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RECENT RESEARCH ON FAST DISSOLVING TABLETS – A REVIEW

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ABSTRACT

Fast dissolving tablet technology is a topic of current interest in pharmacy and therapeutics. Fast dissolving tablets (FDTs) are tablets that dissolve or disperse in saliva within few seconds and these combine the advantages of both liquid and tablet dosage forms. Several conventional methods and commercial technologies are developed for the formulation and manufacture of FDTs. The requirements, advantages, formulation methods and technologies of FDTs along with a review of recent research in this area are discussed in this article.

Key words: Fast Dissolving Tablets, Formulation Technologies, Recent Research, Review

INTRODUCTION

Fast Dissolving Tablets – A Novel Type of Tablets

Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route[1] . Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms[2] . To overcome these problems, Fast Dissolving Tablets (FDTs) have been developed as innovative drug delivery systems. FDTs are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water[3]. Fast dissolving drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. Currently these tablets

are available in the market for treating many disease conditions like hypertension, migraine, dysphasia, nausea, vomiting, Parkinson's disease, schizophrenia and pediatric emergency[4-8].

Several drugs belonging to various pharmacological categories [9,10] such as Analgesics and Anti-inflammatory Agents (fenbufen, flurbiprofen, ibuprofen, indomethacin,mefenamic Acid, nabumetone, piroxicam, sulindac) ; Anthelmintics (albendazole, cambendazole, praziquantel, pyrantel embonate, thiabendazole) ; Anti-Arrhythmic (amiodarone, disopyramide, flecainide acetate, quinidine sulphate);Anti-Epileptics(carbamazepine,parametha dione,phenobarbitone, phenytoin, valproic acid); Anti-Hypertensives (amlodipine, carvedilol, diltiazem, felodipine, nicardipine, nifedipine, reserpine) ; Anti-protozoals (diloxanide furoate, metronidazole, nitrofurazone, omidazole, tinidazole) ; Anxiolytics, Sedatives, Hypnotics and Neuroleptics (alprazolam, barbitone, bromazepam, chlormethiazole, chlorpromazine, flupenuiixol decanoate, lorazepam, methaqualone, nitrazepam, zopiclone) are formulated as fast dissolving tablets (FDTs). FDTs are also called as orodispersible tablets, fast disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, mouth dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt Tablets.[11-13] However, of all the above terms United States Pharmacopoeia (USP) approved these dosage forms as FDTs.

United States Food and Drug Administration (USFDA) defined FDTs as "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue.

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

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

Challenges in formulating Fast dissolving tablets Palatability

As most drugs are unpalatable, FDTs usually contain the medicament in a taste-masked form. Upon administration, it disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance [14].

Mechanical strength

In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only Wow tab and durasolv technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi-dose bottles.

Hygroscopicity

Several orally disintegrating 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[15].

Amount of drug

The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be less than 400 mg for insoluble drugs and 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers[16].

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming recipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite [17].

Size of tablet

The ease of administration of a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Conventional methods used for the preparation of Fast dissolving tablets

1. Addition of superdisintegrants

A disintegrant is used in formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit.

Examples of Superdisintegrants are Cross linked cellulose (Croscarmellose, Ac-Di-Sol, Primellose, Solutab, Vivasol) ; Crosslinked PVP (Crospovidone, Kollidon , Crosspovidon M, Polyplasdone) ; Crosslinked starch (Sodium starch glycolate, Explotab, Primogel); Cross linked alginic acid (Alginic acid NF, Satialgine); Natural superdisintegrant (Soy polysaccharides, Emcosoy) The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets. Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disitegrant for FDTs by enhancing the porosity of agar by water treatment. Sodium starch glycolate, crospovidone and croscarmellose are some of the popular superdisintegrants [18].

2. Direct compression

It is the easiest way to manufacture tablets. Conventional equipments, commonly available recipients and a limited number of processing steps are involved in direct compression. Sawant et al. prepared orodispersible tablets of ondansetron HCl by direct compression using superdisintegrants and they reported that in vitro, dispersion time of FDTs has been found to be 5 minutes where as conventional tablets have shown 30-35 minutes [19-20].

3. Freeze drying or Lyophilization

Freeze drying is a 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 manufacture of FDTs 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. Thew 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[21].

4. Sublimation

To generate 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 phthalic anhydride may be compressed along with other recipients into a tablet. Ravikumar et al. prepared aceclofenac FDTs by sublimation method using camphor as subliming agent and sodium starch glycolate together with croscarmellose sodium as superdisintegrant [22].

5. Spray drying

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 or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium.

6. Mass extrusion

In this method active blend is softened using the solvent mixture of water-soluble polyethylene glycol and methanol and then subsequent expulsion of softened mass through the extruder or syringe is made to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking [23].

