are incorporated for preventing sedimentation of dispersed drug particles and shrinking of units while freezing respectively. Procedure for the preparation of fast dissolving tablet using this technique is schematically given in figure 11. A solution or dispersion of the drug is prepared, filled into the blister cavities and are kept in a liquid nitrogen tunnel to freeze. This frozen solvents are then sublimed to produce porous wafers. For packing, blister packs are used to protect Zydis units from moisture.<sup>30</sup>

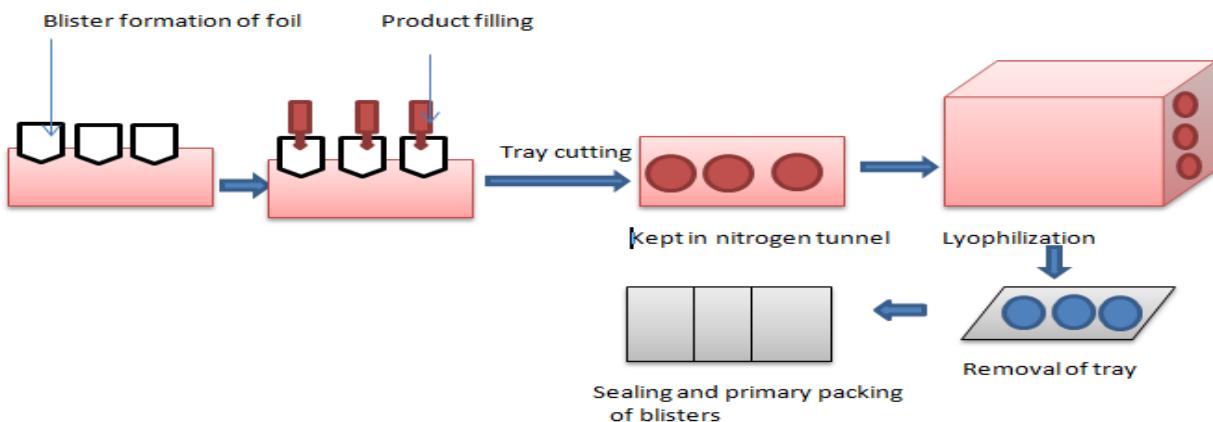


Figure 11: Schematic flowchart of the Zydis technology

#### Advantages:

- Zydis units are having faster dissolution with enhanced bioavailability.
- Tablets obtained are self-preserved.

#### Disadvantages:

- Process is expensive.
- Tablets obtained are not stable at high temperature and humidity.
- Very lightweight and fragile tablets obtained.

### 4.2.2 OraSolv Technology

Orasolv technology was first developed by CIMA labs. This technique uses the concept of effervescence (evolution of carbon dioxide) for the preparation of fast dissolving tablets. The procedure for the preparation of fast dissolving tablets by this technique involves preparation of microparticles. To the polymeric dispersion of suitable polymer like (ethyl cellulose, methyl cellulose, acrylate and meth acrylic acid) resins drug along with mannitol are added under continuous stirring and after that magnesium oxide are added. Dry the mixture for one hour at 50°C delumped and again keep drying for an hour at 50°C. After drying, screened (8 mesh sieves) and drying again for another one hour at 60°C. A schematic flow of the procedure is given below in figure 12. Here, magnesium oxide and mannitol are release promoters as they help in drug release from the polymeric coating. Microparticles formed along with other excipients and effervescent agents are compressed into tablets.<sup>31</sup>

