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FAST DISSOLVING TABLETS: A NOVEL APPROACH TO ENHANCE THE BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop FDTs with improved patient compliance and convenience. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. FDTs or orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes various ideal properties, characteristics, challenges in formulation, suitability of drug candidates, various technologies developed for FDT, patented technologies, evaluation methods and various marketed products.

KEYWORDS: Fast dissolving tablets, Oral route, Excipients, Superdisintegrants.

INTRODUCTION

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.[1] 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. Fast Dissolving tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[2]

Ideal Properties of Fast Dissolving Tablets

1. A Fast Dissolving Tablets should be dissolve or disintegrate in the mouth (in saliva) within seconds.
2. It should not require any liquid or water to show its action.[3]
3. Be compatible with taste masking and Have a pleasing mouth feel.
4. Be portable without fragility concern.
5. The excipients should have high wettability, and the tablet structure should also have a highly porous network.
6. It should not leave minimal or no residue in the mouth after oral administration of the tablet.
7. It should be less effective by environmental conditions like humidity, temperature etc.
8. More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.[4,5]
9. Be adaptable and amenable to existing processing and packaging machinery.
10. Allow the manufacture of tablets using conventional processing and packaging Equipments at low cost.[6]
11. Allow high drug loading.
12. Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.

Limitations of Fast Dissolving Tablets.[7-9]

a. The tablets usually have insufficient mechanical strength. So, careful handling is required.
b. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
c. Drugs with relatively larger doses are difficult to formulate into Fast Dissolving Tablets. e.g. Antibiotics like amoxicillin with adult dose tablet containing about 500 mg of the drug.

d. Patients who concurrently take anti-cholinergic medications may not be the best candidates for Fast Dissolving Tablet.
e. Similarly patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Salient Feature of Fast Dissolving Drug Delivery System[10]

1. Ease of Administration to the patient who cannot swallow.
2. No need of water to swallow the dosage form.
3. Rapid dissolution and absorption of the drug, which will produce quick onset of action.
4. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach (pre-gastric Absorption). In such cases bioavailability of drug is increased and improves clinical performance through a reduction of unwanted effects.
5. Good Mouth Feel property.
6. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided.
7. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
8. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
9. Benefit of liquid medication in the form of solid preparation.
10. Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
11. Pre-gastric drug absorption avoids the first-pass metabolism; the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.[10]
12. Rapid drug therapy intervention.
13. New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension.[11]

Criteria for Drug Selection[12]

a. It should not have bitter taste.
b. The dose should be less than 20 mg.
c. Molecular weight should be small to Moderate.
d. Should be of good solubility in water and saliva.
e. It should have partially non-ionized at the oral cavities p^H.
f. It should have ability to diffuse and partition into the epithelium of the upper GIT (log p > 1, or preferably > 2)
g. Should have extensive First pass metabolism.
h. Should have oral tissue permeability.

Challenges in the Formulation of Fast Dissolving Tablets[13]

1. Mechanical strength and disintegration time

Disintegration time will be delayed if the mechanical strength is strong. So a good compromise between these two parameters is always essential.

2. **Taste masking**

Effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

3. **Mouth feel**

The particles generated after disintegration of the mouth dissolving tablets should be as small as possible. Orodispersible tablets should leave minimal or no residue in mouth after oral administration. Moreover addition of flavors and cooling agents like menthol improves the mouth feel.

4. **Sensitivity to environmental conditions**

Orodispersible tablets generally should exhibit low sensitivity to environment conditions such as humidity and temperature.

5. **Cost**

The technology adopted for a mouth dissolving tablets should be acceptable in terms of cost of the final product.

Need for Development of Fast Dissolving Tablets[14]

The need for non-invasive delivery systems persists due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

Patient factors

Fast disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

1. Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
2. Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
3. Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.
4. Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.
5. Mentally challenged patients, bedridden patients and psychiatric patients.

Effectiveness factor

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 formulations 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 fraction of absorption in the oral cavity and pre-gastric segments of GIT.

Manufacturing and marketing factors

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, value-added product line extension and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under treated patient populations.

Ingredients Commonly used for Fast Dissolving Tablets Preparation

In the formulation of Fast Dissolving Tablets the most important additives are as follows-

1. Superdisintegrants[15]

Fast Dissolving Tablet requires faster disintegration, that's why superdisintegrants is needed in formulating Fast Dissolving Tablets. Superdisintegrant used is the one that effective at low concentration and have greater disintegrating efficiency and they are more effective intra-granularly. The problem is, it is hygroscopic therefore not used with moisture sensitive drugs. And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Example: croscarmellose sodium, crospovidone, carmellose, carmellose calcium, sodium starch glycolate ion exchange resins (e.g. Indion 414) Sodium starch glycolate has good flowability than croscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

Selection of Superdisintegrants[16]

Although superdisintegrants primarily affect the rate of disintegration, but when used at high levels they can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate superdisintegrants for a particular formulation should:

- Produce rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.
- Be compactable enough to produce less friable tablets.
- Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.
- Have good flow, since it improves the flow characteristics of total blend.

Mechanism of Action of Superdisintegrants[17]

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

- By porosity and capillary action.
- By swelling.
- Because of heat of wetting.
- Due to release of gases.
- By enzymatic action.
- Due to disintegrating particle/particle repulsive forces.
- Due to deformation.

