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# ORALLY FAST-DISPERSING DRUG DELIVERY SYSTEM - A REVIEW

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## ABSTRACT

Recent development in drug delivery system are going on aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. Novel technologies with improved performance, patient compliance, and enhanced quality have emerged in the recent past. Oral fast-dispersing dosage forms, three-dimensional Printing (3DP) and electrostatic coating are a few examples of a few existing technologies with the potential to accommodate various physico-chemical, pharmacokinetic and pharmacodynamic characteristics of drugs. This article provides a comprehensive review on various formulation aspects, technologies and evaluation methodologies, suitability of drug candidates, and future prospects of oral fast-dispersing dosage forms.

**Key words:** Improved patient compliances, oral fast–dispersing dosage form, quick-disintegrating tablets

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## INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several fast-dissolving drug delivery systems have been developed. In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving performance, convenience and compliance. Fast Dissolving Dosage Forms disintegrate and/or dissolve rapidly in the saliva without the need for water[1.]Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[2,3.] The advantage of Fast Dissolving Dosage Forms (FDDFs) are increasingly being recognized in both industry and academia.

## BIO-PHARMACEUTICS CONSIDERATION[4]

When new drug delivery system put on, it is must that to consider Biopharmaceutical factor like metabolism and excretion.

**Pharmacokinetics:**

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution while FDT is rapidly disintegrates in oral cavity and dissolution is fast. Due to disintegration of FDT in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of water-soluble drugs and increased volume of distribution (Vd) of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increased.[4]

**Pharmacodynamic:**

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ. Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin. Decreased sensitivity of the CVS to α-adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient[4]

**Advantages of Fast Dissolving Drug Delivery System (FDDTS)[5-9]:**

- Improved compliance/added convenience
- Increased bioavailability
- No water needed
- No chewing needed
- Improved stability

- Suitable for controlled/sustained release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and ameanable to existing processing and packaging machinery
- Cost- effective.

**Salient Features of Fast Dissolving Drug Delivery System**[10]

1. Ease of administration for patients who are mentally ill, disabled and uncooperative.
2. Requires no water.
3. Quick disintegration and dissolution of the dosage form.
4. Overcomes unacceptable taste of the drugs.
5. Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
6. Allows high drug loading.
7. Ability to provide advantages of liquid medication in the form of solid preparation.
8. Cost- effective, hygroscopic, and friable.

**Need of Fast Dissolving Tablets** [11]

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

- Patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients incompliance due to fear of choking.
- Very elderly patients of depression who may not be able to swallow the solid dosage forms.
- An eight-year old patient with allergies desires a more convenient dosage form than antihistamine syrup.
- A middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

**Excipients Commonly Used for FDT Preparation**

Excipients used in FDT contain atleast one disintegrant, a diluent, a lubricant, and optionally a swelling agent, a permeabilizing agent, sweeteners and flavourings. List of various ingredients used with their concentration is given in Table 1.

**Table 1: Name and weight percentage of various excipients.[53]**

| Name of the excipients | Percentage Used |
|---|---|
| Disintegrant | 1 to 15% |
| Binder | 5 to 10% |
| Antistatic Agent | 0 to 10% |
| Diluents | 0 to 85% |

**Role of superdisintegrants in FDT**

The basic approach in development of FDTs is use of disintegrant. Disintegrant play an important role in the disintegration and dissolution of FDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Superdisintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrant, the wetted surface of the carrier increases; this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. Superdisintegrante's are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases. [12-15] List of commonly used superdisintegrants with their concentration in FDTs is given in Table 2.

**Table 2: Commonly used super disintegrants in fast dissolving dosage forms are.[54,55]**

| Sr no. | Superdisintegrant | Optimum Concenteration | Example |
|---|---|---|---|
| 1. | Modified starches | Sodium starch glycolate | 4-6% |
| 2. | Cross linked PVP | Crosspovidone | 2-4% |
| 3. | Modified cellulose | Cross linked sodium carboxymethyl cellulose | 1-3% (direct compression) 2-4% (wet granulation) |
| 4. | Cross linked alganic acid | Alginic acid NF | 1-5% |
| 5. | Natural | Soya polysaccharides, xanthum gum, gellan gum | |
| 6. | Others | Calcium silicate, ion exchange resin (indion 414) | 20-40% |

**Formulation Aspects in developing FDT[16]**

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the FDTs formed vary in various properties such as,

i. Mechanical strength of tablets
ii. Taste and mouth feel
iii. Swallowability
iv. Drug dissolution in saliva
v. Bioavailability
vi. Stability

**Various Approaches For Fast Dissolving Tablets[17,18,19]**

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

**Technologies**

- Conventional
- Patented

Various conventional and patented technologies with their methods, characteristics, advantages and disadvantages and specific examples used in the formulation of fast dissolving drug delivery systems is given in Table 3 and 4.