7. Melt granulation

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[24].

Commercial Technologies

1. 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 material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid idisintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process.Collapse protectants such as glycine prevents the shrinkage of zydis units during freeze-drying process or long-term storage. Zydis products are packced in blister packs to protect the formulation from moisture in the environment [23,25].

2. Wow tab technology (Yamanouchi)

WOW means without water. This technology utilizes conventional granulation and tableting methods to produce FDTs employing low- and high- moldability saccharides. Low moldability saccharides are lactose, mannitol, glucose, sucrose and xylitol. High- moldabillity saccharides are maltose, maltitol, sorbitol and oligosaccharides . When these low- and high- moldable saccharides are used alone tablets obtained donot 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[26].

3. Durasolv technology (CIMA Labs)

The tablets produced by this technology utilize the conventional tableting equipement. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants. Nondirect compressible filers 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 packings into bottles and blisters[27].

4. Orasolv technology (CIMA Labs)

This includes use of effervescent disintegrating agents compressed with low pressure to produce the FDTs. This evolution of carbon dioxide from the tablet produces fizzing sensations, which is a

positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight. As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop pakslov, a special packing to protect tablets from breaking during storage of transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression. Paksolv offers moisture, light and child resistance packing[28].

5. Dispersible tablet technology (Lok, Yugoslavia)

This offers development of FDTs with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and wetting capabilities to the tablet that result in quick disintegration. Disintegrates include starch, modified starches, microcrystalline glucose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrates involves diosintegration of tablets usually less than 1 min[29].

6. *Frosta technology* (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 [30].

7. Pharmaburst technology (SPI Pharma, New Castle)

It utilizes the coprocessed recipients to develop FDTs, which dissolves within 30-40s. This technology involves dry blending of drug, flavour, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles[31].

8. Nanocrystal technology (Elan)

Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tabletting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug[32].

9. Lyo (Pharmalyoc)

Oil in watr emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered[12].

10. Flashtab technology (Ethypharm France)

This technology includes granulation of recipients 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[12,33].

Market products

Some of the popular marketed Fast Dissolving Tablets [11,16,29,35-38] include Felden fast melt (piroxicam) , Febrectol (paracetamol), Nimulid MDT (nimesulide), Romilast (montelukast) , Risperdal MTab (risperidone) , Zolmig Repimelt (zolmitriptan), Relivia Flash dose (tramadol Hcl) , Allegra ODT (fexofenadine), Clonazepam ODT (clonazepam) , Jr. Tylenol Meltways (acetaminophen).

Evaluation Tests

FD Ts are subjected to all evaluation parameters as that for conventional tablets like general appearance, size and shape, thicknes, hardness, uniformity of weight, friability, content of active ingredient, disintegration and dissolution.

Wetting Time

Five circular tissue papers were placed in a Petri dish of 10-cm diameter. 10 ml of water containing 0.5% eosin, a water-soluble dye, was added to the Petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the Petri dish at 25°C.

The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in a replicate of six. Wetting time was recorded using a stopwatch.

Disintegration time

According to the European pharmacopoeia the FDTs should disintegrate within 3 minutes without leaving any residue on the screen. One of the simplest methods is to take 6ml of simulated saliva in a measuring modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the cylinder and places the tablet in it. The liquid is neither shaken nor stirred and DT is noted [34,35].

In vivo disintegration time

In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth [34].

Recent Research on FDTs:

Recent research on FDTs is summarized in Table-1

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 .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.

Table-1: Summary of recent research on FDTs

S. No	Drug (Therapeutic category)	Method / Technique used	Excipients used	Result	Refe rence
1	Albendazole (Broad spectrum anti-helmintic)	Direct compression	Microcrystalline cellulose, Crospovidone, Croscarmellose sodium, PVPK30, Aspartame, Mannitol	Better dissolution rate and improved bioavailability of the drug	39
2	Cetrizine Hydrochloride (Selective H_1 receptor antagonist)	Direct compression	Pearlitol SD 200, Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Aspartame, Colloidal silicondioxide	Maximum drug release (99%) and minimium disintegration time (< 20 sec) was observed.	40
3	Chlorpromazine hydrochloride (Antiemetic)	Direct compression	Sodium starch glycolate, Croscarmellose sodium, Crospovidone , Microcrystalline cellulose, Pregelatinized starch	Enhanced dissolution rate	41
4	Cinnarzine (Histamine H - receptor antagonist)	Sublimation	Croscarmallose sodium, Sodium starch glycolate, Microcrystalline cellulose, Camphor, Sodium saccharine	Rapid dissolution, absorption and onset of action was observed	42
5	Clonazepam (Antiepileptic)	Direct compression	Crospovidone , Croscarmellose, Directly compressible Mannitol, Microcrystalline cellulose,	Enhanced patient compliance	43
6	Aceclofenac (NSAID)	Direct compression	Croscarmellose sodium,Sodium starch glycolate, Microcrystalline cellulose	Enhanced dissolution and decreased disintegration time	44

