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Review article: Fast Dissolving Tablet with Piperine

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ABSTRACT

Fast dissolving Tablets are disintegrating and/or dissolve rapidly in the saliva without the need for water. 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. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. By the addition of piperine in the fast dissolving formulation, its bioavailability increases, hence dosing reduces.

Keywords: FDT, Orodispersible tablets, Fast dissolving/dispersing tablets, Melt in mouth tablets, Mass extrusion, Superdisintegrants.

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INTRODUCTION

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."

Drug delivery through oral route has been the best route of administration since decades. Dispersible tablets are uncoated tablets that produce a uniform dispersion or suspension in water at room temperature without stirring.

It is most widely used routes of administration for the systemic delivery of drugs via various dosage forms. Orally disintegrating tablets also called as orodispersible tablets (ODTs), quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating tablets, rapid disintegrating tablets, porous tablets or rapimelts. However USP approved these dosage forms as ODTs.[1]

The main active compound found in both *Piper longum* and *Piper nigrum* is piperine (1-piperoyl piperidine) which is responsible for bioenhancing effect. The mechanisms for the bioenhancer activity of piperine have been proposed including DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump[2].

1. Fast Melting tablets (FMT) or fast disintegrating/dissolving tablets (FDT) are single unit solid unit dosage forms that disintegrate or dissolve rapidly (in few seconds) in mouth without the need of water or chewing. These dosage forms show good stability, ease of manufacturing and ease of handling by patient. The drug is immediately released from dosage form and is readily available for absorption, improving its onset of action and its bioavailability in some cases (soluble drugs), to some extent it is also possible to achieve absorption of some drugs across the oral mucosa directly into the systemic circulation, avoiding first pass metabolism & its subsequent side effects[3].

2. Upon ingestion, the saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug absorbed in the GIT. Drug is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In these cases bioavailability of drugs is greater than those observed from standard dosage forms[4].

3. The main criteria for fast disintegrating (dissolving) tablet is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 to 60 seconds, without need of water and should have pleasant mouth feel[5].

Figure 1. Conceptual Diagram of MDT

Salient Features & Advantages [--12]

1. FDT passes all the advantages of solid dosage forms like good stability, easy manufacturing, unite and accurate dosing, easy handling etc.

2. Provides rapid drug therapy intervention.

3. Ease of administration to patients who are unable or refuses to swallow a tablet, such as pediatric, geriatric and psychiatric and disabled patients.

4. Does not require water while administration good disintegration and dissolution of the dosage form in oral cavity.

5. Ability to provide advantages of liquid medication in the form of solid preparation.

6. Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.

7. FDTs help avoids hepatic metabolism by allowing pre-grastric drug absorption thus reducing the dose of drug required.

8. Patient's compliance for disabled bedridden patients and for travelling and busy people, who do not have ready access to water.

9. 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.

10. More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.

Limitations of fast dissolving tablets[13]:

1. The tablets usually have insufficient mechanical strength. Hence, careful handling is required

2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly

DESIRED CHARACTERISTICS AND CHALLENGES FOR DEVELOPING FAST DISINTEGRATING DRUG DELIVERY SYSTEMS[8]:

Time required for disintegration

FDTs should disintegrate/dissolve/disperse or melt in mouth without the need of water in very

short duration of time, possibly within 60 seconds.

Taste of the active ingredient

Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

Ease of administration

Fast disintegrating drug delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

Tablet strength, Friability and porosity

In order to allow fast disintegrating tablets to disintegrate in the mouth, they are made of either very porous or soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging.

Hygroscopic nature

Several fast disintegrating drug delivery dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

EXCIPIENT TO BE USED IN FAST DISSOLVING TABLET[14]:

Table.1: Excipients To Be Used In Fast Dissolving Tablet

Name	Characteristics	Example
Superdisintegrant	Increases the rate of disintegration and hence the dissolution. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the super disintegrant.	Crosspovidone, Microcrystalline cellulose, sodium starch glycolate, sodium carboxy methyl cellulose, pregelatinzed starch, Carboxy methyl cellulose, and modified corn starch.
Flavors	Increases Patient compliance and acceptability	Peppermint flavor, cooling flavor, flavoring aromatic oil, clove oil, Flavoring agents include, vanilla, citrus oils, fruit essences.
Sweeteners and sugar based excipients	This is another approach to manufacture ODT by direct compression. Sugar based excipients acts as bulking agents .These exhibits high aqueous solubility and	Artificial sweeteners like Aspartame, Sugars derivatives. Bulking agents like dextrose, fructose, isomalt, lactilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol

	sweetness, and hence impart taste masking property and a pleasing mouth feel.	
Binder	Maintains integrity of dosage form prior to administration	Polyvinylpyrrolidone(PVP), Polyvinylalcohl(PVA), Hydroxy propyl, methylcellulose.
Color	Enhances appearance and organoleptic properties of dosage form	Sunset yellow, Amaranth, Red iron oxide
Lubricants	Lubricant helps reduce friction and wear by introducing a lubricating film between mechanical moving parts of tablet punching machine	Stearic acid, Magnesium stearates, talc, polyethylene glycol, magnesium lauryl sulfate.
Fillers	Enhances bulk of dosage Form	Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate,

LIST OF SUPERDISINTIGRANT[15]:

Table.2: List of Superdisintegrant

Superdisintegrants	Example	Mechanism of Action	Special Comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Cross linked Cellulose	Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Cross linked PVP	Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch	Cross linked	-Swells 7-12 folds in < 30 seconds	-Swells in three
Glycolate Explotab® Primogel®	Starch		dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Cross linked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation

ROLE OF SUPERDISINTEGRANTS IN FDT[16-19]:

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. Superdisintegrant'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.

Mechanism of action of disintegrants[20]:

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

a. By capillary action

b. By swelling

c. Because of heat of wetting

d. Due to release of gases

e. By enzymatic action

f. Due to disintegrating particle/particle repulsive forces

g. Due to deformation

TECHNOLOGY USED FOR MOUTH DISSOLVING TABLETS:

Table.3: Technology Used For Mouth Dissolving Tablets:

NON-PATENTED	PATENTED
Freeze drying	Zydus technology
Tablet molding	Orasolv technology
Spray drying	Durasolv technology
Sublimation	Wowtab technology
Direct compression	Fashtab technology
Melt granulation	Oraquick technology
	Frosta technology

NON PATENTED TECHNOLOGY:

1 Freeze-Drying or Lyophilization[21]:

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. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls 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 are placed in refrigerated cabinets to continue the freeze-drying. 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 major disadvantages of lyophillization 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 Molding[22]

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 air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses 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. 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[23]

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 crosscarmellose or crosspovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4 Sublimation:[24]

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

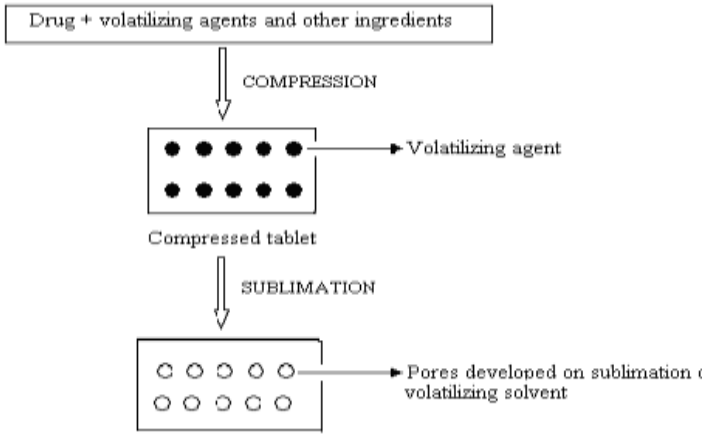

Figure.1: Step Involved In Sublimation

5 Direct compression[25]

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. Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction superdisintegrants and a better understanding of their properties have increased the popularity of this technology. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration.

Table.4: ideal requirements, advantages and limitations of direct compression:

S. No	Ideal requirements	Advantages	Limitations
1	Flowability	Cost effective production	Segregation
2.	Compressibility	Better stability of API	Variation in functionality
3.	Dilution Potential	Faster dissolution	Low dilution potential
4.	Stability	Simple validation	Poor compressibility of API
5.	Controlled Particle Size	Low microbial contamination	Lubricant sensitivity

6. Melt granulation[26]

In this process, FDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) like PEG-6-stearate. Super polystate is a waxy material with melting point of 33-37°C and a hydrophilic- lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of FDTs by melt granulation method where granules are formed by the molten form of this material.