➢ **Porosity and capillary action (Wicking)**

Capillary action (fig 1) is always the first step in tablet disintegration. Suitable aqueous medium into which tablet is placed, penetrates into the tablet and replaces the air adsorbed on the particles there by weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

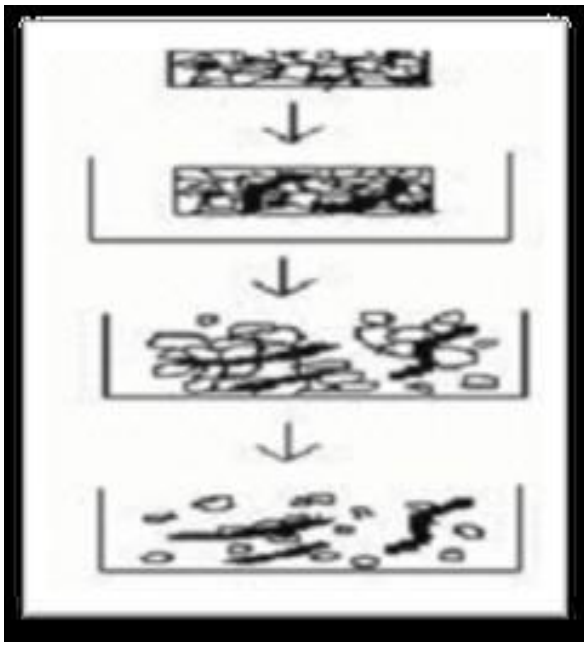


Fig 1: Porosity and capillary action (Wicking)
(*Disintegrant pull water into the pores and reduces the physical bonding forces between the particles)*

➢ **Swelling**

The general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor

disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is to penetrate in the tablet and disintegration is again slows down.

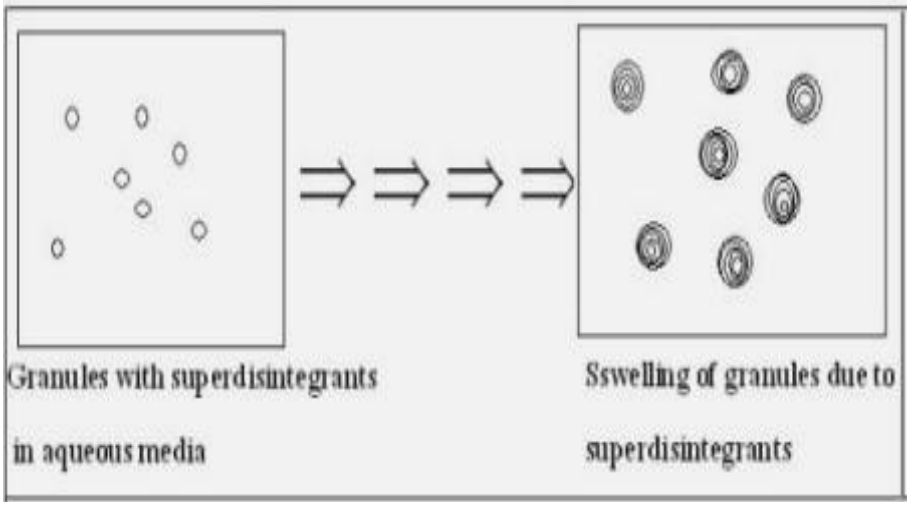


Fig: 2: Swelling of Granules due to Superdisintegrants

Swelling index of the superdisintegrants is commonly studied in simulated saliva. Volume occupied by the material at the end of 4 h should be noted and swelling index is calculated by the formula.
Swelling Index = [(Final volume - Initial volume)/initial volume)] x 100.

- **Because of heat of wetting (air expansion)[17]**

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

- **Due to release of gases**

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression.

- **By enzymatic reaction**

Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

- **Due to disintegrating particle/particle repulsive forces**

Another mechanism of disintegrating attempts to explain the swelling of tablet made with 'non- swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory (Fig 2) based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

- **Due to deformation: (Elastic recovery)**

Most materials, which undergo a plastic deformation during compression, try to return to their initial shape as soon as possible (stored potential energy). In the tablet matrix, there is no means to recover the former shape. But as soon as water penetrates into the tablet matrix and the forces, which keep the particles together, are diminished, those particles have the ability to expand back.

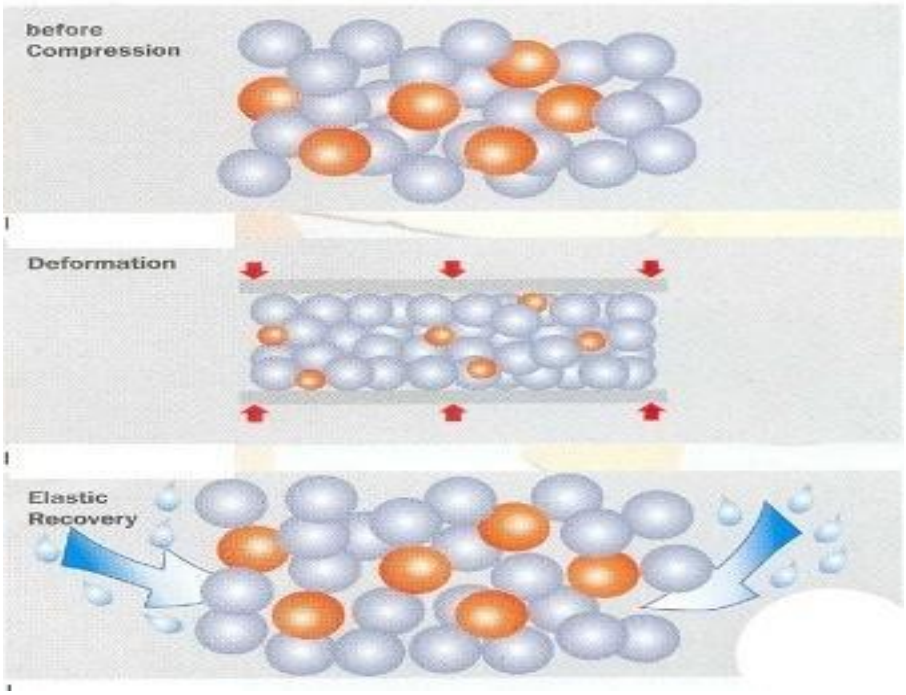


Fig 3: Elastic recovery

In (fig 3) elastic particles are shown before compression (red). After compression, these particles are plastically deformed. After penetration of water into the tablet, these particles return back to their initial shape.

2. Taste-Masking Agents[15]

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

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

3. Sweeteners

Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products, although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Saccharin or its sodium and calcium salts are used as sweeteners.

Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted. Some commonly used sweeteners are:

Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose, Maltose, aspartame, Glycerin, sugars derivatives etc.

4. Binders

- Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage.
- Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol.
- The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet.
- The temperature of the excipient should be preferably around 30–350C for faster melting properties.
- Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

Example: Binders commonly used are cellulosic polymers such as ethyl cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC), alone or in admixtures povidones, polyvinyl alcohols and acrylic polymers.

Acrylic polymers used are the ammoniomethacrylate copolymer, polyacrylate and polymethacrylate. Among the cellulosic.

5. Antistatic Agent

An antistatic agent is a compound used for treatment of materials or their surfaces in order to reduce or eliminate buildup of static electricity generally caused by the triboelectric effect. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling.

Example: colloidal silica (Aerosil), precipitated silica (Sylod.FP244), micronized or non micronized talc, maltodextrins, beta-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearyl fumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant.

6. Lubricants

Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

7. Flavours

Example**:** Peppermint flavour, clove oil, anise oil, eucalyptus oil. Flavoring agents include, vanilla, citrus oils, fruit essences etc.

8. Fillers

Example: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc.

9. Surface Active Agents

Example: sodiumdoecylsulfate, sodiumlaurylsulfate, Tweens, Spans, polyoxyethylene stearate.

Formulation Methodology Employed For Fast Dissolving Tablets

Conventional Technologies

Freeze Drying or Lyophillization[15]

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. Lyophillization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless.

Advantage

Pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects.

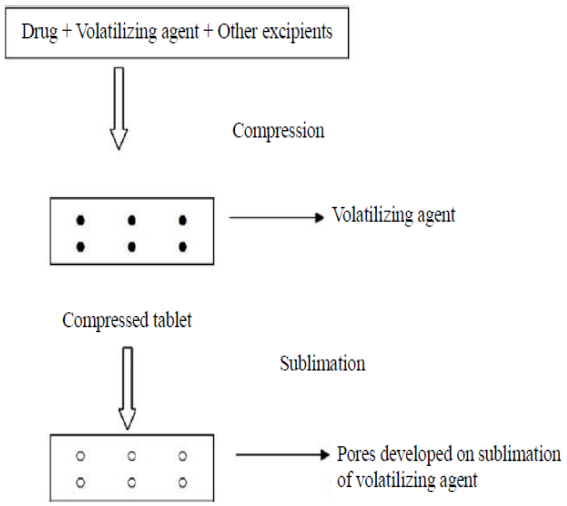
Disadvantage

(i) Due to high cost of equipments lyophillization is relatively expensive and time consuming manufacturing process.

(ii) Fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition.[18, 19]

Sublimation[17]

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Fast dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.



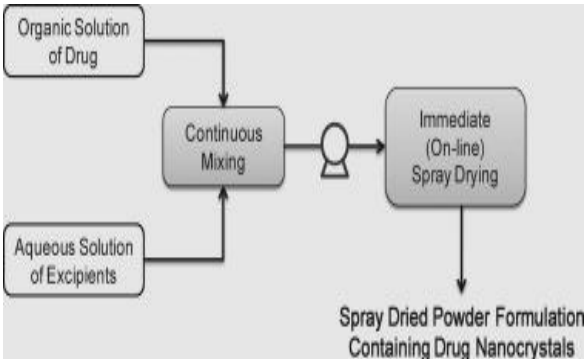
Steps Involved in sublimation

Spray Drying[15]

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet.

The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscarmellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into

tablets. Tablets manufactured by this method disintegrated in < 20 sec. in an aqueous medium.



Principle of the Spray-Drying

Moulding

Molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying.

Advantage

(i) Moulded tablets posess porous structure, which facilitates rapid disintegration and easy dissolution.
(ii) Moulded tablets offer improved taste due to water-soluble sugars present in dispersion matrix.

Disadvantage

But moulded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs.[20] However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength.

Different moulding techniques can be used to prepare mouth-dissolving tablets:

Compression moulding: The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

Heat moulding: A molten matrix in which drug is dissolved or dispersed can be directly moulded into Fast Dissolving Tablets.

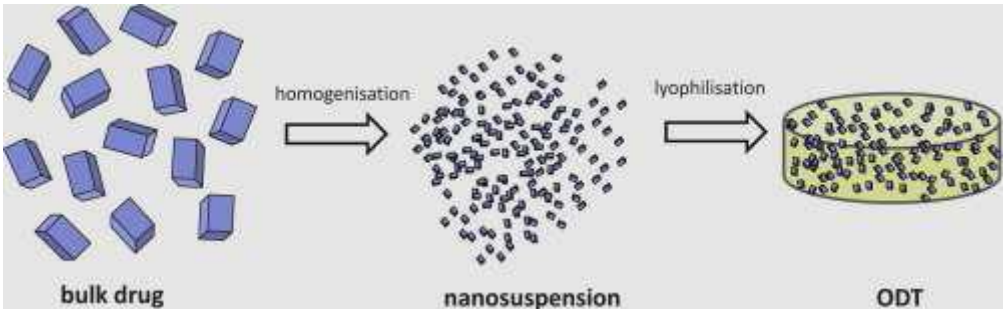
No vacuum Lyophillization: This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

Mass Extrusion[21, 22]

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and there by masking their bitter taste.

Nanonization[23]

In this process, the particles of the drug are reduced in size to nanoparticles by milling the drug in the proprietary wet milling process. The agglomeration can be prevented by surface adsorption of the nanocrystals. These are then compressed and changed into a tablet. This technique is very useful for less water soluble drugs. The bioavailability of the drug is increased as the disintegration time is reduced to a significant extent.



FDT by Nanonization

Patented Technologies For Preparing Fast Dissolving Tablets

The main patented technologies for Fast dissolving tablets are as follows-

Zydis Technology

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 during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the

manufacturing process. Collapse protectants such as glycines prevent the shrinkage of zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.[24,25]

Orasolv Technology

Orasolv technology has been developed by "CIMA" labs. This technology involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet equipments are used for preparation of tablets. Less force of compaction is used for manufacturing to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system.

