Review Article CODEN: IJPRNK ISSN: 2277-8713
Rajesh Asija, IJPRBS, 2013; Volume 2(4): 442-463 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

FAST DISINTIGRATION TABLETS - A REVIEW

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Accepted Date: 24/08/2013; Published Date: 27/08/2013

Abstract: From all drug delivery systems, oral drug delivery remains the most preferred option for administration for various drugs. Through this route tablet, capsule, suspension, solutions, syrups are administered. In recent trends fast dissolving technology is most important and useful for geriatric, pediatric and mentally ill patients. Fast dissolving tablets (FDTs) are tablets that dissolve or disperse in saliva within few seconds without water. Recent developments in the technology have prompted scientists to develop orally fast disintegrating tablets with improved patient compliance and convenience.

Keywords: Fast Dissolving Tablet, Recent technologies, Rapid disintegration, Conventional techniques

PAPER-QR CODE

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Access Online On:

www.ijprbs.com

How to Cite This Article:

Rajesh Asija, IJPRBS, 2013; Volume 2(4): 442-463

INTRODUCTION:

The FDTs emerged with an objective to improve patient compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients. This disorder of dysphagia is associated with many medical conditions including stroke, parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy. One study showed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste. Rapid breakdown or fast disintegrating tablet of the type of those intended to undergo disaggregation in the mouth in contact with the saliva in less than 60 seconds, preferably in less than 40 seconds, forming a suspension which is easy to swallow. It is better known by the phase "oral disintegrating tablets".

The Center for Drug Evaluation and Research (CDER) defines FDTs as a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed under the tongue. The European Pharmacopoeia however defines a similar term, orodispersible tablets, or tablets intended to be placed in the mouth where it disperses rapidly before swallowing. FDTs are known by various names such as "fast-melting, fast dissolving, mouth melts, mouth dissolving, quick disintegrating, porous tablets, rapid melts or orodispersible tablets." As the tablet disintegrates in mouth, this can enhance the clinical effect of drug through pregastric absorption from the mouth, pharynx and esophagus[1]. In such cases, bioavailability of drug is significantly enhanced by avoiding first pass hepatic metabolism than those observed with conventional tablets. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction it has been shown in table 1.

Table 1: Some of promising drugs candidate for fast disintegrating tablets[1]:

CATEGORY	EXAMPLES
1. Antibacterial agents	Ciprofloxacin, Tetracycline, Erythromycin, Rifampicin, Penicillin, Doxycyclin, Nalidixic Acid, Trimethoprim, Sulphacetamide, Sulphadiazine etc.
2. Anti Helmintics	Albendazole, Mebendazole, Thiabendazole, Livermectin, Praziquantel, Pyrantel Embonate, Dichlorophen, etc.
3. Anti Depressants	Trimipramine maleate, Nortriptyline HCl, trazodone HCl, Amoxapine, Mianserin HCl, etc.
4. Anti Diabetics	Glibenclamide, Glipizide, Tolbutamide, Tolazamide, Gliclazide, Chlorpropamide etc.
5. Analgesics/Anti-Inflammatory agents	Diclofenac Sodium, Ibuprofen, Ketoprofen, Mefenamic Acid, Naproxen, Oxyphenbutazone, Indomethacin, Piroxicam, Phenylbutazone,etc.
6. Anti Hypertensives	Amlodipine, Carvedilol, Diltiazem, Felodipine, Minoxidil, Nifedipine, Prazosin HCl, Nimodipine, Terazosin HCl etc.
7. Anti Arrhythmics	Disopyramide,Quinidine Sulphate, Amiodarone HCl,etc.
8. Anti Histamines	Acrivastine, Cetrizine, Cinnarizine, Loratadine, Fexofenadine, Triprolidine,etc.
9. Anxiolytics, Sedatives Hypnotics and	Alprazolam,Diazepam,Clozapine,
10. Neuroleptics	Amylobarbitone, Lorazepam, Haloperidol, Nitrazepam, Midazolam Phenobarbitone, Thioridazine, Oxazepam,etc.
11. Diuretics	Acetazolamide, Clorthiazide, Amiloride, Furosemide Spironolactone, Bumetanide, Ethacrynic Acid,etc.
12. Gastro-intestinal agents	Cimetidine, Ranitidine HCl, Famotidine, Domperidone, Omeprazole, Ondansetron HCl,etc.
13. Corticosteroids	Betamethasone,Beclomethasone, Hydrocortisone, Prednisolone, MethylPrednisolone, etc.
14. Anti Protozoal agents	Metronidazole, Tinidazole, Omidazole, Benznidazole,

