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Review Article

Fast dissolving tablets: a novel approach

Md. Mubashshir Momin*, Asish Dev

Oriental College of Pharmacy, Sanpada, Navi Mumbai-400 705, India

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ABSTRACT

An oral route of drug administration is the most popular route of administration. It have wide acceptance up to 50-60% of total dosage forms. Tablet is the most popular dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance. Mouth dissolving tablets (FDT) or fast dissolving tablets; (FDT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/disperse in saliva within few seconds. Fast dissolving tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. This article reviews the Need, advantages, challenges, limitations, mechanism of superdisintegrants, various formulation technologies (conventional and patented), marketed product of Fast dissolving tablets.

Introduction

Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of already used drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. [1] Recently the European Pharmacopoeia adopted the term orodispersible tablet as a tablet to be placed in the mouth where it disperses rapidly before swallowing and which disintegrates in less than 3 min. [2] The basic approach used in development of FDT is the use of superdisintegrants like Cross linked carboxymethylcellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab), Polyvinilpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The technologies used for manufacturing fast dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. [3-5] A fast dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrants in the oral cavity without the need of water or chewing. Most fast dissolving delivery system films must include substances to mask the taste of the active ingredient. [6-8] The fast dissolving tablets display a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pregastric absorption. To fullfil these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid deaggregation of the matrix. [9-10]

Salient Features of Fast Dissolving Drug Delivery System

[11-12]
1. Ease of administration for patients who are mentally ill, disabled and non-co-operative.
2. Quick disintegration and dissolution of the dosage form.
3. Overcomes unacceptable taste of the drugs.
4. Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
5. Allows high drug loading.
6. Ability to provide advantages of liquid medication in the form of solid preparation (Adaptable and amenable to existing processing and packaging machinery)
7. Cost-effective.

Significance of Oral Disintegrating Tablets (ODT) [13-15]

- Accurate dosing Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.
- Enhanced bioavailability Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.
- Rapid action Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Patient compliance. Convenient for patients who are traveling and do not have immediate access to water.
- Ease of administration Convenient to administer specially for geriatric, pediatric, mentally disabled and bedridden patients who have difficulty in swallowing.
- Obstruction free No risk of physical obstruction when swallowed, thus providing improved safety and compliance.
- Enhanced palatability Good mouths feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.
- Simple packaging. It can be packaged in push through blisters.
- Business avenue Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.
- Cost effective Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

Challenges In The Formulation Of FDTs [16-17]

A. Rapid disintegration of tablet.
B. Avoid increase in tablet size.
C. Have sufficient mechanical strength.
D. Minimum or no residue in mouth.
E. Protection from moisture.
F. Compatible with taste masking technology.
G. Not affected by drug properties.

Approaches
Techniques For Preparing FDTs [18-22]

Many techniques have been used for the formulation of Fast dissolving tablets.
1. Freeze drying / lyophilization
2. Tablet moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion
7. Cotton candy process
8. Phase transition
9. Melt granulation

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. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. 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.

Tablet molding

Molding process is of two type i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic 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 possess a porous structure that hastens dissolution. Compared to the lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

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.

Sublimation

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 excipients into a tablet. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec.
Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique.

(a) Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar based excipients

This is another approach to manufacture FDT by direct compression. The use of sugar based excipients especially bulking agents like Dextrose, Fructose, Isomalt, Lactitol, Maltitol, Maltose, Mannitol, Sorbitol, Starch hydrolysate, Polydextrose and Xylitol, which display high aqueous solubility and sweetness and hence impart taste masking property and a pleasing mouthfeel. Sugar-based excipients are classified into two types on the basis of moulding and dissolution rate.

Type 1: Saccharides (Lactose and Mannitol) exhibit low mouldability but high dissolution rate.

Type 2: Saccharides (Maltose and Maltitol) exhibit high mouldability and low dissolution rate.

Mass-extrusion

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 tablet.

Cotton candy process

This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. This technique involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have better flow properties and compressibility. This matrix is milled and blended with active ingredients as well as excipients and subsequently compressed to FDTs.

Phase transition

Kuno et al proposed a novel method to prepare FDTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, FDTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point.

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 by impeller blades.

Evaluation of FDTs [23-29]

General Appearance

The general appearance of a tablet, its visual identification and over all ‘elegance’ is essential for consumer acceptance. These include tablet’s size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws.

Tablet Thickness

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

Uniformity of Weight

IP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be satisfactory method of determining the drug content uniformity.

Hardness

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

Friability

Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F%) is given by the formula,

\[ \text{Friability} = \frac{(I.W - F.W)}{I.W} \times 100 \]

In vitro Disintegration Test

Disintegration of fast disintegrating tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo conditions. A modified version of the simple but novel method developed was used to determine disintegration time of the tablets.

Wetting Time

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was
placed in a small Petri dish (ID = 65 cm) containing 6 ml of Sorenson’s buffer (pH 6.8). A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

In vitro Dispersion Time
In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson’s buffer (pH 6.8). Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

Super Disintegrants Used In FDTs
As day’s passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly.

