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Review Article

Fast dissolving Tablets: New-fangled Drug Delivery System
A Comprehensive Review


Bapatla College of Pharmacy, Bapatla, University College, Visakhapatnam yalamarty College of Pharmaceutical Sciences
Dr. Samuel George Institute of Pharmaceutical Sciences
Email: uday.pharma777@gmail.com
Phone no: 9885177214

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Abstract

Now a day’s Fast Disintegrating tablets have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Orodispersible tablets have emerged as an alternative to conventional oral dosage forms. These are the tablets, which will rapidly disintegrate in the mouth without need of water. Recent development in fast disintegrating technology mainly works to improve the disintegration quality of these delicate dosage forms without affecting their integrity. This article focuses on the patented technologies available and the advances made so far in the field of fabrication of fast disintegrating tablets. The ultimate aim is to provide the tablet that quickly disintegrates or dissolves upon contact with saliva and also provides a good mouth feel.

Keywords: Fast disintegrating tablets, direct compression, Disintegration time, Super- Disintegrates, Dysphasia.

Introduction

Difficulty in swallowing (Dysphasia) is common among all age groups, especially in elderly, and is also seen in swallowing of conventional tablets and capsules. Geriatric and paediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms. Another study shows that an estimated 50% of the population suffers from this problem. These studies show an urgent need for a new dosage form that can improve patient compliance. Solid dosage forms that can be dissolved or suspended with water in the mouth for easy swallowing are highly desirable for the paediatric and geriatric population, as well as other patients who prefer the convenience of readily administered dosage forms. In order to allow fast disintegrating tablets to dissolve in the mouth, they are made of either very porous or soft moulded matrices or compressed into tablets with very low compression force. Fast disintegrating drug delivery (FDDTs,) can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, sublimation. The oral fast-disintegrating tablets are also 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. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The reason of this article is to review different technologies and evaluation parameters currently employed in the formulation of orodispersible tablets.

Necessary Criteria for Fast Dissolving Drug Delivery System

The tablets should:

- No need of water while swallowing, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablets using conventional processing and packaging equipment at low cost.
• Have an acceptable taste masking property.
• Be harder and less friable.

Salient Features of Fast Dissolving Drug Delivery System

• Ease of administration to patient who refuses to swallow a tablet, such as paediatric, geriatric patients and psychiatric patients.
• No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
• Rapid dissolution and absorption of drug, which will produce quick onset of action.
• Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
• Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improve clinical performance through a reduction of unwanted effects.

Advantages of Fast Dissolving tablets:

Fast dissolving technology offers:
• Improved patient compliance
• Not require of water
• Better taste
• 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 amenable to existing processing and packaging machinery
• Cost- effective
• Rapid drug therapy intervention
• Best for patent with oesophageal problems and have difficulties of deglutition tablets.
• improve bioavailability
• Have acceptable taste and pleasant mouth feeling.
• Leave minimum residue.
• Small packaging size, and easy handling by patients

Limitations to Fast dissolving tablets

i) Drugs with relatively larger doses are difficult to formulate into FDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
ii) Patients who concurrently take anticholinergic medications may not be the best candidates for FDT. Similarly patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Need to formulate Fast dissolving tablets

The need for non-invasive drug delivery systems continues 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. FDT is one such dosage form which is useful for
• Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
• Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
• Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.
• Mentally challenged patients, bedridden patients and psychiatric patients.
• 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.

Ideal characteristics of Fast dissolving tablets:

i) Mechanical strength and disintegration time
FDTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many FDTs are fragile and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

ii) Taste masking
Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

iii) Mouth feel
FDT should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDT should be as small as possible. FDT should leave minimal or no residue in mouth after oral administration. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.

iv) Sensitivity to environmental conditions
FDT generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in a FDT are meant to dissolve in minimum quantity of water.

v) Cost - The technology used for a FDT should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

vi) Hygroscopicity- Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity, which calls for specialized product packaging.

Formulation aspects of Fast Dissolving tablets

Fast disintegrating tablets have different characteristics as compare to traditional dosage forms. Taste-masking is of critical importance in the formulation of an acceptable FDT. Traditional tablet formulations generally do not focus on Taste masking issues, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to
of the FDT technologies incorporate unique forms of taste masking as well. 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: (final volume-initial volume/initial volume) X 1008.