DuraSolv Technology

DuraSolv is Cimas second-generation fast-dissolving/ disintegrating tablet formulation. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tableting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.[26]

Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". The active ingredients may constitute upto 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldability saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs.[27]

Flash Dose Technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets. Flash dose tablets consist of self binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.[28]

Flashtab Technology

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.[29]

OraQuick

KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics and anti-infectives.[30]

Pharmaburst Technology

Pharmaburst™ is a "Quick Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch faces mouldablilty saccharine are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldablilty saccharides.[30]

Nanocrystal Technology

For fast disintegrating 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 & patent-protected technology elements.
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations.
- Exceptional durability, enabling use of conventional packaging equipment & formats (bottles &/or blisters).
- Wide range of doses (up to 200mg of API per unit).
- Use of conventional, compendial inactive components.
- Employment of non-moisture sensitive in-actives.

Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into FDT dosage forms because manufacturing losses are negligible.[31,32]

Preformulation Studies Fast Dissolving Tablet[35]

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It is expressed in g/ml. This was determined by pouring an accurately weighed quantity of blend into a graduated cylinder and then the volume and weight was measured.

$$D_b = M / V_b$$

Where, Bulk density = D_b, Weight of powder = M and Volume of packing = V_b

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus).
It is expressed in g/mL and is given by $D_t = M / V_t$

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

Compressibility

The compressibility index (Carr's Index) was determined by using following equation,

$$\text{Carr's Index (\%)} = [(D_t - D_b) \times 100] / D_t$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Angle of Repose (q)

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder heap was measured and angle of repose was calculated using following equation,

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

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

Where, θ is the angle of repose is the height in cms r is the radius in cms.

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.

S.No	Angle of repose (^{o})	Type of flow
1	<20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	>34	Very poor

Drug Excipient Compatibility Study

This study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. Compatibility of the drug with excipients was determined by FT-IR spectral analysis.

Evaluation of Fast Dissolving Tablet[36-39]

General Appearance

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in Kg/cm^2

Friability (F)

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport.

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Twenty tablets were weighed and loss in weight (%) was calculated. The friability (F) is given by the formula,

$$\% \text{ Friability} = [(W_1-W_2)100]/W_1$$

Where, W_1= Weight of tablet before test, W_2 = Weight of tablet after test

***In - Vivo* Disintegration Test**

The time for disintegration of ODTs is generally < 1 min and actual disintegration time that patience can experience ranges from 5 to 30 s. The standard procedure are that the test was carried out on 6 tablets using the apparatus specified in I.P. -1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting Time

Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The Washburn Equation, (Washburn, 1921), is one of the most common equations for describing liquid penetration into porous solids. It states that the liquid penetration rate is directly proportional to that pore radius and is affected by the hydrophilicity of the powders, the liquid surface tension (i), the cosine of the contact angle θ and inversely proportional to the liquid viscosity (h).

$$d\,x2/dt = \text{ricos}\,\theta / (2\,h)$$

Where x being the liquid penetration distance, thus x^2 the liquid penetration area, r is the capillary radius, i is the surface tension, h is the liquid viscosity, t is the time and θ is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6 mL of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C.

Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small culture dish (i.d. = 6.5 cm) containing 6 ml of water.[40] A tablet was placed on the paper and the time for complete wetting was measured. The wetted tablet was again weighed. Water absorption ratio, *R*, was calculated using the formula;

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

Where, W_a and W_b are the weight after and before water absorption, respectively.

Drugs that Formulated into Fast Dissolving Drug Delivery Systems

CATEGORY	EXAMPLES
Antibacterial Agent	Ciprofloxacin, Tetracycline, Erythromycin, Rifampicin, Penicillin, Doxycyclin, Nalidixic Acid, Trimethoprim, Sulphacetamide, Sulphadiazine etc.
Anti Helmintics	Albendazole, Mebendazole, Thiabendazole, Livermectin, Praziquantel, Pyantel Embonate, Dichlorophen etc.
Anti Depressants	Trimipramine Maleate, Nortryptyiline HCL, Trazodone HCL, Amoxapine, Mianserin HCL, etc.
Anti Diabetics	Glibenclamide, Glipizide, Tolbutamide, Tolazamide, Gliclazide, Chlorpropamide etc.
Analgesics/Anti-inflammatory agents	Diclofenac Sodium, Ibuprofen, Ketoprofen, Mefenamic Acid, Naproxen, Oxyphenbutazone, Indomethacin, Piroxicam, Phenylbutazone etc.
Anti Hypertensive's	Amolidipine, Carvedilol, Diltiazem, Felodipine, Minoxidil, Nifedipine, Prazosin HCL, Nimodipine, Terazosin HCL etc.
Anti Arrhythmics	Disopyramide, Quinidine Sulphate, Amiodarone HCL etc.
Anti Histamines	Acrivastine, Cetrizine, Cinnarizine, Loratadine, Fexofenadine, Triprolidine etc.
Anxiolytics, Sedatives, Hypnotics and Neuroleptics	Alprazolam, Diazepam, Clozapine, Amylobarbitone, Lorazepam, Haloperidol, Nitrazepam, Midazolam, Phenobarbitone, Thioridazine, Oxazepam, etc.
Diuretics	Acetazolamide, Clorthiazide, Amiloride, Furosemide, Spironolactone, Bumetanide, Erthacrynic Acid, etc
Gastro-intestinal agents	Cimetidine, RanitidineHCL, Famotidine, Domperidone, Omperazole, Ondasetron HCL etc.
Corticosteroids	Betamethasone, Beclomethasone, Hydrocortisone, Prednisolone, Methyl Prednisolone etc.
Anti Protozoal Agents	Metronidazole, Tinidazole, Omidazole, Benznidazole etc.