Requirements of fast dissolving tablets

- Have a pleasing mouth feel
- Have an acceptable taste masking property
- Should be harder and friable
- Leave minimal or no residue in the mouth after oral administration
- Exhibit low sensitivity to environmental conditions such as humidity and temperature
- Allow the manufacture of tablet using conventional processing and packaging equipments

Ideal Properties of Fast Dissolving Tablets

They should:

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

Advantages of fast dissolving tablets

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients
- Patient's compliance for disabled bedridden patients and for travelling and busy people, who do not have ready access to water
- Good mouth feel property of FDTs helps to change the basic view of medication as "bitter pill", particularly for pediatric patients due to improved taste of bitter drugs
- Convenience of administration and accurate dosing as compared to liquid Formulations
- Benefit of liquid medication in the form of solid preparation
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved

clinical performance by reducing side effects

- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension

Limitations of fast dissolving tablets

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly
- Drugs with relatively large doses are difficult to formulate into FDTs

Selection of Drugs:

The ideal characteristics of a drug for in vivo dissolution from an ODT include:

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue Unsuitable drug characteristic for ODT;
- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release[2].

Factors to be considered for Selection of Superdisintegrants:

- **Disintegration**:

The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressure necessary to provide rapid disintegration in the mouth.

- **Compactibility:**

It is desirable to have ODT with acceptable hardness and less friability at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed.

- **Mouth feel:**

Large particles can result in a gritty feeling in mouth. Thus, small particles are preferred. If the tablet form a gel-like consistency on contact with water, However, it produces a gummy texture that many consumer find objectionable.

- **Flow:**

In typical tablet formulation, suprdisintegrants are used at 2-5 wt % of the tablet formulation. With ODT formulation, disintegrant level can be significantly higher[3].

Important Criteria for Excipient used in Formulation of ODTs:

- It must be able to disintegrate quickly.
- Their individual properties should not affect the ODTs.

- It should not have any interaction with drug and other excipieints.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When selecting binder (a single or combination of binders) care must be taken in the final integrity and stability of the product.
- The metlting point of the excipients used should be in the range of 30-35ºC34.
- The binder may be in liquid, semi solid, solid or polymeric in nature[4,5].

Conventional techniques used in the preparation of fast dissolving drug delivery system:

1. Freeze-drying or lyophilization:

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. Commonly used excipients with their uses and examples employed in manufacturing of fast dissolving tablets using Freeze-drying are listed on next page. A typical procedure involved in the manufacturing of fast dissolving tablets using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs areplaced in refrigerated cabinets to continue the freezedrying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped.

The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The Zydis formulations consist of a drug physically trapped in a water-soluble matrix (saccharine mixture and polymer), which is freeze dried to produce a product that dissolves rapidly when placed in mouth. The ideal candidate for Zydis technology should be chemically stable and water insoluble and particle size preferably less than 50 micron. Water soluble drugs might form eutectic mixtures and not freeze adequately, so dose is limited to 60 mg and the maximum drug limit is 400 mg for water insoluble drug as large particle sizes might present sedimentation problems during manufacture.