PATENTED TECHNOLOGY:

1. Zydis technology[27]**:**

Zydis 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 sec. The drug is physically trapped in a water soluble matrix, and then freeze dried to produce a product that rapidly dissolves. 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.

Limitation:

***** The amount of drug could be incorporated should generally be less than 400mg for insoluble drugs amount and much more less than that amount of 60mg for soluble drugs.

***** The particle size of the insoluble drugs should not be less than 50µm and not more than 200µm to prevent sedimentation during processing.

2. Orasolv technology[28]:

It is CIMA lab's first fast dissolving formulation. Tablets are prepared by direct compression at low compression force in order to minimize oral disintegration and dissolution time. Orasolv technology is an example of slightly effervescent tablet that rapidly dissolve in mouth. The active medicaments are taste masked and dispersed in saliva due to the action of effervescent agents.

Advantages:

***** The Orosolv technology formulation does not have very much hygroscopic characteristics.

***** The Orosolv technology formulations can accommodate very high doses.

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

3. Durasolv technology[29]:

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants. Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in to bottles and blisters.

4. Wow tab technology[30]:

Yamanouchi patented this technology. WOW means without water. This technology utilizes conventional granulation and tableting methods to produce MDTs employing low- and high-moldability saccharides. Low moldability saccharides are lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides are used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration.

Advantages:

***** Offers Superior mouth feel due to the smooth melt action.

***** It is suitable for both conventional bottle and blister packaging.

***** Bit more stable to the environment than the Zydis and orasolv.

5. Flashtab technology[31]:

This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types. Disintegrating agents include reticulated polyvinylpyrrolidine or carboxy methylcellulose. Swelling agents include carboxy methylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

6. Oraquick[32]:

This technology is patented by K.V.S. Pharmaceuticals. It utilizes taste masking microsphere technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of microparticles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat sensitive drugs. Oraquick product dissolves within few seconds.

7. Frosta technology[33]:

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

- Porous and plastic material,
- Water penetration enhancer, and
- 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.

DRUGS TO BE PROMISING INCORPORATED IN FAST DISSOLVING TABLETS[34-37]:

Table 5: Drugs To Be Promising Incorporated In FDT

Class	Examples
Analgesics and Anti-inflammatory Agents	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.
Anthelmintics	Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, Praziquantel, Pyrantel Embonate, Thiabendazole
Anti-Arrhythmic Agents	Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate

Anti-Epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid
Anti-Hypertensive Agents	Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.
Anti-Protozoal Agents	Benznidazole, Clioquinol, Decoquinate, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole
Anxiolytic, Sedatives, Hypnotics And Neuroleptics	Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam, Clotiazepam, Clozapine, Droperidol, Ethinamate, Flunanisone, Flunitrazepam, Fluopromazine, Flupenuiixol Decanoate, Fluphenazine Decanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, Perphenazine Pimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone.

LIST OF MOUTH DISSOVING TABLET AVAILABLE IN MARKET[38]

Table.6: Mouth Dissolving Tablet Available In Indian Market

Brand name	Active ingredient	Company
Veirid MD	Domperidone	Shreyam Health Care
Zotacet MD	Cetirizine Hcl	Zota Pharma
Olanex Instab	Olanzepine	Ranbaxy
Orthoref MD	Rofecoxib	Biochem
Valus	Valdecoxib	Glenmark
Nimulid-MD	Nimesulide	Panacea
Topmide	Nimesulide	Antigen Health Care
Mosid MT	Mosapride	Torrent

