A Recent Approach on Fast Dissolving Tablets

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ABSTRACT

The novel concept of fast dissolving drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. One important drawback of this dosage forms for some patients, is the difficulty to swallow. Fast-dissolving drug delivery systems offer a solution for these problems. Such FDTs can be administered anywhere and anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients. The excipients that are currently used as well as those that are expected to be used for the future development of improved FDTs are described in the review paper.

Keywords: Fast Dissolving Tablets, Drug Delivery System.

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INTRODUCTION

Oral administration is the most popular route for systemic effect due to its ease of ingestion, pain avoidance, versatility and most importantly, patient compliance [1]. Convenience of administration and patient compliance are gaining significant importance in the design of oral dosage forms. The Oral route of administration is considered as the most widely accepted route, but the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing. Dysphagia this problem is most common for pediatric and geriatric and bedridden patients. Recently more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients [2]. Thus, a new drug delivery system known as Fast Dissolving/Disintegrating (FDDDS) / melt-in-mouth tablets gaining importance by designing to be absorbed through the buccal and esophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from Fast Dissolving formulations may be even greater than that observed in conventional oral dosage forms [3].

Advantages of fast dissolving tablets [4-6]

- Ease of Administration to the patient who cannot swallow the solid dosage forms especially elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and improve clinical performance through a reduction of side effects.

Disadvantages of fast dissolving tablets

- Drugs with relatively larger doses are difficult to formulate in to FDTs [7]. Fast dissolving tablet is hygroscopic in nature so must be kept in dry place and requires special packaging for proper stability & safety of the products [8].
- Containdication in patients who concurrently take anticholinergic medicine, sometime it possesses unpleasant mouth feeling and insufficient mechanical strength [9-10].

Suitable Drug Candidates for fast dissolving tablets

There are some examples of different category of drugs molecule that are suitable drug candidate for preparation of FDTs as shown in Table 1 [11-14]
Table 1: List of some suitable drugs for fast dissolving tablets

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Name of category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anti emetics</td>
<td>Metoclopramide, Ondansetron, Metoprazine</td>
</tr>
<tr>
<td>2</td>
<td>Analgesic and anti inflammatory agent</td>
<td>Aloxiprin, Etodolac, Meclofenamic acid, Sulindac, Naproxen</td>
</tr>
<tr>
<td>3</td>
<td>Anti -bacterial agents</td>
<td>Ciprofloxacin HCL, Clarithromycin</td>
</tr>
<tr>
<td>4</td>
<td>Anti-diabetics</td>
<td>Acetohexamide, Chlorpropamide, Gliclazide</td>
</tr>
<tr>
<td>5</td>
<td>Anti-epileptics</td>
<td>Beclamide, Ethotoin, Methoin, Primidone</td>
</tr>
<tr>
<td>6</td>
<td>Anti- hypertensive agent</td>
<td>Amlodipine, Carvedilol, Isradipine, Reserpine</td>
</tr>
<tr>
<td>7</td>
<td>Anti-malarials</td>
<td>Amodiaquine, Chloroquine, Quinine sulphate</td>
</tr>
<tr>
<td>8</td>
<td>Anti-neoplastic agents and immunosuppressants</td>
<td>Aminoglutethimide, Amsacrine, Busulphan, Etoposide, Lomustine</td>
</tr>
<tr>
<td>9</td>
<td>Anti-thyroid agents</td>
<td>Carbimazole, Propylthiouracil</td>
</tr>
<tr>
<td>10</td>
<td>Diuretics</td>
<td>Acetozolamideamiloride, Bendrofluazide, Cholorothiazide, Metolazone</td>
</tr>
<tr>
<td>11</td>
<td>Enzyme</td>
<td>All the Enzyme</td>
</tr>
<tr>
<td>12</td>
<td>Gastro-intestinal agents</td>
<td>Bisacodyl, Cimetidine, Cisapride, Domperidone, Famotidine, Loperamide, Sulphasalazine</td>
</tr>
<tr>
<td>13</td>
<td>Histamine H₂ receptor antagonist</td>
<td>Acrivastine, Astemizole, Cyclizine, Dimenhydrinate, Loratidine</td>
</tr>
<tr>
<td>14</td>
<td>Opioid analgesic</td>
<td>Codien, Dextropropoxyphene, Diaminophene</td>
</tr>
<tr>
<td>15</td>
<td>Stimulants</td>
<td>Amphetamine, Dexamphetamine, Dexfenfluramine</td>
</tr>
</tbody>
</table>

Manufacturing technique for FDTs

Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. FDTs can be prepared by using this technique because of the good availability of improved excipients especially super-disintegrants and sugar based excipients [15]. The technique of direct compression is schematically represented in Fig. 1

Super-disintegrants

The rate of disintegration gets affected by the addition of superdisintegrants and hence the dissolution. Other ingredients like water-soluble excipients and effervescent agents also increase the disintegration [16-17].