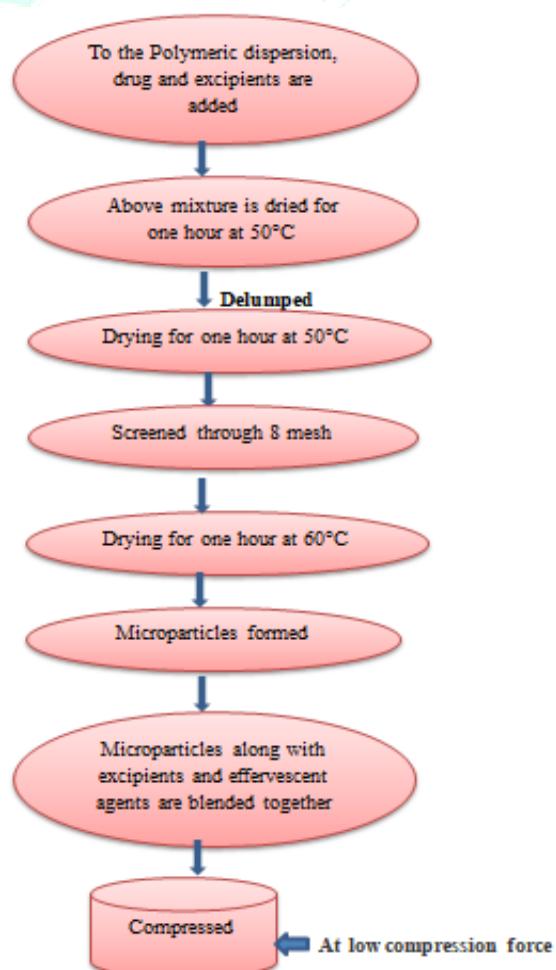


Figure 12: Schematic flowchart of the OraSolv technology

**Advantages:**

- As tablets are compressed under low compression force, coated particles for taste masking of drug escape from fracture during tablet compression.

**Disadvantages:**

- Tablets obtained have less mechanical strength and brittle in nature.
- Special handling and packaging system required for orasolv as these tablets are more brittle and weaker than conventional tablets.

**4.2.3 Durasolv Technology**

The Durasolv technology is the patented formulations of CIMA labs. These are the second generation fast dissolving tablets produced by CIMA labs. They composed of drug, filler and a lubricant. This technique tablets are produced by using conventional tablet equipment with good rigidity.<sup>32</sup>

**Advantages:**

- Best suitable technique for formulation required low amount of drug.
- Tablets are having high mechanical strength than orasolv technology.
- For packing, conventional packing like blister packs can be used.

**Disadvantages:**

- This technique is not suitable for high amount of active ingredients as at high compression force, bitter drugs can be exposed to patient's taste buds.

**4.2.4 Wow tab technology**

This technology was patented by Yamanouchi Pharmaceutical Co. WOW indicates "Without Water". Direct compression method using sugar based excipients forms the base for wow tab technology. For the surface treatment of type 1 saccharide with type II saccharide, Fluidized bed granulation is used. Benadryl fast melt tablets are the

example of tablet produced by this technology. Tablets produced by this technique found to more stable in environmental conditions compared to Zydis and Orasolv as here combination of two different saccharides helps to obtain a tablet having adequate hardness and faster dissolution. Low mould ability saccharides help in rapid dissolution whereas high mould ability saccharides have good binding property. The active ingredient is mixed with saccharides having low mould ability (e.g. lactose, glucose, and mannitol) and granulated with saccharide having high mould ability saccharide (e.g. maltose and oligosaccharides) further compressed into tablet. The active ingredients may constitute up to 50% w/w of the tablet weight and 5-10% of high molded sugar was found to be sufficient to get desired hardness and disintegration property.<sup>33</sup>

**Advantages:**

- Tablets are having adequate hardness and faster dissolution.

**Disadvantages:**

- No Significant change in bioavailability of the drug.

**4.2.5 Flashdose technology / Cotton Candy process**

Fusiz patented the Flash dose technology. First commercial product launched by Biovail Corporation was Nurofen meltlet; a fast dissolving tablet having ibuprofen which melts in mouth.. These tablets consist of "FLOSS" i.e nothing but self -binding shearform matrix. By flash heating process shearform matrix are prepared. By using a unique spinning mechanism a floss-like crystalline structure produced appears like cotton candy. The procedure for preparation of fast dissolving tablet by this technique is mentioned as schematic flow in figure 13. In flash heating processes sugar is subjected to centrifugal force and temperature gradient simultaneously which results in increase in temperature of the mass to create an internal flow condition. The flowing mass exits through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further recrystallized. Crystalline sugar incorporating the active drug is then compressed into a tablet.