Table .7: Mouth Dissolving Tablet Available In International Market

Brand name	Active ingredient	Company
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Nurofen FlashTab	Lbuprofen	Boots Healthcare
Benadryl Fastmelt	Diphenhydramine	Pfizer
Zolpidem ODT	Zolpidem tartrate	Bioavail
Nasea OD	Ramosetoron	Yamanouchi
Feldene Melt	Piroxicam	Pfizer
Maxalt-MLT	Rizatriptan benzoate	Merck
Imodium Instant melts	Loperamide HCL	Janssen
Childrens Dimetapp ND	Loratadine	Wyeth Consumer Healthcare
Zofran ODT	Ondansetron	Glaxo Smith Kline
Risperidal M-Tab	Ripseridone	Janssen
Aricept ODT	Donepzil HCL	Eisai and Pfizer
Fazalco	Clonzapine	Alamo Pharmaceuticals
Febrectol	Paracetamol	Prographarm

PREFORMULATION STUDIES FAST DISSOLVING TABLET[39]:

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

1. Bulk Density (Db):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/ Vb$$

Where, M is the mass of powder; Vb is the bulk volume of the powder.

2. Tapped Density (Dt):

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

$$Dt = M / Vt$$

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

3.Angle of Repose (q):

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

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

$$q = \tan\text{-}1 (h / r)$$

Where, q is the angle of repose.; h is the height in cms; r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Relationship between angle of repose and powder flow property.

Table.8: Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose (°)	Type of Flow
1	< 20	Excellent
2	20-3-	Good
3	30-40	Passable
4	> 34	Very poor

4.Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give

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

Where, Dt is the tapped density of the powder and; Db is the bulk density of the powder.

Table.9: Relationship Between % Compressibility and Flow Ability

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
< 40	Very very poor

5.Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density; Db is the bulk density.

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

6. Identification and Compatibility study of drug sample:

It was confirmed by melting point determination and also by FT-IR spectral analysis Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

EVALUATION OF THE MOUTH DISSOLVING TABLET:

1) Weight variation[40]:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in Table .

Table 10: Weight Variation Specification As Per Ip[41]

Dosage Forms	Average Weight	Percentage Deviation
Uncoated and film coated tablets	80 mg or less	10
	More than 80mg but less than 250 mg	7.5
	250 mg or more	5
Capsules, Granules and Powders(single dose)	Less than 300 mg	10
	300 mg or more	7.5
Powders for parenteral use	More than 40 mg	10
Pessaries and Suppositories	All weighs	5

2) Hardness:

Hardness or tablet crushing strength, the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

3) Friability (F)[42]:

Friability of the tablet determined using Roche friabilator or Electro lab friabilator . This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

6) Wetting time[43]:

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.

$$dl/dt = r¡cosq/(4hl)$$

Where l is the length of penetration, r is the capillary radius, ¡ is the surface tension, h is the liquid viscosity, t is the time, and q is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 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 37o. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, 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 a wetting time.

7) In vitro dispersion time:

Tablet was placed in 10 ml phosphate buffer solution, pH 6.8±0.5°C. Time required for complete dispersion of a tablet was measured.

8) In-vitro disintegration time[44]:

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±20C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±20C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

9) Thickness Variation:

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer. The mean SD values were calculated.

10) Stability study (Temperature dependent):[45]

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 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 ° C

11) Water absorption ratio[46]:

A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determine by using following formula Where, Wb is the weight of tablet before water absorption. Wa is the weight of tablet after water absorption.

$$R = 100 \times \frac{Wa - Wb}{Wb}$$

FAST DISSOLVING TABLET WITH PIPERINE: LITERATURE REVIEW

A number of worker have reported the preparation, evaluation and characterization the use of Norfloxacin as fast dissolving tablet. Norflaxacin is an antimicrobial drug and with piperine its absorption power increases in an interesting manner.

Peter Christian Schmidt et al[47], have formulated and evaluated fast dispersible ibuprofen tablet. A direct compression method was used to prepare these two types of tablets containing coated ibuprofen as a high dosed model drug. The selected tablet formulation, containing 26% galactomannan and 5% crospovidone, disintegrates before the galactomannan starts to swell. These tablets disperse in water within 40 s and show a crushing strength of 95 N. To develop an orodispersible tablet, a rotatable central composite design was applied to predict the effects of the quantitative factors mannitol and crospovidone as well as compression force on the characteristics of the tablet.

Swamivelmanickam M et al[48]**,** have given an overview of Mouth Dissolving Tablets. Mouth dissolving tablets are advantageous particularly for pediatric, geriatric and mentally ill patients who have difficulty in swallowing conventional tablets and capsules.