The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2. Tablet moulding:

The preparation of fast dissolving tablets using molding technology employs water-soluble ingredients so that the tablet dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of

the mouth. Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by airdrying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. Mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30˚C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

3. Spray drying:

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing fast dissolving tablets. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose sodium or crospovidone are used as superdisintegrants. Tablets manufactured from the spraydried powder have been reported to disintegrate in less than 20 seconds in aqueous medium.

4. Sublimation:

The key to rapid disintegration of fast dissolving tablets is preparation of a porous structure in the tablet matrix. To generate such a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and pthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents. Vacuum drying technique has been very often used by researchers to sublime the volatile ingredients and thus maximize the porous structure in the tablet matrix. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

5. Direct compression:

There was no much attention to the direct compression of pharmaceuticals in the previous days (late 1950s). Now a day's great deal of attention has been given to both product and process development. The availability of new materials, new

forms of old materials and the invention of new machinery has allowed the production of tablets by simplified and reliable methods. In early 1960's, the introduction of spray dried lactose (1960) and avicel (1964) had changed the tablet manufacturing process and opened avenues of direct compression tableting. Previously, the word direct compression was used to identify the compression of a single crystalline compound (i.e. sodium chloride, potassium chloride, potassium bromide, etc.) into a compact form without the addition of Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of fast dissolving tablets because of the availability of improved excipients especially superdisintegrants and sugar based excipients. Direct compression, using directly compressible excipientsis the most commonly used method of preparing fast dissolving tablets. Directly compressible excipients are very coarse and granular in nature and give a coarse dispersion in the mouth with decreased mouth feel and compliance. It is very difficult to prepare fast dissolving tablets with drugs having very low bulk density, higher dose and poor flow property using this technique.

6. Dry granulation technique:

The fast dissolving tablets has been prepared by means of dry granulation technology, which has the following advantages over other techniques of preparation:

1. It can be used for all types of drugs including moisture sensitive and heat sensitive.

2. It can be used for drugs having very low bulk density

3. It can be used for poorly compressible drugs and drugs having poor flow property.

4. The tablets can be packed into regular bottles, blister, strip pack or sachets.

5. The tablets can be stored in bulk in drums to be packaged subsequently. Moreover conventional tablet packaging feeders can be used for packing purpose. The process of dry granulation is cost effective as it avoids solvents, and the processes of drying like freeze drying, spray drying etc.

6. This reduces overall reduction in capital expenditure (conventional processing, packaging, and storage facilities). These dosage forms may be in the form of tablets, wafers, granules, or granules packed as such along with other pharmaceutically acceptable additives in a suitable package which upon contact with water, saliva or aqueous solution disintegrates within a few seconds.

7. Cotton candy process:

The cotton candy process is also known as the "candy floss" process and forms the basis of the technologies such as Flash Dose (Fuisz Technology). A fast dissolving tablets is formed using a candyfloss or shear form matrix; the matrix is formed from saccharides or polysaccharides

processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candyfloss can then be milled and blended with active ingredients and other excipients and subsequently compressed into fast dissolving tablets. However the high processing temperature limits the use of this technology to thermo stable compounds only.

8. Mass extrusion[6]:

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent 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 for bitter drugs and thereby achieve taste masking.

New orally disintegrating dosage forms:

Oral films and wafers:

Oral films and wafers are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water.

They have the advantage of a large specific surface area for disintegration. One or a combination of the following processes like hot-melt extrusion; solid dispersion extrusion, rolling and solvent casting are used to manufacture these films. A major limitation of these dosage forms is low drug loading capacity and limited taste masking option.

Phase transition

Kuno et al proposed a novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. Heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low/little compatibility.

Melt granulation:

Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated byimpeller blades. Perissutti et al prepared carbamazepine fast-release tablets by melt granulation technique using polyethylene glycol 4000 as a melting

binder and lactose monohydrate as hydrophilic filler.

Nanonization:

A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (up to 200 mg of drug per unit).