**Table 3 :Various conventional technologies used for the preparation of fast dissolving dosage forms.[56-60]**

| Technique | Method | Characteristics |
|---|---|---|
| Freeze drying /lyophilization | The drug is dissolved or dispersed in aqueous solution of a carrier. The mixture is poured into the preformed wells of blister packs. the trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. Finally the blisters are packed and shipped. | Tablets are highly porous, having high specific surface area, dissolve rapidly and show improved absorption and bioavailability. |
| Moulding | Water soluble ingredient with hydro-alcoholic solvent is molded into tablet under pressure lower than that used in conventional tablet compression. | Very Less compact than compressed tablets, porous structured that enhances disintegration/dissolution and finally absorption increased. |
| Sublimation | Inert solid ingredients that volatilize rapidly like urea, camphor, ammonium | Porous structure that enhance dissolution by using volatile material |

| | | |
|---|---|---|
| | carbonate, bicarbonate were added to other tablet ingredients and the mixture is compressed into tablets. The volatile material is then removed via sublimation. | or solvent. |
| Spray drying | Uses hydrolyzed and un-hydrolyzed gelatin as supporting agent, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent and an acidic or alkali material to enhance disintegration/dissolution. | Disintegrate within 20 seconds. |
| Mass extrusion | Involve softening of active blend using the solvent mixture of water soluble polyethylene glycol, methanol expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets. | The dried product can be used to coat granules of bitter tasting drugs and there by masking their bitter taste. |
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| Sublimation | Inert solid ingredients that volatilize rapidly like urea, camphor, ammonium carbonate, bicarbonate were added to other tablet ingredients and the mixture is compressed into tablets. The volatile material is then removed via sublimation. | Porous structure that enhance dissolution by using volatile material or solvent. |
| Spray drying | Uses hydrolyzed and un-hydrolyzed gelatin as supporting agent, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent and an acidic or alkali material to enhance disintegration/dissolution. | Disintegrate within 20 seconds. |

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| Direct compression | Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. | It is most cost effective tablet manufacturing technique. |
| Cotton candy process | Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT.(35-36) | It can accommodate high doses of drug and offers improved mechanical strength. |
| Compaction:<br>a) Melt granulation | Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. | It melts in the mouth and solubilizes rapidly leaving no residue. |
| b) Phase-transition process | Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. | The compatibility increased and so sufficient hardness gained by the formulation. |
| Nanonization | Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. | It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit.) |

| | | |
|---|---|---|
| Fast Dissolving Films. | a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxyl ethyl cellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. | The thin films size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste. |

**Table 4: Advantages and disadvantages of Patented technologies [61]**

| Technique | Novelty | Advantage | Disadvantage |
|---|---|---|---|
| zydis | First to market, a unique freeze dried tablet with the active drug in a water soluble matrix, which is then transformed into blister pockets and freeze dried to remove water | Quick dissolution, self preservation and improved bioavailability | Expensive process and poor stability at higher temperature and humidity |
| Orasolv | Unique taste masking and lightly compressed | Taste masking is two-fold and quick dissolution | Low mechanical strength |
| Durasolv | Similar to orasolv but better mechanical strength | Higher mechanical strength and good rigidity | Inappropriate with large doses |
| Wowtab | Compression molded tablets, proprietary taste masking | Adequate dissolution and hardness | No significant change in bioavailability |
| Flashdose | Unique spinning mechanism producing floss like crystalline structure as cotton candy | High surface area for dissolution | High temperature required to melt the matrix, limit the use of heat sensitive drugs, sensitive to moisture and humidity |
| Flashtab | Compressed dosage form containing drug as microcrystals | Only conventional tablet technology is required | - |
| Oraquick | Uses patented taste masking technology | Faster efficient production for heat sensitive drugs | - |
| Ziplet | Incorporation water insoluble inorganic excipients for excellent physical performance | Good mechanical strength , handling property, can accommodate high dose and weight | As soluble component dissolve the rate of water diffusion in to tablet decreases because of the formation of viscous concentrated solution. |

## EVALUATION OF FDTS[20]

Evaluation parameters of tablets mentioned in the pharmacopoeias need to be assessed, along with some special tests are discussed here.