A Promising Future in Fast Dissolving Drug Delivery System (FDDS)[41,42]

Most of products are available in the same strengths as traditional dosage forms. There are not commercially available fast dissolving drug products for all our patient needs. Pharmacist may wish to consider compounding as a unique way to treat the unmet needs of individual patients. Pharmacists have been altered to exercise additional care when dispensing new prescription for this kind of drug delivery. More products need to be commercialized to use this system properly. Special *In vitro* and *In vivo* test methods to study the performance of these products are required.

Future challenges[43,41]

Fast dissolving intraoral products face many challenges as given below, these challenges are related to new technologies and products as they mature.

- Most of the drugs need taste masking.
- Tablets are fragile and must be protected from water. So special packaging is needed.
- A novel manufacturing process is a challenge, due to new equipment, technology and process.
- Limited drug loading due to technology limitation, taste masking and tablet size.
- Need more clinical trials to study more clinical/medical benefits.
- Older patient benefits by change in taste, flavor and dissolve too fast.
- Cost of the product is a major challenge.
-

Table -List of Marketed Fast Dissolving Systems[44]

S.No	Trade Name	Active Drug	Manufacturer
1.	Abilify Discmelt	Aripiprazole	Otsuka American/Bristol-Myers Squibb.
2.	Allegra ODT	Fexofenidine	Sanofi Aventis
3.	Aricept ODT	Donepezil	Eisai Co.
4.	Alavert Quick Dissoving Tablets	Loratidine	Wyeth
5.	Bendryl Fastmelt	Diphenydramine & Pseudoephedrine	Warner Lambert, NY, USA.
6.	Claritin Redi Tab	Loratidine	Schering Plough Corp.,USA.
7.	Cibalgina Duefast	Ibuprofen	Eurand International
8.	Clarinex Reditabs	Desloratidine	Scheung-Plough
9.	Clonazepam ODT	Clonazepam	Par Pharmaceutical
10.	Fazaclo	Clozapine	Azurpharma
11.	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
12.	Felden Fast Melt	Piroxicam	Pfizer Inc., NY, USA
13.	Gaster D	Famotidine	Yamanouchi Pharma Tech.Inc.
14.	Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharma.Co.,Inc.
15.	Klonopin Wafers	Clonazepam	Roche
16.	Maxalt MLT	Rizatriptan	Merck And Co.,NJ,USA.
17.	Nurofen Flash Tab	Ibuprofen	Ethypharm
18.	Olanex Instab	Olanzapine	Ranbaxy Lab,Ltd.New Delhi, India.
19.	Propulsid Quicksolv	Cispride Monohydrate	Janssen Pharmaceutics
20.	Pepcid RPD	Famotidine	Merck And Co., NJ, USA.

S.No	Name of the Drug	Category	Reason for formulation into Fast Dissolving System	Technology used	Superdisintegrants used	Result	Reference
1	Aceclofenac	Non steroidal anti-inflammatory	To improve the patient compliance without compromising the therapeutic efficacy	Direct compression	Croscarmellose Sodium, Sodium Starch Glycolate, crospovidone.	Formulation containing 10% of croscarmellose as superdisintegrant shows best drug release i.e., 99.21% in 30min compare to other formulations.	[45]
2	Aceclofenac	Non-steroidal anti-inflammatory	To show the effect of various superdisintegrants on the disintegration time and drug release rate.	Wet granulation method	Croscarmellose sodium, sodium starch glycolate, starch 1500.	The formulation containing starch 1500 and croscarmellose in equal proportions showed the fast disintegration as compared to the other formulations.	[46]
3	Aceclofenac	Non-Steroidal anti-inflammatory	To enhance safety and efficacy, better compliance, solve the problem of difficulty in swallowing, enhance onset of action provide stable dosage form.	Direct compression	Sodium starch glycolate, yellow sweet potato starch, crospovidone	The formulation containing 6.6% of yellow sweet potato starch show good dissolution efficiency and rapid dissolution.	[47]
4	Aceclofenac	Non-Steroidal anti-inflammatory.	To enhance dissolution rate.	Wet granulation, Direct compression	Starch citrate, crospovidone	Formulation prepared by wet granulation technique show better results compared to direct compression technique	[48]
5	Aceclofenac	Non-Steroidal anti-inflammatory	To improve solubility, dissolution rate and bioavailability.	Co-grinding method, physical mixing, direct compression.	Aegle marmelos gum, modified aegle marmelos gum (carriers), croscarmellose sodium.	Modified aegle marmelos gum could be used as a potential carrier in the solubility and dissolution rate enhancement of poorly soluble drug. Increased wettability, dispersibility, surface area and solubilisation effect of aegle marmelos gum and modified aegle marmelos gum enhances the solubility of water insoluble drugs.	[49]
6	Aceclofenac	Non-Steroidal anti-inflammatory	To enhance better patient compliance, and onset of action.	Sublimation method and Direct compression.	Crospovidone, sodium starch glycolate, camphor(subiliming agent)	Formulation containing 8%w/w of crospovidone was found to be better formulation when compared to others.	[50]
7	Aceclofenac	Non-Steroidal anti-inflammatory	To investigate the effect of different concentration of	Wet granulation method	Sodium starch glycolate and polyplasdone XL-10	Formulation containing 5% polyplasdone XL 10 shown rapid	[51]