Mechanism of Action of Disintegrants [30-32]
The tablet breaks to primary particles by one or more of the mechanisms listed below.
1. By capillary action
2. By swelling
3. Because of heat of wetting
4. Due to release of gases
5. By enzymatic action
6. Due to disintegrating particle/particle repulsive forces
7. Due to deformation

<table>
<thead>
<tr>
<th>Superdisintegrants</th>
<th>Example</th>
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<tbody>
<tr>
<td>Crosscarmellose®</td>
<td>Crosslinked Cellulose</td>
</tr>
<tr>
<td>Ac-Di-Sol®</td>
<td></td>
</tr>
<tr>
<td>Nymee ZSX®</td>
<td></td>
</tr>
<tr>
<td>Primellose®/Solutab®</td>
<td></td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>Crosslinked PVP</td>
</tr>
<tr>
<td>Crosspovidon M®</td>
<td></td>
</tr>
<tr>
<td>Kollidon®</td>
<td></td>
</tr>
<tr>
<td>Polyplasdone</td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Crosslinked Starch</td>
</tr>
<tr>
<td>Explotab®</td>
<td></td>
</tr>
<tr>
<td>Soy polysaccharides</td>
<td>Natural super Disintegrant</td>
</tr>
<tr>
<td>Emcosoy</td>
<td></td>
</tr>
<tr>
<td>Alginic acid NF</td>
<td>Crosslinked alginic acid</td>
</tr>
<tr>
<td>Satialgine</td>
<td></td>
</tr>
</tbody>
</table>

Drug candidates for fast dissolving tablets [34]
Antibacterial agents: Ciprofloxacin, Tetracycline, Erythromycin, Rifampicin, Penicillin, Doxycyclin, Nalidixic acid, Trimethoprim, Sulphacetamide, Sulphadiazine.
Antihelmintics: Albendazole, Mebendazole, Thiabendazole, Livermectin, Praziqantel, Pyrantel Embonate, Dichlorophen.
Antidepressants: Trimipramine Maleate, Nortriptyline HCl, Trazodone HCl, Amoxapine, Mianserin HCl.
Antidiabetics: Glibenclamide, Glipizide, Tolbutamide, Tolazamide, Gliclazide, Chlorpropamide.
Antihypertensives: Amlodipine, Carvediyl, Diltiazem, Felodipine, Minoxidil, Nifedipine, Prazosin HCl, Nimodipine, Terazosin.
Antiarrhythmics: Disopyramide, Quinidine sulphate, Amiodarone HCl.
Antihistamines: Acrivastine, Cetirizine, Cinnarizine, Loratadine, Fexofenadine, Triprolidine.
Anxiolytics, sedatives hypnotics and neuroleptics: Alprazolam, Diazepam, Clozapine, Amylobarbitone, Lorazepam, Haloperidol, Nizatadine, Midazolam phenobarbitone, Thiordizine, Oxazepam.
Diuretics: Acetazolamide, Clorthiazide, Amiloride, Furosemide, Spironolactone, Bumetanide, Ethacrynic acid.
Gastro-intestinal agents: Cimetidine, Ranitidine HCl, Famotidine, Domperidone, Omeprazole, Ondansetron HCl, Granisetron HCl.
Corticosteroids: Betamethasone, Beclomethasone, Hydrocortisone, Prednisone, Prednisolone, Methyl prednisolone.
Antiprotozoal agents: Metronidazole, Tinidazole, Omizadole, Benznidazole, Clioquinol, Decoquinate.

Conclusion
The development of a fast-dissolving tablet also provides an opportunity for a line extension in the marketplace; a wide range of drugs (For example, neuroleptics, cardiovascu lar drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage form. Pharmaceutical marketing is another reason for the increase in available fast dissolving/ disintegrating products.
As a drug entity nears the end of its patent life, it is common for Pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast dissolving/disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer.

Table 2: List of Marketed product of FDTs [35-36]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Trade Name</th>
<th>Active Drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Febrecol</td>
<td>Paracetamol</td>
<td>Progrpharm, Chateauneuf, France</td>
</tr>
<tr>
<td>2</td>
<td>Zeplar TM</td>
<td>Selegilline</td>
<td>Amarin Corp. London, UK</td>
</tr>
<tr>
<td>3</td>
<td>Zoming-ZMT</td>
<td>Zolmitriptan</td>
<td>AstraZeneca, Wilmington, USA</td>
</tr>
<tr>
<td>4</td>
<td>Zeplar TM</td>
<td>Selegilline</td>
<td>Amarin Corp. London, UK</td>
</tr>
<tr>
<td>5</td>
<td>Pepcid RPD</td>
<td>Famotidine</td>
<td>Merck and Co., NJ, USA</td>
</tr>
<tr>
<td>6</td>
<td>Zofran ODT</td>
<td>Ondansetron</td>
<td>Glaxo Wellcome, Middlesex, UK</td>
</tr>
<tr>
<td>7</td>
<td>Tempra Quiclets</td>
<td>Acetaminophen</td>
<td>Bristol Myers Squibb, NY, USA</td>
</tr>
<tr>
<td>8</td>
<td>Maxalt MLT</td>
<td>Rizatriptan</td>
<td>Merck and Co., NJ, USA</td>
</tr>
<tr>
<td>9</td>
<td>Zyminda</td>
<td>Olanzapine</td>
<td>Eli Lilly, Indianapolis, USA</td>
</tr>
<tr>
<td>10</td>
<td>Claritin redi Tab</td>
<td>Loratidine</td>
<td>Schering Plough Corp., USA</td>
</tr>
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Conflict of interest statement
We declare that we have no conflict of interest.

References