Fast dissolving films:

It is a newer developing front in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, CMC, HPMC, HEC, HPC, PVP, PVA etc.), drug and other taste masking ingredients are dissolved in non-aqueous solvent to prepare non-aqueous solution, which on evaporation of solvent forms a film. Resin adsorbate or coated micro particles of the drug can be incorporated into the film if the drug is bitter. This film when placed in mouth, melts or dissolves rapidly and release the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 sec with instant drug delivery and flavored taste. Each technology has a different mechanism, and each fast-dissolving / disintegrating dosage form varies regarding the following:

* Mechanical strength of final product;

* Drug and dosage form stability;

* Mouth feel;

* Taste;

* Rate of dissolution of drug formulation in saliva;

* Swallow ability;

* Rate of absorption from the saliva solution;

* Overall bioavailability.

Patented technologies for fast dissolving tablets[7,8]

1) Zydis technology (Cardinal Health Inc.):

Zydis was first marketed technology and introduced by R. P.Scherer Corporation (Cardinal Health, Inc.) in 1986. It is a unique freeze-dried oral solid dosage form, that can be administered without water and it dissolves instantly on tongue in less than 3 seconds. The Zydis tablet is produced by lyophilizing the drug in a matrix. The matrix consists of water soluble saccharides and polymer (gelatin,dextran, alginates) to provide rapid dissolution and to allow sufficient physical strength to withstand handling. Orasolv ®technology can accommodate a wide range of active ingredient from 1 mg to 500 mg. The effervescence occurs due to chemical reaction between organic acid such as citric acid, fumaric acid or maleic acid and abase such as sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate, which result in generation of CO251,52. Effervescent disintegration agents evolve gasby means

of chemical reaction called effervescent couple. Carbonates such as sodium bicarbonate, sodium carbonate,potassium bicarbonate and potassium carbonate, magnesium carbonate, and acids like citric, tartaric,fumaric, adipic and succinic are used. Microparticles, effervescent agents, and other ingredient such as flavors,sweeteners, colorants, and lubricants are blended and compressed at a low degree of compaction. The major disadvantage of Orasolv® technology is its low mechanical strength. The tablets produced are soft and friable and need to be packaged in specially designed pack.

2) Durasolv® technology (Cima Labs, Inc.):

Durasolv® is Cima's second-generation fastdissolving/disintegrating tablet formulation. Durasolv® has muchhig her mechanical strength than Orasolv due to the use of higher compaction pressures during tableting.Durasolv® product is thus produced in a faster and more cost-effective manner. It is so durable that it can be packaged in either traditional blister packaging or vials. This technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike Orasolv®,the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in Durasolv® may become fractured during compaction, exposing the bitter-tasting drug to a patient'staste buds. Therefore, Durasolv® technology is best suited for formulations including relatively small doses of active compound. The tablets made by this technology consist of a drug, fillers, and lubricants, prepared by using conventional tableting equipment, and have good rigidity.Durasolv® product is so durable that it can be packed in either traditional blister pack or vials. Due to higher force of compaction used, tablets prepared are rigid It is one of the appropriate technologies for product requiring low amounts of active ingredients.

3) **Orasolv Technology:**

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution 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 Wowtab Technology Wowtab technology is patented by Yamanouchi Pharmaceutical Co. WOW meaning "Without Water ". In this process, combination of low mould ability 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 in to tablet. Flashtab technology Prographarm laboratories have patented the Flashtab technology.

Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion spheronisation. All the processing utilized conventional tabletting technology.

4) Wow tab Technology: Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "WithoutWater". In this process, combination of low mouldability saccharides and high mouldabilitysaccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed witha low mouldability saccharide (e.g. lactose, glucose, and mannitol) and granulatedwith a highmouldability saccharide (e.g. Maltose, oligosaccharides) and compressed

***5)* EFVDAS technology (Elan Corporation):**

EFVDAS or Effervescent Drug Absorption System is a drug delivery technology that has been used in the development of a number of both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use. The granular contents of the sachets can beadded to boiling water to produce pleasant-flavored solutions. In these cases the effervescence of the granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, acetaminophen,cimetidine, naproxen, and acetaminophen and codeine combination product.