			superdisintegrants on the release profile.			drug release when compared to other formulations.	
8	Aceclofenac	Non-Steroidal anti-inflammatory	To increase the drug release profile in short duration of time.	Direct compression	Crospovidone, sodium starch glycolate, croscarmellose.	Formulation containing 6% croscarmellose sodium can be effectively used as superdisinegrant in aceclofenac fast dissolving tablets.	[52]
9	Aceclofenac	Non-Steroidal anti-inflammatory	to investigate the effect of a natural superdisintegrant and synthetic superdisintegrants by comparing the formulations	Direct compression	Sodium starch glycolate, Ac-di-sol, plantago ovate (natural superdisintegrant)	Formulations containing 2.5%, 5%,7.5% 10% natural superdisintegrant showed better disintegrating property other synthetic superdisintegrant.	[53]
10	Aceclofenac	Non-steroidal anti-inflammatory	To study the effect of functionality differences of superdisintegrants on tablet properties and to provide information on storage conditions of these tablets.	Direct compression	Crospovidone, Croscarmellose Sodium,Sodium Starch Glycolate	The dissolution parameters were consistent with disintegration times of croscarmellose sodium and sodium starch glycolate.	[54]
11	Aceclofenac	Non-steroidal anti inflammatory drug	To improve the dissolution of aceclofenac through the formulation of mouth-dissolving tablets with appropriate mechanical strength, which would disintegrate in oral cavity, in less than 30 seconds, and would provide immediate relief from pain due to its faster dissolution in gastrointestinal tract.	Direct compression , sublimation	Croscarmellose sodium	The method of preparation of formulation significantly affect the disintegration time, percentage friability, and release of drug. so by adopting a systematic formulation appoarch, an optimum point can be reached in the shortest time with minimum efforts and direct compression technique would be the best alternative when compared to wet granulation technique.	[55]
12	Alfuzosin	Alpha adrenoceptor blocker	For rapid disintegration and dissolution characteristics with increased bioavailabilty	Sublimation method	Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate, Camphor(Subliming Agent)	Formulation containing 10%w/w of crospovidone and 30%w/w of camphor as shown faster drug release compared to other formulations.	[56]
13	Alfuzosin Hydrochloride	Alpha adrenoceptor blocker	To enhance patient compliance	Sublimation method	Crospovidone, Croscarmellose Sodium,Sodium Starch	Formulation containing 17%w/w of crospovidone and 13%w/w of camphor showed better results.	[57]

					Glycolate, Camphor(Subliming Agent)		
14	Amlodipine besylate	Anti-anginal	To prepare mouth dissolving tablet of amlodipine using different superdisintegrants by sublimation method.	Direct compression and sublimation methods	Ac-di-sol, sodium starch glycolate, kollidon-CL, camphor (subliming agent)	4% Ac-di-sol as a superdisintegrant in the formulation show good dissolution efficiency and rapid dissolution.	[58]
15	Atenolol	Anti hypertensive	To formulate a convenient dosage form for administration and to achieve better patient compliance.	Effervescent method, direct compression	Sodium starch glycolate, Ac-Di-Sol	Formulation containing 4%sodium starch glycolate, 3% Ac-Di-Sol were considered to be the best formulations.	[59]
16	Atenolol	Anti-hpertensive	To Improve the Onset action and avoidance of water which is highly desirable in this type of disease conditions	Direct compression	Croscarmellose	Formulation containing 8.96% of croscarmellose sodium shows better drug release when compared to others.	[60]
17	Atenolol	Anti hypertensive	To prepare melt-in -mouth tablets of atenolol with enhanced dissolution rate.	Direct compression, sublimation method.	Camphor, menthol	The formulation containing 15%w/w camphor showed better drug release than other formulations.	[61]
19	Atenolol	Anti hypertensive	To formulate orodispersible tablets using super disintegrants and sublimating agents	Direct compression , sublimation	Sodium starch glycolate, croscarmellose sodium	Formulation prepared by sublimation technique show better results compared to other techniques.	[62]
20	Azithromycin Dihydrate	Antibiotic	To enhance dissolution rate and mask bitter taste.	Direct compression, wet granulation	Crospovidone, Croscarmellose Sodium,Sodium Starch Glycolate, Avicel, Aerosil	Formulation containing 8.4% of sodium starch glycolate undergo rapid drug release than the other formulations.	[63]
21	Baclofen	Centrally acting skeletal muscle relaxant	Rapid absorption, rapid onset of action, increased bioavailability	Direct compression	Ac-Di-Sol, Sodium Starch Glycolate, Crospovidone,	The formulation containing 7.5% Ac-Di-Sol shows better drug release at the end of 6 min indicates good bioavailability of the drug.	[64]
22	Carbamazepine	Anti-depressant	To enhance the dissolution rate and bioavailability	Direct compression	Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Indion-414, β- cyclodextrin (complexing agent)	Formulation containing 10% croscarmellose sodium was better and satisfies all criteria as a fast dissolving agent.	[65]
23	Carbamazepine	Tricyclic antidepressants	To formulate a fast dissolving tablets of carbamazepine by	Wet granulation method	Natural superdisintegrant – Plantego ovate	The formulation contain 25% natural superdisintegrant like	[66]

			using different concentrations of natural superdisintegrant plantego ovate seed powder and mucilage			mucilage plantego ovate exihibited faster drug dissolution and satisifies all the criteria as fast dissolving tablet.	
24	Carbamazepine	Anti -Depressant	To study the effect of various carriers on Solid Dispersion Technique	Solid Dispersion	Cros Carmellose Sodium	Formulation containing 10% croscarmellose and mannitol as carrier shows better results and satisfies all other criteria for fast dissolving tablets.	[67]
25	Cefixime	Cephalosporin antibiotic	To formulate mouth dissolve tablet that disintegrate rapidly in mouth and formulate tasteless complex of drug cefixime.	Direct compression	Sodium starch glycolate, croscarmellose, crospovidone, kyron T-314.	Batch formulated with 7.5% crospovidone was the best formulation among all the formulations.	[68]
26	Cetrizine HCL	Non-sedative anti histamine	To formulate mouth dissolving tablets that have quick onset of action, not require water for swallowing of the tablet, less disintegration and dissolution time, hence providing faster relief to the patient.	Sublimation method, direct compression	Camphor, mannitol	Formulation containing 1.5% camphor and 8% mannitol considered to be best one.	[69]
27	Cetrizine dihydrochloride	Anti histaminic	To prepare mouth dissolving tablets of cetrizine in the oral cavity with enhanced dissolution rate and hence, improved patient compliance.	Direct compression	Sodium starch glycolate, croscarmellose, crospovidone	Crospovidone and croscaramellose sodium are better disintegrants for the formulations of mouth dissolving tablets of cetrizine dihydrochloride	[70]
28	Celecoxib	Non steroidal anti-inflammatory	To improve the dissolution rate	Hot melt extrusion method and Direct compression	Sodium starch glycolate	Formulation containing 2.82% sodium starch Glycolate showed better drug release.	[71]
29	Chlorpromazine HCL	Anti-emetic	To enhance the dissolution rate	Direct compression	Croscarmellose Sodium, Sodium Starch Glycolate, crospovidone, L-HPC, pregelatinised starch	Formulation containing 5% crospovidone shows better patient compliance and effective therapy among all the superdisintegrants	[72]
30	Chlorthalidone	Anti- hypertensive	To improve its dissolution rate and bioavailability.	Solid dispersion technique (co-	Polyvinyl pyrrolidone K-12 (carrier), crospovidone.	It is possible to enhance dissolution rate and bioavailability by using	[73]