Excipients commonly used for FDT preparation

Mainly seen excipients in FDT are as at least one disintegrant, a diluent, a lubricant and optionally, a swelling agent, a permeabilizing agent and flavourings.

Role of superdisintegrants in FDT

The basic approach in development of FDTs is use of disintegrant. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. super disintegrates are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the super disintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Common disintegrants used in this formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmelllose (NS-300), carmelllose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have super-disintegrant property and are widely used in pharmaceutical industry.

Role of binders in FDT

Main role of Binders is to keep the composition of these FDT together during the compression stage. Binders are used to impart smooth texture and disintegration characteristics to the system. commonly used binders are cellulose polymers such as ethcellulose, hydroxypropylcellulose (HPMC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures, povidones, polyvinyl alcohols, and acrylic polymers. The most commonly acrylic polymers are used as ammonio-methacrylate copolymer (Eudragit. RL and RS), polyacrylate (Eudragit. NE), and polymethacrylate (Eudragit. E). The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast-dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredient.

Role of glidants and diluents in FDT

The most commonly known as antistatic agents, which are colloidal silica (Aerosil), precipitated silica (Sylod.FP244), micronized or non micronized tule, maltodextrins, beta- cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearyl fumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. Commonly used Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols, and, preferably, mannitol.

Tastemasking of FDT

Taste masking of bitter or with objectional-tasting drug substances is critical for any orally-administered dosage form. Less commonly, active pharmaceutical ingredients to be incorporated are tasteless and do not require taste masking. Sugar based excipient are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. And the basic requirement for designing FDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used. There are various approaches of taste masking of bitter drugs for FDT.

- A drug solution or suspension can be applied to a substrate followed by polymer coating.
- Drug particles are coated directly.
- Granulation of the drug with certain excipients followed by the polymer coating.

Mechanism of action of disintegrants

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

- a) By capillary action
- b) By swelling
- c) Due to disintegrating particle/particle repulsive forces
- d) Due to deformation
- e) Because of heat of wetting
- f) Due to release of gases
- g) By enzymatic action

a. By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient 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.

b. By swelling

The most widely accepted 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 unable to penetrate in the tablet and disintegration is again slows down.

c. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain
Disintegration of Tablet by Wicking and Swelling.

Swelling of tablet made with ‘non-swellable’ disintegrants. “Guyot- Hermann” has proposed a particle repulsion theory based on the observation that nonswelling 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.

d. Due to deformation

“Hess” had proved that during tablet compression, disintegranted particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression.

e. Because of heat of wetting (air expansion)

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 can not describe the action of most modern disintegrating agents.

f. 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 or can be added in to two separate fraction of formulation.

g. 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.

**Fig. 1.4: Disintegration by Deformation and Repulsion**

This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

**TECHNOLOGIES**

Various researchers practiced FDTs using technologies

**Disintegration by Deformation and Repulsion**

Direct compression, disintegrant addition, freeze-drying, lyophilization or sublimation, moulding, mass extrusion, spray drying, cotton-candy process, oral films/wafers, nanocrystal technology. These technologies differs by method resulting dissimilarity in mechanical strength, stability of drug and product, mouth feel and taste, swallow-ability, rate of drug dissolution in saliva, absorption rate from saliva, and bioavailability. Above technologies were described under conventional and patented technologies.

**CONVENTIONAL TECHNOLOGIES**

i. Freeze Drying.
ii. Tablet Moulding.
iii. Direct Compression
iv. iv Spray Drying.
v. Sublimation.

**PATENTED TECHNOLOGIES**

i. Zydis Technology.
ii. Orasolv Technology.
iii. Durasolv Technology.
iv. Wowtab Technology.
v. Flashdose Technology.
vi. Flashtab Technology.

**Freeze Drying or Lyophilisation**

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. The lyophilisation process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation. Through lyophilization the highly porous tablet may be formed. The disadvantage of lyophilized drug is that have poor stability when stored under stressed condition. However, the use of freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

**Moulding**

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally or partially in the molten carrier to form solid solution and the remaining particles stay undissolved and dispersed in the matrix. Drug disintegration time, dissolution rate and mouth feel will depend on the type of dispersion or dissolution. Moulded tablets disintegrate more rapidly and offer improved taste
because the dispersion matrix is, in general made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

**Sublimation**

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe., 1975, Knitsch et al.,1979 and Roser and Blair., 1998, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane) were compressed along with other excipients into a tablet. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix. Koizumi et al., 1997 applied sublimation technology to manufacture tablets that rapidly dissolve in saliva. Mannitol is used as a matrix former, and camphor was used as a sublimating agent.