**1. General Appearance:**

- Shape
- Size
- Colour
- Taste
- Surface texture
- Presence or absence of odour

**2 Hardness/crushing-strength:**

A significant strength of FDT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for an FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet may be measured using conventional hardness testers.

**3. Friability:**

To achieve % friability within limits for an FDT is a challenge to the formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

**% Friability =loss in weight / initial weight * 100**

**4. Wetting time and water absorption ratio**

Wetting time of dosage form is related with the contact angle. Wetting time of the FDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10-cm diameter. Ten millilitres of water-soluble dye (eosin) solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted ($W_b$ ). The wetted tablet from the petridish is taken and reweighed ($W_a$ ). The water absorption ratio, *R* can be then determined according to the following equation:

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

**5. Moisture uptake studies**

Moisture uptake studies for FDT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a desiccators over calcium chloride at 37°C for 24 h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrant) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded**.** [21,22]

**6. Disintegrating test**

The time for disintegration of FDTs is generally <1 min and actual disintegration time that patient can experience ranges from 5 to 30 s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for FDT should mimic disintegration in mouth with in salivary content**.** [23]

**7. Dissolution test**

The development of dissolution methods for FDTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent FDT. Other media such as 0.1 N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for FDT much in the same way as conventional tablets. USP dissolution apparatus 1 and 2 can be used. USP 1 Basket apparatus may have certain applications, but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. Kancke proposed USP 2 Paddle apparatus, which is the most suitable and common choice for FDTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of FDT is very fast when using USP monograph conditions; hence, slower paddle speeds may be utilized to obtain a profile.

The USP 2 Paddle apparatus at 50-100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste-masked drug should match that of the finished product to maximize the value of the test. High-performance liquid chromatography (HPLC) is often required to analyze dissolution aliquots due to presence of UV absorbing components, specifically flavors and sweetener. Excipient to drug ratio may be higher since the formulation is

designed to have good taste and mouth feel, decreasing the detection of the drug to background (excipient) in the UV spectrophotometer. [24]

## SOME OTHER PATENTED TECHNOLOGIES:

### (a) Nanocrystal Technology[25]

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

Nano-Crystal™ Fast dissolving technology provides for: -

- ·Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix
- ·Product differentiation based upon a combination of proprietary and patent-protected technology elements
- ·Cost-effective manufacturing processes that utilize conventional, scalable unit operations
- ·Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters)
- ·Wide range of doses (up to 200mg of API per unit)
- ·Use of conventional, compendial inactive components
- ·Employment of non-moisture sensitive inactives.

### (b) Dispersible tablet technology

Lek, Yugoslavia patents this technology. It offers development of FDT with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that result in quick disintegration Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethylcellulose and cyclodextrins. Combination of disintegrants improved disintegration of tablets usually less than 1 min. [26]

### (c) Pharmaburst technology[27]

SPI Pharma, New Castle, patents this technology. It utilizes the co-processed excipients to develop FDT, which dissolves within 30-40 s. This technology involves dry blending of drug,

flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

**(d) Frosta technology**[28]

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

i. Porous and plastic material,
ii. Water penetration enhancer, and
iii. Binder.

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet.

## RECENT PATENTS ON FAST DISSOLVING TECHNOLOGY

**Naima Mezaache N *et al,* (2010)** filed US Patent on quick dissolve compositions and tablets based thereon. The invention provides a composition useful for making oral dosage form capable of dissolving in the mouth in less than 40 sec. without the need for a conventional superdisintegrant and having a friability of less than 1% wherein the composition includes liquiflash particles and an excipient mass. A preferred excipient mass according to the invention contains a directly compressible inorganic salt; a cellulose derivative. Preferably, the liquiflash particles and the excipient mass are combined in the proportions such that the active ingredient remains substantially within the microspheres when the composition is compressed to obtain a dosage form having a hardness of 20to 50 N. The composition of the invention allow for the fabrication of oral dosage having improved hardness and friability.[29]