6) Multiflash technology (Prographarm):

Multiflash is a multi-unit tablet composed of coated micro granules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the oesophagus after being swallowed with a minimum amount of water. This tablet avoids mucosal adhesion, and coated pellets can match various dissolution rates.

7) Pharmaburst technology:

SPI Pharma, New castle, patents this technology. It utilizes the coprocessed excipients to develop ODT, which dissolves within 30-40seconds. 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.

8) Advantoltm 200

ADVANTOLTM 200 is developed by SPI Pharmaceutical it uses directly compressible excipient to produce "Soft-Melt" tablet by involving co-processing technology. The tablets are produced by conventional technique and equipment. The tablets produced are robust with good mechanical strength. [7]

9) Advatab *technology:*

Advatab is developed by Eurand international the tablet having short disintegration time of

30 seconds and administered without water. Eurand international has its own registered technological products Microcaps® and Diffucaps®. The combination product of Advatab and Microcaps has advantages such as ideal dosage form with superior taste and soft mouth feel but the disadvantage is taste masking of unpleasant drug. [9]

10) Ceform technology:

Ceform technology involves microsphere formation of active ingredients along with excipients opening. The microspheres are formed in fast spinning machine, the centrifugal force is responsible for throwing the drug blend through small heated opening. The heat liquefies drug blend to form sphere. The sphere are compressed into tablets. The simultaneous drug and excipient processing offers unique microenvironment that enhances solubility and stability. [10]

11) Cotton candy technology:

The cotton candy process is patented by Fuise. This process involves spinning mechanism to produce floss like structure as appears in cotton candy. The floss formation increases the surface area very high that increases the dissolution rate. The flossy material mixed with excipients and then compressed into tablet. The tablet shows improved mechanical strength accommodates larger doses of drug but limitation is thermo labile substances as the process involves high temperature. [11]

12) Flashdose (fuisz)

The technology Flash dose has been patented by "Fuisz". A new form of ibuprofen as meltin- mouth tablets, Nurofenmeltlet prepared using flash dose technology. " Biovail Corporation" launched first commercial product by name Nurofenmeltlet. Flash dose tablets consists of self binding shear form matrix termed known as "floss". Floss is compressed along with excipients and tablets are rigid possessing good mechanical strength. [12,7]

13) Frosta technology

Frosta technology patented by Akina. The technology consists of use of plastic granules that are compressed at very low compression pressure along with water penetration enhancer, and binder. The tablet produced possess excellent hardness and rapid disintegration intime the range of 15 to 30 sec. [13]

14) Lyoc technology (Farmalyoc):

Lyoc technology is patented technology of farmalyoc, marketed in USA that produces fast dissolving tablet by subjecting an aqueous solution, suspension, oil in water emulsion to freeze drying or sublimation process along with active pharmaceutical ingredients and excipient. The technique require large amount of inert filler which makes the tablet less porous thus increasing the disintegration time. The tablet produced becomes dense and possess poor mechanical strength. [14]

15) Shearform technology:

In this technology, a shear form matrix, 'Floss' is prepared. Feedstock prepared

with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. The flowing mass comes out through the spinning head that flings the floss. The produced floss is amorphous in nature. So by various techniques, it is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the flossbefore recrystallising it. [10,13]

EVALUATION OF FDT'S

Evaluation of blend

1] Angle of Repose

The flow characteristics are measured by angle of repose (θ). Improper flow of powder is due to frictional forces between the particles. These frictional forces are determined by angle of repose. Angle of Repose defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula. [15,16]

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

Where θ = Angle of repose,

h = Height of the pile,

r = Radius of the base of pile.