**Spray Drying**

This method involves spray drying of a blend containing Solution dispersion for spray comprises hydrolyzed and nonhydrolyzed gelatine as supporting agent for the matrix, mannitol as bulking agent, and sodium starch glycolate or crosscarmellose as disintegrant. Additionally, improvement of disintegration and dissolution was achieved with inclusion of an acid (citric acid) and an alkali (sodium bicarbonate). Porous powder obtained by spray drying of dispersion was blended with other excipients subsequently compressed into tablets having disintegration time of 20 secs.

**Mass Extrusion**

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their obnoxious taste.

**Direct Compression**

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Pharmaceutical companies can use conventional manufacturing equipment and commonly available ingredients. This method can be applied to manufacturing FDTs by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility and sweetness, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations.

**Phase transition process**

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93-95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol (Kuno et al., 2005).

**Melt granulation**

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin (Dong et al., 2007). This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG – 6 – stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilises rapidly leaving no residues (Abdelbary et al., 2004).

**Three-dimensional Printing (3DP)**

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

**IMPORTANT PATENT TECHNOLOGIES FOR MOUTH DISSOLVING TABLETS**

**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 alginites 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 glycine prevent the shrinkage of zydus units during freeze drying process or long term storage. Zydus products are packed in blister packs to protect the formulation from moisture in the environment.

**Ceform Technology™**

In Ceform technology microspheres containing active drug ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly-spinning machine. The centrifugal force of the rotating head of ceform machine throws the dry drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquifies the drug blend to form a sphere without adversely affecting drug stability. The microspheres are then blended and/or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microspheres can be incorporated into a wide range of fast dissolving tablets such as Flashdose, EZ chew, Spoon Dose, as well as conventional tablets.

**Durasolv Technology™**

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

**Advantages**

Durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting.

The Durasolv product is thus produced in a faster and in more effective manner.

**Disadvantages**

It is not compatible with larger doses of active ingredients because the formulation is subjected to high pressures on compaction.

The drug powder coating may fractured during compaction, exposing the bitter tasting drug to patient’s taste buds.

**Otrasolv Technology™**

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

**Advantages**

The Orosolv formulations are not very hygroscopic. The formulation can accommodate high doses.

It also provides a distinct, pleasant sensation of effervescence in the mouth.

**Disadvantages**

A weaker and more brittle tablet in comparison with conventional tablets. Poor mechanical strength. The cost of fast dissolving tablets is higher than the cost of standard tablets made by direct compression. Manufacturing requires a controlled environment at low relative humidity.

**Wowtab Technology™**

Wowtab Technology is patented by Yamanouchi Pharmaceutical Company WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

**Flashtab Technology™**

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion- spheronisation. All the processing utilized conventional tableting technology.

**OraQuick Technology**

**Ziplets™ and AdvaTab™**

AdvaTab™ and Ziplets™ were patented technology intended to produce patient responsive orally disintegrating tablets with a fast disintegration (<30 sec) in the mouth without water with a pleasing taste, outstanding mouth feel, and customised release profiles. These technologies produce tough tablets, as incorporates a proprietary external lubrication system during tablet production, having suitability for bottles or blister packs. These technologies can mingle numerous technologies in one product like Micorcaps® technology, for agreeable taste and mouth-feel; and/or Diffucaps® technology, for traditional release profiles.

**OraQuick™ technology**

“MicroMask” technology patented by KV Pharmaceutical was utilised for designing OraQuick™, a fast-dissolving/disintegrating tablet formulation. Microspheres prepared with this technology had superior mouth feel over taste masking alternatives. The matrix that surrounds and protects the drug in microencapsulated particles was extra supple thus compressed tablets possess significant mechanical strength without disturbing taste masking. The taste masking process not only eliminates employment of any kind of solvents leading to faster and more efficient production but also utilises lower heat of production thus was fit for thermalabile drugs. OraQuick™ comprises a porous, plastic substance, a water penetration enhancer and a binder with quick dissolution (in a few sec) and good taste masking. Tablet was compressed using highly plastic granules prepared from the porous plastic
material, the water penetration enhancing agent, and the binder.