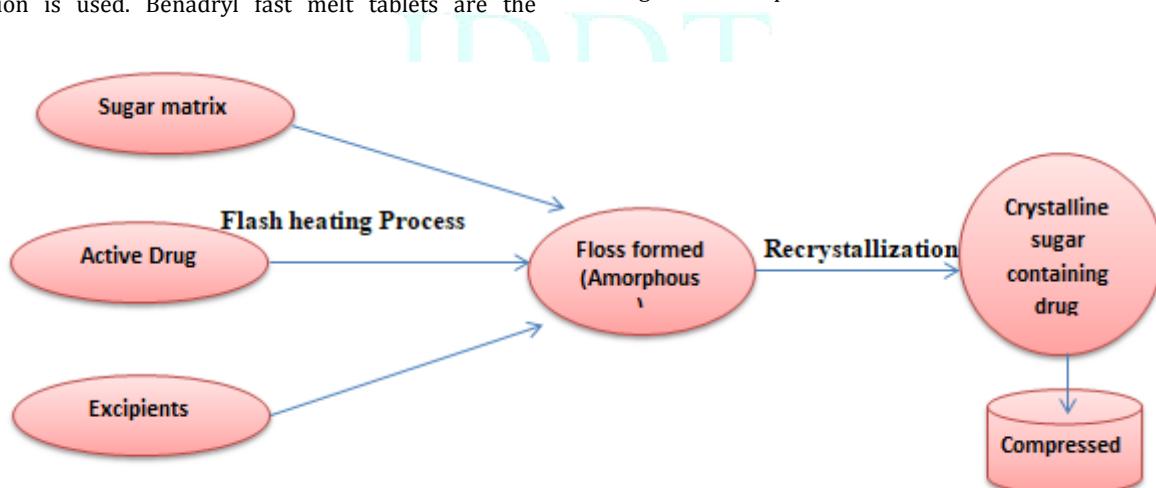


Figure 13: Schematic flowchart of the Flashdose technology

**Advantages:**

- Fast dissolving tablets produced by this technology can accommodate drug up to 600 mg.
- Tablets produced by this technology have very large surface area for dissolution and thus disperse and dissolves quickly once placed on the tongue.

**Disadvantages:**

- Highly friable, soft and moisture sensitive tablets are the major drawbacks.

**4.2.6 Flashtab Technology**

Flashtab Technology has been patented by Prographarm laboratories. In this technology, fast dissolving tablets are prepared by using microcrystals of active ingredients. Conventional techniques like coacervation, extrusion-spheronization, simple pan coating and microencapsulation were used for the preparation of microgranules of drugs. Excipients are used in granular form composed of disintegrating agents, swelling agents and direct compressible sugar. The process used in this technology is the same as of conventional tabletting technology and produced tablets disintegrates within one minute. Procedure for the preparation of fast dissolving tablet by this technique is given in figure 14. Drug in the microcrystal form and excipients in granular form are blended together to compress the tablet.<sup>34</sup>

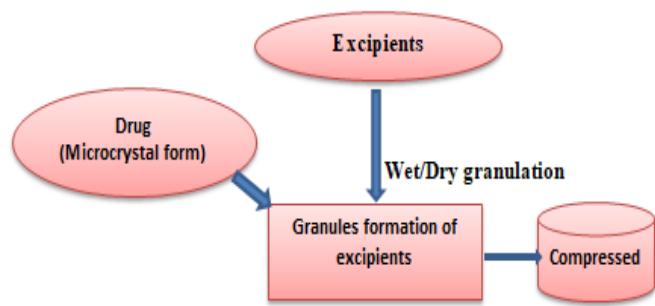
**Advantages:**

- Tablets obtained have good physical resistance and disintegrates in the mouth less than one minute.