Table No. 2 Angle of Repose as an Indicator of Powder Flow Properties

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

2] BULK DENSITY

It is defined as the ratio of weight of blend in gms to the loose bulk volume (untapped volume) incm3. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. The bulk density depends on partical size distribution, shape and cohesiveness of particles. [15]

Bulk density is denoted by **Db**

Therefore **Db = W/Vb**

Where W = Weight of sample in gm,

Vb = Bulk volume of blend in cm^3.

3] TAPPED DENSITY

It is defined as mass of powder per unit tapped volume. When particles are packed loosely, lots of gaps between particles are observed. Hence bulk volume increases making the powder light. On the other hand, smaller particals may shift between larger particles, the powder assume low bulk volume or high bulk density. Such powders are called heavy powders.[16] A standard procedure used for obtaining bulk density or its reciprocal bulkiness is given, below A sample of about 50 cm3 (blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface or on pad three times from a height of 1 inch at two second interval. The tapped density is then obtained by dividing the weight of sample in gms by final volume in cm^3.

Tapped density is denoted by **Dt**

Therefore **Dt = W/Vt**

Where W = Weight of sample in gm.

Vt = Tapped volume of blend in cm3.

4] Bulkiness

Specific bulk volume or reciprocal of bulk density is called bulkiness or bulk. Bulkiness increases with a decrease in particle size. In mixture of material of different sizes, howeverthe smaller particle shifts between the larger particles and tends to reduce the bulkiness. [17]

The bulkiness can be calculated by the following formula:

Bulkiness= 1/Dt

5] Void Volume (10)

The volume of the spaces is known as the void volume "v" and is given by the formula

v=Vb-Vt

Where Vb = Bulk volume (volume before tapping),

Vt = Tapped volume (volume after tapping) true volume

6] Porosity

The porosity of powder is defined as the ratio of void volume to the bulk volume of the powder. The porosity is denoted as €.

The porosity of the powder is given by

€= Vb-Vt/ Vb = 1- Vt/Vb

Porosity is frequently expressed in percentage and is given as

% € = (1 - **Vt / Vb**) x100

The porosity of powder is of great significance for the type of packaging required

during transportation where powder subject to vibrations, during storage, and in tablet

machine when passes through hopper or feed frame. [15]

7] Hausner's ratio:

Hausner ratio is an indirect index of ease of powder flow. **Hausner** ratio is the ratio of tapped density to bulk density. Lower

the value of **Hausner** ratio better is the flow property.

It is calculated by following formula. [16]

Hausner ratio = Dt/ Db.

Table No. 3 Hausner's ratio as an Indicator of Powder Flow Properties

Sr. No	Hausner's ratio	Type of Flow
1	<1.18	Excellent
2	1.19-1.25	Good
3	1.3-1.5	Passable
4	>1.5	Very Poor

Table No. 4 Relationship between % compressibility and flow ability

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-335	Poor
33-38	Very poor
<40	Very very poor

8] Carr's index (or) % Compressibility

It indicates powder flow properties. This property is also known as compressibility. It is

expressed in percentage and is denoted by I

Definition: The compressibility is defined as the percent ratio of difference between tapped

density and bulk density to tapped density. [10]

$$\text{Therefore } I = \frac{Dt - Db}{Dt} \times 100$$

EVALUATION OF TABLET:

1] General appearance

General appearance of a tablet, such as size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency is essential for consumer acceptance and batch to batch uniformity. [18]

a) Size and shape: A compressed tablet size and dimensions are determined by the tooling during compression. Size and shape can be dimensionally described, monitored and controlled. The thickness of the tablet can be measured with help of micrometer and vernier caliper. The tablet thickness should be controlled within a± 5% variation of a standard value.[12]

b) Organoleptic properties:

Colour: Colour uniformity(non uniformity is referred as mottling)is also one of the measure characteristics. As it plays a very vital role in patient acceptance. For colour evaluation used reflectance spectrophotometry, tristimulus colorimetric and microreflectance photometer.[18]

Odour: Presence of an odour in a batch of tablets could indicate a stability problem.