7	Ebastine (Second generation non –sedating H_1 receptor antagonist)	Sublimation	Microcrystalline cellulose, Mannitol, Ammonium bicarbonate, Sodium saccharine, PVP, Camphor	Improved dissolution, faster disintegration (<1 min)	45
8	Etoricoxib (NSAID)	Direct compression	Urea, Cros carmellose, Avicel	Better patient compliance, quick disintegration, rapid dissolution	46
9	Granisetron hydrochloride	Direct compression	Croscarmellose, Crospovidone	Enhanced dissolution rate	47
10	Isoxsuprine hydrochloride (Vasodilator)	Direct compression	β-cyclodextrin, Sodium starch glycolate, Ac-di-sol, Crospovidone, Microcrystalline cellulose, Mannitol	High release rate	48
11	Levo cetrizine hydrochloride (Non sedative anti-histaminic)	Direct compression	Croscarmellose, Primojel, Crospovidone, Microcrystalline cellulose	Improved bioavailability, with rapid onset of action	49
12	Lornoxicam (NSAID)	Direct compression	Sodium starch glycolate, Crospovidone, L-hydroxy propyl cellulose, β-cyclodextrin, Directly compressible Mannitol, Aspartame	Better patient compliance, enhanced dissolution	50
13	Losartan potassium (Anti-hypertensive)	Direct compression	Polyplasdone Explotab, Croscarmellose, Microcrystalline cellulose, Mannitol	Enhanced patient compliance & rapid onset of action	51
14	Meclizine hydrochloride (Antiemetic)	Direct compression	Pearlitol SD 200, Avicel pH 102, Crospovidone XL 10	Rapid disintegrate-on, quick onset of action	52
15	Metoprolol tartrate (Anti-hypertensive)	Direct compression	Crospovidone, Croscarmellose, Microcrystalline cellulose, Aspartame, Talc	Improved bioavailability, rapid onset of action	53

16	Montelukast sodium (Anti-neoplastic)	Direct compression	Crospovidone, Sodium starch glycolate, Mannitol Microcrystalline cellulose,	Enhanced dissolution rate	54
17	Famotidine (Histamine H_2-receptor antagonist)	Direct compression	Avicel pH102	Rapid disintegration, Rapid onset of drug action	55
18	Naproxen (NSAID)	Direct compression	Sodium starch glycolate, Croscarmellose sodium, Crsspovidone,	Rapid disintegration	56
19	Oxcarbazepine (NSAID)	Wet granulation	Avicel pH 102, Aerosil	Pleasant taste, low disintegration time, enhanced dissolution	57
20	Ramipril (Anti-hypertensive)	Wet granulation	Sodium bicarbonate, Polyvinyl pyrrolidone, Citric acid, Mannitol	Rapid disintegration and dissolution	58
21	Rizatriptan benzoate (Serotonin 5-HT receptor agonist)	Mass extrusion	Eudragit EPO, Sodium starch glycolate, Croscarmellose sodium, Crospovidone , Pearlitol SD200,	Complete taste masking , rapid disintegration and dissolution	59
22	Rosiglitazone maleate (Antidiabetic)	Direct compression	Sodium starch glycolate, Croscarmellose sodium, Crospovidone, Microcrystalline cellulose,	Improved patient compliance	60
23	Salbutamol sulphate (β_2 receptor agonist)	Direct compression	Primogel, L-hydroxy propyl cellulose, Microcrystalline cellulose, Mannitol-D	Rapid dissolution and rapid onset of action	61
24	Aceclofenac (NSAID)	Sublimation	Camphor, Crospovidone, Kyron T-314	Enhanced absorption and increased bioavailability	62
25	Telmisartan (Anti-hypertensive)	Direct compression	Skimmed milk powder, Poloxamer-188, Crospovidone	Better solubility, rapid disintegration and high dissolution rate	63

26	Repaglinide (Antidiabetic)	Direct compression	β-cyclodextrin, Crospovidone, Croscarmellose, Sodium starch glycolate	Improved dissolution rate and enhanced bioavailability	64
27	Amlodipine besylate (Dihydro pyridine calcium antagonist)	Sublimation	Aspartame, Sodium stearyl fumarate, Microcrystalline cellulose, Starch potato, Sodium starch glycolate, Camphor	Rapid onset of action	65

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