**Ramesh (2009)** filed US Patent on oral fast dissolving films for erectile dysfunction bioactive agents. A noval edible polymer based film dosage form manufactured using natural, synthetic, semisynthetic , Pharmaceutically acceptable polymer addressing the issue of difficulty in swallowing tablets and capsule dasoge form and handling and storage difficulties associated with liquid dosage forms, that also include materials such as emulsifying agent, suspending agents, buffering agents, effervescence agent, colorants, flavorants, sweetener and specified amount of bioactive agent for erectile dysfunction. A flexible film dosage form containing sildenafil citrate, tadalafile,or vardenafil is presented.[30]

**Shimizu *et al*,(2008)** filed US Patent on Orally disintegrating tablets. An orally disintegrable tablet, of the present invention, which comprises (i) fine granules having an average particle diameter of 400 .mum or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive, has superior disintegrability or dissolution in the oral cavity so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged or children and easily administered without water. Also, because the tablet of the present invention contains fine granules having the average particle diameter such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration.[31]

**Venkatesh *et al*, (2008)** filed US Patent on Orally disintegrating tablet compositions of lamotrigine. The compositions of the present invention composition comprise a therapeutically effective amount of particles comprising lamotrigine, in combination with granules comprising a disintegrant, and a sugar alcohol and/or a saccharide. These compositions are useful in treating epilepsy and bipolar disorder, particularly for patients with dysphagia, and to improve compliance with bipolar patients.[32]

**Ahmed *et al*, (2006)** filed US Patent on Non effervescent, orally disintegrating solid Pharmaceutical dosage form comprising Clozapine and methods of making and using the same. The present invention is directed to non effervescent ,orally disintegrating dosage forms comprising free base clozapine that are substantially free of acids,water soluble polymers, taste masking polymers and coatings, and methods of making and using the same.[33]

**Dancer *et al*, (2006)** filed US Patent on Crystalline base of escitalopram and orodispersible tablets comprising escitalopram base. The present invention relates to the crystalline base of the well known antidepressant drug escitalopram, S-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofu-rancarbonitrile, formulations of said base, a process for the preparation of purified salts of escitalopram, such as the oxalate, using the base, the salts obtained by said process and formulations containing such salts, and a process for the preparation of purified escitalopram free base or salts of escitalopram, such as the oxalate, using the hydrobromide, the salts obtained by said process and formulations containing such salts. Finally the present invention relates to an orodispersible tablet having a hardness of at least 22 N and an oral-disintegration time of less than 120 s and comprising an active pharmaceutical ingredient adsorbed onto a water soluble filler wherein the active pharmaceutical ingredient has a

melting point in the range of 40-100.degree. C., as well as a method for making such an orodispersible tablet.[34]

**Wang, Wen-Che *et al* ,(2005)** filed US patent on Fast dissolving tablet and method of preparing fast dissolving tablet. The fast dissolving tablet comprises a pharmaceutically active ingredient, a starch, a hydrophilic polymer, a surfactant, and excipients. A method of preparing the fast dissolving tablet is also disclosed. A method of preparing a fast dissolving tablet, comprising: providing a first solution comprising a hydrophilic polymer and a starch; providing a second solution comprising a pharmaceutically active ingredient and a surfactant; blending the first and second solutions to form a plurality of granule powders by a granulating; blending the granule powders and excipients; and performing a compression-moulding process to form the tablet.[35]

**Fu *et al* , (2004)** filed US Patent on Highly plastic granules for making fast melting tablets. A fast-melting pharmaceutical tablet comprises a porous, plastic substance, a water penetration enhancer and a binder. One or more drugs can be incorporated into the formulation at different stages of the process so as to afford a pharmaceutically active tablet. Methods of making the pharmaceutical tablet entail combining the porous, plastic material, the water penetration enhancing agent, and the binder so as to form highly plastic granules, which are compressed into tablets. The resulting tablets dissolve rapidly in the mouth and have good hardness with low brittleness. The tablets are particularly valuable to those who have difficulty swallowing conventional pills.[36]