Taste: Taste is important in consumer acceptance of mouth dissolving tablet.

2] Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. Hardness sometime termed as the tablet crushing strength. The force is measured in kg/cm2 and the hardness of about 3-5 kg/cm2isconsidered to be satisfactory for uncoated tablets.

Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester, Pfizer tester, strong cobb tester, Erweka tester and Schleunigertester. [12]

3] Friability test

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. Roche friabilator was employed for finding the friability of the tablets. [19]

20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes (i.e. for 100 revolutions). The tablets were dedusted and weighed again.

The percentage of weight loss was calculated using the formula

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, and

W2 = Weight of tablet after test.

4] Weight Variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The weight variation test would be satisfactory method of determining the drug content uniformity of tablet. [18]

The total weight of 10 or 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Table No. 5 Weight Variation Specification as per IP.

Average Weight of	% Deviation
80 mg or less	±10
80 mg-250 mg	±7.5
More than 250	±5

Table No. 6 Weight Variation Specification as per USP.

Average Weight of Max.	% Deviation
130 or less	±10
130-324	±7.5
More than 324	±5

5] Disintegration

The USP device to rest disintegration was six glass tubes that are 3inches long, open at the top, and held against # 10 mesh screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2ºC, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. The Standard motor driven device is used to move the basket assembly containing the tablet up and down through the distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs may used in the test. [12]

***a. In Vitro* Dispersion time test**

In Vitro disintegration time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and

In Vitro dispersion time was performed. [12]

***b. In Vivo* Disintegration test**

The test was carried out on 2 or 3 tablets using in the mouth in six healthy volunteers and the time in second required for complete disintegration of the tablet was measured. [20]

***c.* Modified disintegration test**

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 time for ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10

cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted. [7]

6] Uniformity of dispersion

Two tablets were kept in 100ml water and gently stirred for 2 minutes. The dispersion was passed through 22 meshes. The tablets were considered to pass the test if no residue remained on the screen. [10]

7] **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. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is

affected by the hydrophilicity of the powders. [15]

dl/dt = rγcosq/(4hl)

Where l = the length of penetration,

r = the capillary radius,

γ= the surface tension,

h=the liquid viscosity,

t = the time, and

q= the contact angle.

It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease 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 6ml 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 370. [12]

8] Water Absorption Ratio

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed. [19]

Water absorption ratio, R was determined by using following formula were given

R= Wa-Wb / Wb x 100

Where Wa=The weight of tablet after water absorption,

Wb=The weight of tablet before water absorption.

10] Taste/ Mouth sensation

Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch was tested for the sensation by placing the tablet on the tongue. The healthy human volunteers were used for evaluation of mouth feel. Taste evaluation was done by a panel of 5 members using time intensity method. Sample equivalent to dose of drug was held in mouth for 10 secs. Taste were recorded instantly and then after 10 secs, 1, 2, 4and 6 minutes. Volunteer's opinion for the taste were rated by giving different score values i.e. .0 = good, 1= tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful. [9]

11] *In Vitro* Dissolution Test

In-vitro dissolution study was performed by using USP Type II Apparatus at given rpm. Water or specific buffer, 900 ml was used as dissolution medium which maintained at 37±0.5°C. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2 min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at peak. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded. [14]

12] Stability Study (Temperature Dependent)

The fast dissolving tablets are packed in suitable packaging and stored under the following

conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C

(ii) 50 ± 1°c

(iii)37 ±1 ° C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C. [12]

CONCLUSION

Fast dissolving tablets (FDTs) are innovative drug delivery systems and have potential advantages over conventional dosage forms, with their improved patient compliance, convenience, bioavailability and rapid onset of action. FDTs formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. There is a clear opportunity for new enhanced oral products arising within this market segment. A wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage form. Though considerable research has been done in the formulation development and technologies for FDTs, more intensive investigations are to be carried out in this promising area to result in newer cost effective technologies and better products.

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