**4.2.8 Other Patented Technologies:**

Table 4: Patented technologies available in the preparation of fast dissolving tablets

S. No.	Technology	Patented by	Disintegration Time	Main Mechanism
1	Dispersible technology	Lek in Yugoslavia	Less than one minute	Improved disintegration and dissolution by incorporation of 7 to 10 % of organic acids and disintegrating agents
2	Advatab Technology	Eurand	Less than 30 seconds	---
3	Nanocrystal Technology	Elan	---	decreasing the particle size of drugs, followed by lyophilization
4	Pharmaburst™ technology	SPI Pharma	Within 30 to 40 seconds	Involves the use of co-processed excipients
5	Lyoc Technology	Cephalon Corporation	-	Freeze drying
6	Frosta Technology	Akina	15 to 30 seconds	Used the concept of formulation of plastic granules followed by compression at low pressure which leads to increase in porosity
7	Ziplet Technology	Eurand International	-----	Incorporation of water insoluble inorganic excipients

**Figure 14: Schematic flowchart of the Flashtab technology****4.2.7 Oraquick technology**

This technology has been patented by K. V. S. Pharmaceuticals. In this technology, fast or mouth dissolving tablets are produced by utilizing a patented taste masking technique. Micromask i.e. taste masking microsphere has been used in this technology which provides good and superior mouthfeel over taste masking alternatives, good mechanical strength, and fast dissolution of the product.

**Advantages:**

- Appropriate for heat sensitive drugs due to its lower heat of production
- Tablets obtained have significant mechanical strength
- Fast dissolution with good taste masking.

## 5. MARKETED FAST DISSOLVING TABLETS

Some of the marketed preparations for fast dissolving tablets are mentioned in table 5.

**Table 5: Fast dissolving tablets available in the market based on their technology<sup>35,36</sup>**

S. No.	Product	Example	Active Ingredient	Therapeutic Indication	Manufactured By (Company)
1	Zydis	Feldene Melt 20mg	Piroxicam	Osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.	Pfizer Limited
2	Orasolv Technology	Fazaclor®	Clozapine	Antipsychotic drug	Cima labs
3	Durasolv Technology	Parcopa	Levodopa and carbidopa	Parkinson's disease	Sun Pharma
4	Wow tab Technology	Benadryl fast melt tablet	Diphenhydramine Hydrochloride	Antihistamine, allergy, sinus	Pfizer Limited
5	Flash dose Technology	Ralivia Flashdose®	Tramadol Hydrochloride	Opioid analgesic	Biovail
6	Flash Tab Technology	Nurofen® Flashtab®	Ibuprofen	NSAID	Athena
7	Oraquick Technology	Hyoscyamine sulphate ODT	Hyoscyamine sulphate	Used in diarrhea, gastrointestinal ulcers, irritable bowel syndrome.	Ethex corporation
8	Advatab Technology	Advatab Cetirizine	Cetirizine	Antihistamine used to relieve allergy symptoms such as watery eyes, runny nose, itching eyes/nose, sneezing, and hives.	ADARE Pharmaceuticals
9	Lyoc Technology	Sparfon Lyoc	Phloroglucinol Hydrate	Antispasmodic. reduce spasmodic pain, abdominal pain , and visceral pain of the lower abdomen.	Cephalon
10	Ziplet Technology	Cibalgin duefast	Ibuprofen	NSAID	Novartis

## 6. EVALUATION

Tablet formulation consists of two types of evaluation i.e. pre-compression studies and post compression studies. In below given table 6 and 7, pre-compression and post compression parameters are discussed along with their method respectively.