Mahajan Uday et al[15], have given an overview of formulation technology of Fast Dissolving Tablet. the development of Fast or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an opportunity for product line extension in the many elderly persons will have difficulties in taking oral dosage forms because of hand tremors and dysphasia. Swallowing problems also are common in young individuals because of their underdeveloped muscular and nervous systems.

Lakshmit O. Bhagya et al[49], used black peppr (pipper nigrum Linn.) as antibacterial agent against gram positive and gram negative bacteria and found that acetone extract of black pepper displaced excellent inhibitioin on the growth of gram positive bacteria[49].

Priyanka Nagar et al[46]**,** have prepare, formulated and evaluated the Oral Disintegrating Tablets. Formulation of a convenient dosage form for oral administration, by considering swallowing difficulty especially in case of geriatric and pediatric patient leads to poor patient compliance. To troubleshoot such problems a new dosage form known as orally disintegrating tablet (ODT), has been developed which rapidly disintegrate & dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form.

Jain Abhishek, Sharma Ankur et al[50], have formulated and evaluated fast dissolving tablet of aceclofenac using superdisintigrant crosspovidone, crosscarmelose sodium and sodium starch glycolate and surfactant lauryl sulphate by direct compression method.

Tiwari Vijay, Pillai Krishna et al[51], have prepared and evaluated fast dissolving tablet of celocoxib using solid dispersion of celocoxib and sorbitol by hot melt extrusion process and superdisintigrant (sodium starch glycolate), binder (polyvenylprrolidone), Sweetner (saccharine sodium), flavor (menthol).

Bhaedwj Sudhir[52] has formulated fast dissolving tablet of Diclofenac sodium using sugars i.e. sorbitol, mannitol and polymer like HPMC, PVP by direct compression method. The tablet were evaluated for hardness, friability, weight variation, In-Vitro dispersion time and In-Vitro dissolution study.

Sapna Kashyap et al[53], have developed a boon to pediatric and geriatric: Fast Disintegrating Tablet. Fast Disintegrating Tablets aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, to achieve better patient compliance. FDTs can be administered anywhere and anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients. This article will focuses on the technologies available and the advances made so far in the field of abrication of fast dissolving tablets.

Acharya SG et al[54], have give the review of piperine as bioenhancer. Structural modification of piperine provides selective inhibitors of various cytochrome P450 enzymes. Inhibition of these enzymes by piperine results in enhance bioavailability of drugs Norfloxacin and Ciprofloxacin.Thus piperine is absorption enhancer and a potent inhibitor of drug metabolism.

Manavan Rajappan et al[55], have prepared the suspension of norfloxacin with piperine. And evaluated their bioavailability by comparing the suspension of norfloxacin without piperine and with piperine. And found that norfloxacin with piperine improved their oral bioavailability.

Hence on the basis of above literature we can conclude the fallowing point, listed as below[54]:

1. Rapid onset of action and may offer an improved bioavailability because piperine provides selective inhibitors of various cytochrome P450 enzymes. Inhibition of these enzyme enhance bioavailability of drugs.
2. Thus piperine is absorption enhancer and a potent inhibitor of drug metabolism.
3. Since bioavailability is increased so it's dosing is reduced.
4. Piperine also produces Antioxidant, Anti-platelet, Anti-inflammatory, Antihypertensive, Hepatoprotective, Antithyroid, Antitumor, Antiasthmatic activities and found to be

Fertility Enhancer so combination of these categories drug with piperine may enhance the potency and frequency of the drug.