**Ahmed *et al* , (2004)** filed US Patent on Ondansetron orally disintegrating tablets . An ondansetron solid orally disintegrating dosage form for oral administration having at least one first water-dispersible component or water-insoluble cellulose derivative, a component having a --CHOH functional group, a disintegrating agent and at least one lubricant is provided. The dosage form can comprise ondansetron, a hydrophilic polymer such as microcrystalline cellulose, a component having a --CHOH functional group such as mannitol or xylitol and a disintegrating agent such as crospovidone. The lubricant may be a mixture of magnesium stearate, sodium stearyl fumarate and colloidal silicon dioxide. The present invention provides a non-effervescent tablet comprising the ondansetron dosage form. Another aspect of the invention is the treatment of emesis such as nausea and vomiting caused b cancer chemotherapy and radiation by the administration of the ondansetron formulation of the present composition. Finally, a process of forming an ondansetron disintegrating tablet using the ondansetron dosage form is disclosed.[37]

**Tobyn *et al* , (2003)** filed US Patent on Fast melt multiparticulate formulation for oral delivery. A drug formulation for gastrointestinal disposition, said formulation comprising a free flowing plurality of particles comprising an active ingredient and a water soluble excipient, wherein the particles have a mean diameter of greater than 10-1mm and formulation is capable of dissolving or dispersing in patient's mouth with in 1 minute after the administration without the co-administration of a fluid.[38]

**Cutler *et al*, (2002)** filed US Patent on composition and method for rapid dissolving formulation for dihydroergot amine and caffeine for the treatment of migraine. The present invention is an improvement in the treatment of migraine headaches. By administering dihydroergotamine alone major limitation of the past treatments circumvented thereby allowing for higher efficacy with fewer side effects of treatment with lower doses.[39]

**Allen Loyd V *et al*, (2001)** filed US patent on Particulate support matrix for making a rapidly dissolving dosage form. According to one aspect of the invention, there is provided a particulate matrix comprising a first polymeric component having a predetermined net charge when in solution, a second polymeric (solubilizing) component having a predetermined net charge when in solution of the same sign as the net charge of the first polymeric component, and a bulking agent, characterized in that the second polymeric component has a solubility in aqueous solution greater than that of the first polymeric component. According to another aspect of the invention, there is provided a rapidly dissolving pharmaceutical dosage form comprising: a particulate support matrix comprising a first polymeric component having a predetermined net charge when in solution, a second polymeric component having a predetermined net charge when in solution of the same sign as the net charge of the first polymeric component, and a bulking agent, and wherein the second polymeric component has a solubility in aqueous solution greater than that of the first polymeric component; and a pharmaceutical ingredient mixed with the particulate support matrix. The support matrix is generally substantially completely disintegrable within less than about 20 seconds when the dosage form is introduced into an aqueous environment so as to release the pharmaceutical ingredient to the aqueous environment.[40]

**Herreid Richard M *et al*, (2000)** filed US patent on Method for making fast dissolving bouillon cubes in which method for producing a fast dissolving low fat bouillon cube includes surface of providing a bouillon powder which is free-flowing to a die having a residual of water on a surface. The bouillon powder is compressed at low pressure, thereby forming a fast dissolving bouillon cube. The invention is a method of producing a fast dissolving low fat bouillon cube

which includes providing a bouillon powder. The powder has substantially no wateradded to it. A compression surface of a punch is cleaned with water, leaving a residue of water on the compression surface. A die is filled with bouillon powder and the bouillon powder within the die is compressed with the compression the punch to form a low density fast dissolving bouillon cube.[41]

## CLINICAL STUDIES

In vivo studies have been performed on oral fast-disintegrating dosage forms to investigate their behaviour in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Zydis's residence time in the mouth and stomach, and its trans it through the esophageal tract, was investigated using gamma-scintigraphy. Its dissolution and buccal clearance was rapid[42]**;** the esophageal transit time and stomach emptying time were comparable to traditional tablets, capsules, or liquid forms. A decreased inter subject variability in transit time was also observed[43,44]**.** Zydis also showed good therapeutic efficacy and patient acceptability - particularly in children[45.46] or when easy administration and rapid onset of action were required (such as for patients undergoing surgery)[47,48]. The fast disintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability**.** Increased bioavailability and improved patient compliance were observed in Lyoc formulations for different drugs such as phloroglucinol**,** glafenine[49],spironolactone[50]**,** and propyphenazone[51].Using Zydis, all the drugs that can be absorbed through the buccal and esophageal mucosa exhibited increased bioavailability and side-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism**.** Finally, the suitability of ODTs for long-term therapy was also assessed Lyoc formulations containing aluminium were positively tested in patients with gastrointestinal symptoms[52]**.**

List of some marketed available fast dissolving dosage forms is mentioned in Table 5.