				grinding)		solid dispersion and co-grinding of the drug with the hydrophilic carriers polyvinyl pyrrolidone and crospovidone.	
31	Cinnarizine	H1 receptor antagonist	Mouth dissolving tablets were prepared by effervescent, superdisintegrant addition and sublimation technique by direct compression, from all these techniques, superdisintegrant addition technique was selected based on the least disintegration time	Direct compression	Crospovidone, croscarmellose sodium	Formulation containing 10% L-HPC showed better drug release.	[74]
32	Cinnarizine	Calcium channel blocker.	For sufficient mechanical integrity content uniformity, acceptable palatability, rapid absorption and onset of action	Sublimation method	Sodium starch glycolate, croscarmellose sodium, camphor (subliming agent)	Formulation containing 12%w/w of croscarmellose sodium and 12%w/w of sodium starch glycolate and 10%w/w of camphor shows effective dissolution than conventional dosage form.	[75]
33	Clonazepam	Anti- epileptic	To enhance patient compliance	Direct compression	Crospovidone, Croscarmellose sodium, Sodium starch glycolate.	The formulation containing 10%w/w of crospovidone show best results compared to the commercial conventional formulation.	[76]
34	Clonazepam	Benzodiazepine derivative	To enhance patient compliance	Direct compression	Crospovidone, Croscarmellose Sodium,Sodium Starch Glycolate, Avicel PH-102	Formulation containing 10%w/w of crospovidone and 35%w/w of microcrystalline cellulose as shown faster drug release compared to the commercial conventional formulations.	[77]
36	Diazepam	Anti-convulsant	To develop a rapidly disintegrating fast dissolving tablet of diazepam that can disintegrate in less than 3 minutes and release 85% of drug within 30 minutes in the oral cavity	Direct compression method	Croscarmellose sodium, Hydroxypropyl beta cyclodextrin (complexing agent)	Rapid drug dissolution was obtained through the formulation of inclusion complex of the drug with Hydroxy Propyl beta cyclodextrin.	[78]
37	Diclofenac	Non-Steroidal anti-	To get fast relief from pain.	Direct	Croscarmellose, Indion 214,	Formulation containing indion 244	[79]

		inflammatory		compression	234, 244	was found to have super disintegrant property compared to indion 214 and 232.	
38	Diclofenac sodium	Non-steroidal anti-inflammatory	To formulate fast dissolving tablets of Diclofenac sodium using different superdisintegrants.	Direct compression	Cross linked carboxy methyl cellulose (Ac-di-sol), sodium starch glycolate (Explotab), cross linked povidone (Polyplasdone XL).	Formulation containing Ac-di-sol as a superdisintegrant shows better result compared to other superdisintegrants used.	[80]
39	Dicyclomine HCL	Anti spasmodic drug	To formulate and characterization mouth dissolving tablets of Dicyclomine Hydrochloride for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of smooth muscle spasm of the GIT.	Direct compression	Crospovidone,sodium starch glycolate, crosscarmellose	Formulation containing 3.4% crospovidone was considered to be the best formulation than others	[81]
40	Domperidone	Anti emetic	To formulate and optimize mouth dissolving tablets of domperidone, having adequate mechanical strength, rapid disintegration and fast action	Direct compression, sublimation	Crospovidone, camphor	The amount of camphor and crospovidone of formulation significantly affect the disintegration time, percentage friability and release of drug. so by adopting a systematic formulation appoarch, an optimum point can be reached in the shortest time with minimum efforts	[82]
41	Domperidone	Anti-emetic	$A3^2$ full factorial design is applied for the optimization of the fast dissolving tablets of the domperidone. The concentration of superdisintegrants (sodium starch glycolate) and the amount of binder (starch paste) were taken as independent variable. The dependent variables selected	Wet granulation method	Sodium starch glycolate	By adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum effects.	[83]

			are disintegration time, wetting time, Q_{30} and friability to find out effect of independent variables on dependent variables.				
42	Etoricoxib	Non-steroidal anti-inflammatory	To prepare optimized fast dissolving tablets of etoricoxib using various sublimating agent	Sublimation and wet granulation technique	Crospovidone, Menthol, Ammonium bicarbonate, Camphor (subliming agents).	Sublimation technique would be an effective alternative approach compared with the use of expensive adjuvants in the formulation.	[84]
43	Etoricoxib	Non-steroidal anti inflammatory drug	To prepare mouth dissolving tablets of Etoricoxib using superdisintegrants in different concentrations.	Direct compression	Primogel , kollidone, Ac-Di-sol, L-HPMC, L-HPC	The formulation containing 8% L-HPC showed better drug release when compared to other formulations.	[85]
44	Felodipine	Calcium channel blocker	To formulate a fast dissolving tablets of felodipine by using co-processed superdisintegrants to increase the water uptake with shortest wetting time, and to increase the disintegration time of the tablets by simple and cost effective direct compression technique	Direct compression	Crospovidone, sodium starch glycolate.	The co-processed superdisintegrants of crospovidone and sodium starch glycolate are superior to physical mixtures of crospovidone and sodium starch glycolate in the formulation.	[86]
45	Flunarizine dihydrochloride	Selective calcium channel blocker	To disintegrate and dissolve rapidly once placed in the oral cavity	Direct compression	Sodium starch glycolate, croscarmellose sodium, crospovidone	Formulation containing 6% crospovidone showed better dissolution profile.	[87]
46	Fexofenadine hydrochloride	Non- sedating anti-histamine	To enhance patient compliance	Sublimation method	Crospovidone, croscarmellose, camphor(subliming agent)	Formulation containing 8% w/w of crospovidone along with 30% w/w of camphor as a subliming agent was found to be a best formulation compared to other formulations.	[88]
47	Fexofenadine HCL	Non-sedating anti-histamine.	To improve bioavailability and enhance patient compliance.	Effervescent method.	Croscarmellose sodium, Crospovidone, sodium starch glycolate, sodium bicarbonate and citric acid (as a effervescent agents).	Formulation containing 8%w/w of crospovidone along with mixture of sodium bicarbonate 24% w/w and anhydrous citric acid 18% w/w was found to be promising and as shown better dispersion time when compared to control formulations.	[89]