**Lyoc (Laboratories L. Lafon, Maisons Alfort, France)**44:
Lyoc utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent in homogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are Comparable with the loosely compressed fast melt formulations.

**Cotton candy process**65-66:
The flashdose® was an FDT fabricated using Shearform™ technology to mask obnoxious taste. Shearform™, a process of making microspheres as an alternative method of taste masking, had been patented by Fuisz. With Shearform™ technology either excipients or excipients and drugs was transformed into shearform matrices known as ‘floss’. Floss was fibrous material analogous to cotton- candy fibres usually made of saccharides like sucrose, dextrose, lactose and fructose at temperature 180–266°F employing a unique spinning mechanism and afterwards compressed into tablet. Thermodurable drug can be incorporated by replacing sucrose with poly maltodextrins and poly dextrose in the fission formulation that gets transformed into fibres at 30–40% temperature with respect to sucrose. Shearform matrices were of two types. Single floss or unifloss consists of a carrier and two or more sugar alcohols including xylitol while dual floss consists of “base floss” comprising a carrier and at least one sugar alcohol generally sorbitol, i.e., first shearform carrier material; and “binder floss” comprising a carrier and xylitol, i.e., second shearform binder matrix. Instantaneous release, delayed release, sustained release, and combinations there of were the controlled-release systems prepared from shearform matrices.

**Pharmaburst technology**67:
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 facesmouldability saccharides are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldability saccharides.

**Frosta®**65
Frosta®; a pharmaceutically active fast melting tablet, patented by Akina, Inc (West Lafayette, IN); comprises a porous plastic substance, a water penetration enhancer and a binder having capability to incorporate one or more drugs into the formulation at different stages of the process. Tablet was compressed form highly plastic granules obtained by combining the porous plastic material, the water penetration enhancing agent, and the binder; it dissolve rapidly in the mouth while possessing good hardness with low brittleness; and valuable for patients facing difficulty while swallowing conventional pills.

**NanoCrystal technology**68:
For FDT, 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 for the fast dissolving tablets. NanoCrystal™ Fast dissolving technology provides for:

- a) Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix
- b) Exceptional durability, enabling use of conventional packaging
- c) Equipment and formats (i.e., bottles and/or blisters).
- d) High amount drug loading (up to 200mg of API per unit).
- e) The particles which are obtain from nanotechnology is shows resistance to moisture.

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.

**Shearform Technology™**69-70
The Shearform technology is based on preparation of floss that is also known as ‘shearform matrix’, which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallisation. The shearform floss, when blended with the coated or uncoated microspheres, is compressed into Flashdose or EZ chew tablets on standard tabletting equipment.

**EVALUATION OF FAST DISSOLVING TABLET**71-75:
FDTs formulations have to be evaluated for the following evaluation test.

**Size and Shape:** The size and shape of the tablet can be dimensionally described, monitored and controlled.

**Tablet thickness:** Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

**Uniformity of weight:** As per I.P. procedure for uniformity of weight was followed, 20 tablets were taken and their
weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

**Average weight of Tablets (mg)**

<table>
<thead>
<tr>
<th>Maximum percentage difference allowed</th>
<th>Average Weight of Tablet</th>
<th>% Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg or less</td>
<td></td>
<td>±10</td>
</tr>
<tr>
<td>More than 80 mg but less than 250 mg</td>
<td></td>
<td>±7.5</td>
</tr>
<tr>
<td>250 mg or more</td>
<td></td>
<td>±5</td>
</tr>
</tbody>
</table>

**Tablet hardness:** Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto hardness tester.

**Friability:** It is measured of mechanical strength of tablets. Roche friability was used to determine the friability by following procedure. A pre weighed tablet was placed in the friablatorr. Friability consists of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilitorr for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as;

%Friability = loss in weight / Initial weight x 100

**In-Vitro Disintegration test:** 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.

**In Vivo Disintegration test:**

The test was carried out on 2 or 3 tablets using in the mouth and the time in second taken for complete disintegration of the tablet was measured in few seconds.