## FUTURE PERSPECTIVE

In future, one can expect the emergence of more novel technologies for FDTs in the days to come, as there are so many advantages of FDT's for the patients. It is reasonable to expect that future trends in innovations of drug delivery systems will continue to bring together different technological disciplines to create novel technologies.

**Table 5: List of marketed Products of FDTs [62]**

| S.No. | Trade Name | Active Drug | Manufacturer |
|---|---|---|---|
| 1 | Felden fast melt | Piroxicam | Pfiser Inc., NY, USA |
| 2 | Claritin redi Tab | Loratidine | Schering plough Corp., USA |
| 3 | Maxalt MLT | Rizatriptan | Merck and Co., NJ, USA |
| 4 | Zyprexia | Olanzapine | Eli lilly, Indianapolis, USA |
| 5 | Pepcid RPD | Famotidine | Merck and Co., NJ, USA |
| 6 | Zofran ODT | Ondansetron | Glaxo Wellcome, Middlesex, UK |
| 7 | Zoming-ZMT | Zolmitriptan | AstraZeneca, Wilmington, USA |
| 8 | Zeplar TM | Selegilline | Amarin Corp., London, UK |
| 9 | Tempra Quiclets | Acetaminophen | Bristol myers Squibb, NY, USA |
| 10 | Febrectol | Paracetamol | Prographarm, Chateauneuf, France |
| 11 | Nimulid MDT | Nimesulide | Panacea Biotech, New delhi , India |
| 12 | Torrox MT | Rofecoxib | Torrent pharmaceuticals , India |
| 13 | Olanex instab | Olanzapine | Ranbaxy lab. Ltd. New-delhi, India |
| 14 | Romilast | Montelukast | Ranbaxy lab. Ltd. New-delhi, India |
| 15 | Benadryl Fastmelt | Diphenhydramine and pseudoephedrine | Warner Lambert, NY, USA |
| 16 | Propulsid Quicksolv | Cisapride monohydrate | Janssen pharmaceutics |
| 17 | Risperdal MTab | Risperidone | Janssen pharmaceutics |
| 18 | Spasfon Lyoc) | Phloroglucinol Hydrate | Farmalyoc |
| 19 | Nurofen FlashTab) | Ibuprofen | Ethypharm |
| 20 | Tempra Quicklets | Paracetamol | Cima Labs,Inc. |
| 21 | Zolmig Repimelt | Zolmitriptan | Cima Labs,Inc. |
| 22 | (NuLev ) | Hyoscyamine Sulfate | Cima Labs, Inc. |
| 23 | Gaster D | Famotidine | Yamanouchi Pharma Tech. Inc. |
| 24 | Cibalgina DueFast | Ibuprofen | Eurand International |
| 25 | Relivia Flash dose | Tramadol HCl | Fuisz Technology, Ltd. |
| 26 | Hyoscyamine Sulfate ODT | Hyoscyamine Sulfate | KV Pharm.Co.,Inc. |
| 27 | Abilify | Aripiprazole | Otsuka /BristolMyers Squibb |
| 28 | Allegra ODT | Fexofenadine | Sanofi Aventis |
| 29 | Aricept ODT | Donepezil | Eisai Co. |
| 30 | Clarinex RediTabs | Desloratadine | Schering-Plough |
| 31 | Alavert Quick Dissolving Tablets | Loratadine | Wyeth |
| 32 | Clonazepam ODT | Clonazepam | Par Pharmaceutical |
| 33 | FazaClo | Clozapine | AzurPharma |
| 34 | Jr. Tylenol Meltaways | Acetaminophen | McNeil Consumer Healthcare |
| 35 | Klonopin Wafers | Clonazepam | Roche |

## CONCLUSION

The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs like chewing, swallowing, patients non-compliance to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of Fast dissolving tablets, which in turn prolongs the patent life of a drug. Keeping in view of the

advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular.

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