48	Glipizide	Anti-diabetic	To formulate and evaluate the fast dissolving sublingual tablet of glipizide.	Wet granulation and sublimation method	Crospovidone, Napthalene (subliming agent)	Amount of naphthalene and crospovidone considerably effects the various parameters such as wetting time, disintegration time, and % friability. So by adopting a systemic formulation approach, an optimum point can be reached in the shortest time with minimum effects.	[90]
49	Glipizide	Anti-diabetic	Sensory study on disintegration time and mouth feel attributes.	Spray drying technique	Mannitol, croscarmellose sodium, microcrystalline cellulose (Diluent)	The co-processed exicipents of mannitol and microcrystalline cellulose are superior to physical mixtures of mannitol and microcrystalline cellulose used in fast dissolving tablets.	[91]
50	Glipizide	Anti- diabetic	To enhance patient compliance.	Direct compression.	Crospovidone, Coscarmellose sodium.	Formulation containing 5% croscarmellose sodium and 3% Polyvinyl pyrrolidone K 30 was selected as a optimized formulation and showed better results compared with marketed formulations.	[92]
51	Glipizide	Anti-diabetic	For sensory study on disintegration time, and mouth feel attributes	Spray drying	Sodium Starch Glycolate, Corn Starch(Anti Adherent)	The co-processed exicipients of mannitol and microcrystalline cellulose showed better results than physical mixtures of microcrystalline cellulose and mannitol.	[93]
52	Granisetron hydrochloride	Anti-emetic	To enhance bioavailability by studying therr methods in the formulation of granisetron HCL	Direct compression, sublimation, effervescent method.	Avicel, camphor, kolliodon CL, ammonium bicarbonate, sodium bicarbonate.	Effervescent method showed better disintegration and drug release as compared to other methods.	[94]
53	Granisetron hydrochloride	Anti-emetic	To improve the therapeutic efficacy	Direct compression	Sodium starch glycolate, Plantago ovate mucilage (natural superdisintegrant)	2.5%, 5%, 7.5%, 1% natural superdisintegrant plantago oate mucilage showed better disintegrating and dissolution property than the most widely used synthetic superdisintegrant.	[95]
54	Granisetron	Anti-emetic	To develop a novel drug	Direct	Croscarmellose Sodium,	Formulation containing 4% w/w of	[96]

	hydrochloride		delivery system for Granisetron HCL by simple and cost effective direct compression method.	compression	Sodium Starch Glycolate, crospovidone	sodium starch glycolate and 2% w/w crospovidone show best results compared to the control tablet formulations.	
55	Granisetron hydrochloride	Selective 5-HT_3 Receptor antagonist.	To improve bioavailability.	Direct compression	Crospovidone, Croscarmellose sodium, Sodium starch glycolate.	Formulation containing crospovidone as fast drug release super disintegrant than other super disintegrants.	[97]
57	Isosorbide mononitrate	Anti anginal drug	To formulate and characterize mouth dissolving tablets of isosorbide mononitrate for rapid dissolutionof drug and absorption, which may produce the rapid onset of action in the treatment of angina pectoris.	Direct compression	Crospovidone	Formulation containing 10% crospovidone was considered to be best formulation.	[98]
58	Isoxspurine hydrochloride	Vasdodilator	To develop and evaluate inclusion complex of isoxspurine hydrochloride β-cyclodextrin using Kneading and coprecipitation methods using DSC.	Kneading and Coprecipitation Method	Ac-di-sol, Sodium Starch Glycolate, crospovidone	Among various formulations the tablets prepared by using 5% ac-di-sol disintegrated rapidly and showed complete release of isoxsuprine HCL within 4 min compared to other.	[99]
59	Loratidine	Anti histamine	To formulate and evaluate mouth dissolving tablets of loratadine using a special preparation technology with a super disintegrating agent.	Direct compression	Croscaramellose sodium	The formulation containing 1.5% croscarmellose sodium and 76% pharmaburstB2Ph.grade showed quicker drug release .	[100]
60	lorazepam	Anti- epileptic	To develop and Optimize Lorazepam by using simple and cost effective methodology	Direct Compression	Crospovidone, sodium bicarbonate, citric acid and tartaric acid (as a effervescent agents).	Formulation containing 8% w/w crospovidone, 18% w/w mixture of sodium bicarbonate- citric acid and tartaric acid was found to be promising formulation.	[101]

CONCLUSION

FDDDS have better patient compliance and may improve biopharmaceutical properties, improves efficacy and better safety, compared with conventional oral dosage forms. After the FDTs, the new products as Fast Dissolving Oral Films (FDOFs) are intended for the application in the oral cavity and they are innovative and promising dosage form especially for use in elder patients. The development of fast dissolving drug products also provides an opportunity for a line extension in market place, a wide range of drugs (e.g. NSAIDS, antiulcer, antihistamine, Hypnotics & sedatives, antipsychotics, antiparkinsonism, antiemetic, antimigrane and antidepressants) can be considered for this dosage form. In future, this system is most acceptable and prescribed due to its quick action i.e. within a minute. Because of increasing patient demand, popularity of these dosage forms will expand the study in future.

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