**Wetting time:** The method reported by Yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson’s buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

**Some of Promising Drug Candidates for Fast Dissolving Tablets**

1. **Antibacterial agents:** Ciprofloxacin, tetracycline, erythromycin, rifampicin, penicillin, doxycycline, nalidixic acid, trimethoprim, sulphacetamide, sulphadiazine etc.
2. **Antihelminthic:** Albendazole, mebendazole, thiabendazole, livermection, praziquantel, pyrantel embonate, dichlorphen etc.
3. **Antidepressants:** Trimipramine maleate, nortriptiyine HCl, trazodone HCl, amoxapine, mianserin HCl, etc.
4. **Antidiabetics:** Glibenclamide, glipizide, tolbutamid, tolazamide, gliclazide, chloropropamide etc.
5. **Analgesics/anti-inflammatory agents:** Diclofenac sodium, ibuprofen, ketoprofen, mafenamic acid, naproxen, oxyphenbutazone, indomethacin, piroxicam, phenylbutazone, e
6. **Antihypertensives:** Amlodipine, carvedilol, diltiazem, felodipine, minoxidil, nifedipine, prazosin HCl, nimodipine, terazosin HCl etc.
7. **Antiarrhythmics:** Disopyramide, quinidine sulphate, amiodarone HCl, etc.
8. **Antihistamines:** Acrivastine, cetirizine, cinnarzine, loratadine, fexofenadine, triprolidine.
9. **Anxiolytics, sedatives hypnotics and neuroleptics:** Alprazolam, diazepam, clozapine, amylorbarbityne, lorazepam, haloperidol, nitrazepam ,midazolam phenobarbital, thiourazide, oxazepam, etc.
10. **Diuretics:** Acetazolamide, clorthiazide, amiloride, furosemide, spironolactone, bumetanide, ethacrynic acid, etc.
11. **Gastro-intestinal agents:** Cimetidine, ranitidine HCl, famotidine, domperidone, omeprazole, ondanseron HCl, granisetron HCl, etc.
12. **Corticosteroids:** Betamethasone, beclomethasone, hydrocortisone, prednisolone, methyl prednisolone, etc.
13. **Antihypertensives:** Metronidazole, tinidazole, omidazole, benzimidazole, clicquolin, decoquinate etc.

**Marketed Products of FDT**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active Drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimulid-MD</td>
<td>Nimesulide</td>
<td>Panacea Biotech, New Delhi, India</td>
</tr>
<tr>
<td>Feldene Fast Melt</td>
<td>Piroxicam</td>
<td>Pfizer Inc., NY, U.S.A</td>
</tr>
<tr>
<td>Zyrif Meltab</td>
<td>Rofecoxib</td>
<td>Zydus, Cadila, India</td>
</tr>
<tr>
<td>Pepcid RPD</td>
<td>Fatomidine</td>
<td>Merck and Co., NJ, U.S.A</td>
</tr>
<tr>
<td>Roliclast</td>
<td>Montelukast</td>
<td>Ranbaxy Labs Ltd., New Delhi, India</td>
</tr>
<tr>
<td>Torrox MT</td>
<td>Rofecoxib</td>
<td>Torrent Pharmaceuticals, Ahmedabad</td>
</tr>
<tr>
<td>Olanex Instab</td>
<td>Olanzapine</td>
<td>Glaxo Wellcome, Middlesex, UK</td>
</tr>
<tr>
<td>Zofran ODT</td>
<td>Ondansetron</td>
<td>Prographearm, Chateauneuf, France.</td>
</tr>
<tr>
<td>Mosid-MT</td>
<td>Mosapride citrate</td>
<td>Merck and Co., NJ, U.S.A</td>
</tr>
<tr>
<td>Febructol</td>
<td>Paracetamol</td>
<td></td>
</tr>
<tr>
<td>Maxalt MLT</td>
<td>RizatRIPTAN</td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSIONS:**

The FDTs have potential advantages over conventional dosage forms, with their improved patient compliance, convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. FDTs formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. These FDTs can be used easily in children who have lost their primary teeth and in geriatric patients who have lost...
their teeth permanently. They remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. As they have significant advantages as both solid and liquid dosage forms, FDTs may be developed for most of the available drugs in near future.

References

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