### 6.1 Pre-compression

**Table 6: Pre-compression parameters along with their method and formula<sup>37</sup>**

S. No.	Parameter	Method										
1	Angle of repose	<p><b>Determined by funnel method.</b></p> <p>Weigh the blend accurately and take in a funnel. Adjust the height of the funnel in such a way that funnel tip touches the apex of the heap of the blend. The blend of drug and excipients was allowed to flow through the funnel freely on to the surface and measure the diameter of the powder cone formed. Angle of repose calculated using the equation:</p> $\tan \theta = h/r$ <p>Where,</p> <p>h is the height of the powder cone</p> <p>r is the radius of the powder cone.</p> <p><b>Relation between Angle of repose and Flow property</b></p> <table border="1"> <thead> <tr> <th>Angle of repose</th> <th>Flow property</th> </tr> </thead> <tbody> <tr> <td>&lt; 0</td> <td>Excellent</td> </tr> <tr> <td>20-3</td> <td>Good</td> </tr> <tr> <td>30-34</td> <td>Passable</td> </tr> <tr> <td>&gt;34</td> <td>Very poor</td> </tr> </tbody> </table>	Angle of repose	Flow property	< 0	Excellent	20-3	Good	30-34	Passable	>34	Very poor
Angle of repose	Flow property											
< 0	Excellent											
20-3	Good											
30-34	Passable											
>34	Very poor											

2	<b>Bulk density</b>	A weighed quantity of blend was poured into a graduated measuring cylinder and volume and weight are measured. <i>BD =Weight of the powder/Volume of the packing.</i>														
3	<b>Tapped density</b>	Take a graduated measuring cylinder and place a known mass of drug-excipients blend. At a height of 10 cm and interval of 2 seconds, the cylinder was allowed to fall under its own weight onto a hard surface and tapping was continues till further no change in volume noticed. <i>Tapped density(TD) = weight of the powder/Volume of the tapped packing</i>														
4	<b>Compressibility index</b>	Carr's compressibility index is used to determine the Compressibility Index of the blends. <i>Carr's compressibility(CI%)=[ (TD-BD)X100]/TD</i>														
		<b>Relation between % Compressibility and Flow ability.</b>														
		<table border="1"> <thead> <tr> <th><b>% Compressibility</b></th> <th><b>Flow property</b></th> </tr> </thead> <tbody> <tr> <td>5-12</td> <td>Excellent</td> </tr> <tr> <td>12-16</td> <td>Good</td> </tr> <tr> <td>18-21</td> <td>Fairly Passable</td> </tr> <tr> <td>23-35</td> <td>Poor</td> </tr> <tr> <td>33-38</td> <td>Very Poor</td> </tr> <tr> <td>&lt;40</td> <td>Very very poor</td> </tr> </tbody> </table>	<b>% Compressibility</b>	<b>Flow property</b>	5-12	Excellent	12-16	Good	18-21	Fairly Passable	23-35	Poor	33-38	Very Poor	<40	Very very poor
<b>% Compressibility</b>	<b>Flow property</b>															
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12-16	Good															
18-21	Fairly Passable															
23-35	Poor															
33-38	Very Poor															
<40	Very very poor															
5	<b>Hausner's Ratio</b>	Similar index used to calculate the flow property of the blend. <i>Hausner's ratio=(Tapped densityx100)/Poured density</i> <i>Hausner's ratio&lt;1.25-Good flow=20% Compressibility Index</i> <i>Hausner's ratio &gt;1.25-Poor flow=33% Compressibility Index</i>														

## 6.2 Post compression

Table 7: Post-compression parameters along with their method and formula<sup>38, 39</sup>