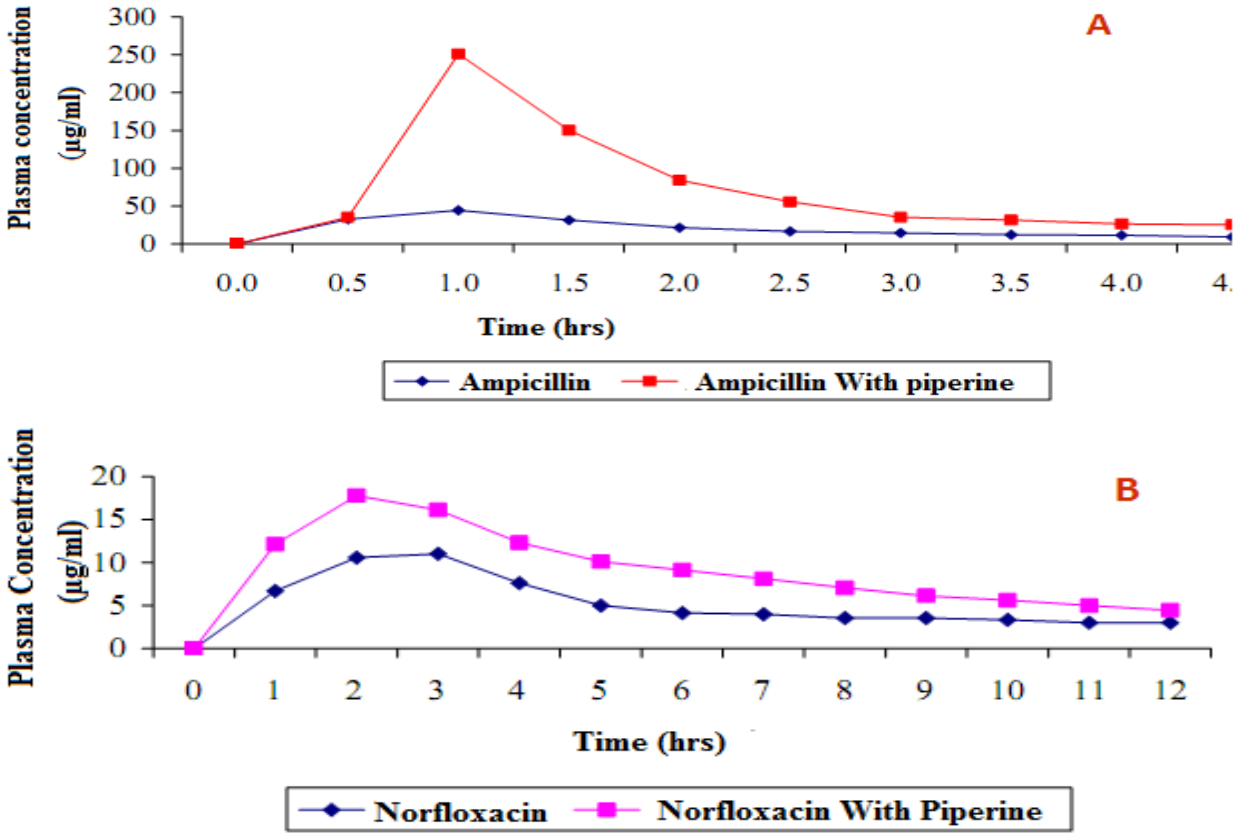

Figure.2: Effect Of Piperine On Bioavailability Of Ampicillin (A) And Norfloxacin (B)

Piperine increased AUC of ampicillin (by 338%, figure A) and norfloxacin (by 174.6%, figure B. This effect may allow to reduce the frequency of administration and adverse effects of these antibiotics.[54]

Future Prospects

These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide based therapeutics those have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach and next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. The developments of enhanced oral protein delivery technology by FDTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide. Piperine obtained from *pepper nigrum* used as bioenhancer, it is a safe herbal drug that reduces the side effects and improves the bioavailability. Available as powder, oil, and extract form of the crude drugs, that may is used with the preparation.

CONCLUSION:

Fast disintegrating tablets technology gained more popularity in last decade. It emerged as a New Drug Delivery system for treating various patients and diseases. FDT offers advantages of both solid and liquid oral dosage forms. This system allows easy self administration without the need of water to swallow. It has provided new area for research and development both for industries and academics. The MDTs 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. MDTs formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. These MDTs can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth. Piperine has been used as bioenhancer for certain antibacterial- antibiotics with promising results. The interaction of piperine with drug-metabolizing enzymes is responsible for oxidation, hydroxylation and glucuronidation. Piperine appears to top in the list of bioenhancer as it has been used as bioenhancer for Allopathic, Ayurvedic and Unani drugs. Piperine enhances Cmax of different drugs significantly.

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