S. No.	Parameter	Method												
1	<b>Tablet thickness</b>	Record the thickness of ten tablets using Vernier caliper. It is an important parameter in counting by counting filling machine as in their counting mechanism, they consider or uses only uniform thickness tablet.												
2	<b>Weight variation</b>	To ensure uniformity of the tablets weight in each batch, weight variation test is carried out. Take 20 tablets and total weight of 20 tablets are noted for each formulation and calculate the average. To find out the weight variation, individual weight of each tablet is also noted for each formulation. Weight variation is given by the formula.  <i>% Weight variation= Individual weight-Average weight/Average weight ×100</i>												
<b>Official weight variations limit as per IP/BP/USP</b>														
		<table border="1"> <thead> <tr> <th>Average weight of tablets (mg) As per USP</th> <th>Maximum percentage difference allowed</th> <th>Average weight of tablets (mg) As per IP/BP</th> </tr> </thead> <tbody> <tr> <td>130 or less</td> <td>10</td> <td>80mg or less</td> </tr> <tr> <td>130-324</td> <td>7.5</td> <td>More than 80mg but less than 250mg</td> </tr> <tr> <td>More than 324</td> <td>5</td> <td>250mg or more</td> </tr> </tbody> </table>	Average weight of tablets (mg) As per USP	Maximum percentage difference allowed	Average weight of tablets (mg) As per IP/BP	130 or less	10	80mg or less	130-324	7.5	More than 80mg but less than 250mg	More than 324	5	250mg or more
Average weight of tablets (mg) As per USP	Maximum percentage difference allowed	Average weight of tablets (mg) As per IP/BP												
130 or less	10	80mg or less												
130-324	7.5	More than 80mg but less than 250mg												
More than 324	5	250mg or more												
3	<b>Hardness</b>	Hardness or crushing strength of the tablet is defined as the force required breaking the tablet across the diameter of the tablet. As hardness of the tablet relates to the breaking, chipping and abrasion while storage and handling of the tablets. To determine the hardness, Monsanto Hardness tester is used. Its unit of measurement is kg/cm <sup>2</sup> .												
4	<b>Friability (F)</b>	Friability test is used to measure the mechanical strength of the tablets. Friability is determined using Roche friabilator contains plastic chambers which will revolve at 25 rpm by dropping the tablets at a 6-inch distance with each revolution for 4 minutes. 20 tablets were weighed from each batch and kept in friabilator and allow the friabilator to rotate at 25 rpm for 4 minutes. Then remove the dust from the tablets and reweighed the tablets again. Friability is the loss in the weight of the tablet and it is given in percentage as  <i>%Friability = loss in weight / Initial weight x 100</i>												
5	<b>Wetting time and water</b>	This method is used to measure the wetting time of a tablet. A tissue paper folded double was taken and cut it into the size of a petridish. Take water around 6 ml and poured onto the tissue												

**absorption ratio**

petridish containing tissue. Place the tablet on the paper and the time taken for tablet to get complete wet is recorded in seconds. By maintain the water at  $37^{\circ}\pm 0.5^{\circ}\text{C}$ , the method was slightly modified. Wetting time is time taken by a tablet to disintegrate when keeping on a tongue motionless. From each batch three trials was done and standard deviations were determined. Equation used for the calculation of water absorption ratio is

$$R = (W_A - W_B) / W_B \times 100$$

Where,  $W_B$  is weight of tablet before water absorption

$W_A$  is tablet weight after water absorption

6	<b><i>in vitro</i> drug release</b>	<i>In vitro</i> drug release profile of the drug was determined by using USP 2 paddle type dissolution apparatus by maintain temperature $37\pm 0.5^{\circ}\text{C}$ rpm (50 or 100) as per their drug profile given in IP and by using specific 900 ml of phosphate buffer as per IP.
7	<b><i>in vitro</i> disintegration time</b>	Complete dispersion time of a tablet can be determined by dropping a tablet in a beaker having 50 ml of Sorenson's buffer pH 6.8. Time required for complete dispersion of a tablet was noted. Select randomly three tablets from each formulations and <i>in vitro</i> disintegration time tests were performed.
8	<b>Modified disintegration test</b>	Standard disintegration tests are having several limitations for performing the disintegration of fast dissolving tablets. Disintegration tests for these tablets should be modified in a manner so that it should show same disintegration in saliva in mouth. For performing the disintegration test, a petridish having 10 cm diameter was taken and filled up with 10 ml of water. Take a tablet and keep carefully in the center of the petridish and note the time required for the tablet to disintegrate completely into fine particles.
9	<b>Stability studies</b>	Fast dissolving tablets of optimized formulation are packed and kept for stability studies as per ICH guidelines and their stability of physical appearance and release property were checked.

## CONCLUSION

Method development of fast dissolving tablets was always being an attractive research topic since last few decades'. Extensive works had been carried out in the development of novel super disintegrating agents and evaluation of new formulation procedures. Even though lots of fast dissolving tablets are available, still continuous improvement and innovation, thus is needed to standardize the novel technology considering taste masking, fast disintegration and quick release. The future improvement may involve modifying drug composition, advanced technique inclusion, biosensor insertion toward achieving new potential in forthcoming trend of invention for bright future.

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