Sugar based excipients

The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel.
Freeze drying or lyophilization

It is one of the first generation techniques for preparing FDTs, in which sublimation of water takes place from the product after freezing. The formulations show enhanced dissolution characteristics due to the appearance of glossy amorphous structure to bulking agents and sometimes to drug [18]. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects. High cost of equipment and processing limits the use of this process [19]. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms [20].

Tablet molding

There are two types of molding process 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). Below Air-drying is done to remove the solvent [21-22]. The tablets manufactured so formed are less compact than compressed tablets and posses a porous structure that hastens dissolution. In the heat molding process a suspension is prepared that contains a drug, agar and sugar (e.g. mannitol or lactose). This suspension is poured in the blister packaging wells, and then agar is solidified at the room temperature to form a jelly and dried at 30 °C under vacum. The main concern about these molded tablets is their mechanical strength, which can be achieved by using binding agents [23].

Cotton Candy Process

A matrix known as ‘floss’, with a combination of excipients, either alone or with drugs is prepared by using shear form technology. The floss is a fibrous material, simillar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F [24-25]. However, other polysaccharides such as polymaltodextrins and poly-dextrose can be transformed into fibers at 30–40% lower
temperature than sucrose. Due to this modification thermolabile drugs can be safely incorporated into the formulation [26]. This process results in a highly porous product and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps are [27]:

- Floss blend
- Floss processing
- Floss chopping and conditioning
- Blending and compression

Sprays-drying

Spray-Drying is used for the preparation of FDTs. The formulations contained hydrolyzed and non hydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. By adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate) disintegration and dissolution were further enhanced. The porous powder was obtained by spray drying the above suspension which was compressed into tablets. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium [28].

Sublimatio

![Fig. 2 Steps involve in sublimation](image)

Sublimation is the technique which has been used to produce FDTs with high porosity, when volatile ingredients are compressed along with other excipients into tablets, a porous matrix is formed which are finally subjected to a process of sublimation. For this purpose inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, urea and urethene) have been used. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix [29-30]. A method using water as a pore-forming material. Fig. 2 Shows the steps of Sublimation Process.
Mass-extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. This softened mass is extruded through the extruder or syringe and a cylindrical shaped extrude is obtained which are finally cut into even segments using heated blade to form tablets. Granules of bitter drugs can be coated using this method to mask their taste [31].

Patented techniques for preparation of FDTs

Nanonization or Nanocrystal technology

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 FDTs. 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) [32].

Fast dissolving films

It is a newer developing front in FDDDS that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (Pullulan, CMC, HPMC, HPC, PVP 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 flavoured taste [33].

Zydis technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These forms a glossy amorphous structure, which imparts strength. Zydis products are packed in blister packs to protect the formulation from moisture in the environment [34-35].

Orasolv technology

It is CIMA lab’s first mouth dissolving formulation which involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet
equipments are used for preparation of tablets. Less force of compaction is used for manufacturing so as to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system [39].

**Wow Tab technology**

WOW means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet [40].

**Lyoc**

Oil in water emulsion is prepared and placed directly into blister pack followed by freeze drying. Nonhomogeneity 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 [42].

**Flash Tab technology**

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 includes reticulated polyvinylpyrollidone or carboxymethyl cellulose. Swelling agents include Carboxymethylcellulose, starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min [43-44].

**Durasolv technology**

The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients [45].

**Oraquick technology**

It utilizes taste masking microsphere technology called as micromask, which provides superior mouthfeel, significant mechanical strength, and quick disintegration of the product [32]. This process involves preparation of microparticles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength [47]. Low heat of production in this process makes it appropriate for heat sensitive drugs. Oraquick product dissolves within few seconds [48].
Ziplets/Advatabs

It utilizes water soluble ingredient combined with one or more effective disintegrants to produce FDTs with improved mechanical strength and optimal disintegration time at low compression force [26]. This technology handles high drug loading and coated drug partials and does not require special packaging, so they can be packed in push through blisters or bottles [38].

Flash dose

Flash dose tablets consist of self-binding shearform matrix termed as “floss”. Shearform matrices are prepared by flash heat processing [29]. Some of examples of Patented FDTs are described in Table 2 with their Innovator name, active ingredients and advantages.

<table>
<thead>
<tr>
<th>Patented Technology</th>
<th>Technique Employed</th>
<th>Innovator Company</th>
<th>Active Ingredient &amp; Brand Names</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zydis</td>
<td>Lyophilization</td>
<td>R.P. Scherer, Corp.</td>
<td>Loratidine (Claritin, RediTab Pharmaceuticals)</td>
<td>Highly porous in nature, faster dissolution rate of tablets than conventional</td>
</tr>
<tr>
<td>Quicksolv</td>
<td>Lyophilization</td>
<td>Janssen Pharma</td>
<td>Cisapride monohydrate (Propulsid Quicksolv)</td>
<td>Short disintegration time, good mouthfeel property of tablets</td>
</tr>
<tr>
<td>Lyoc</td>
<td>Lyophilization</td>
<td>Farmalyoc</td>
<td>Phloroglucinol Hydrate (Spasfon Lyoc)</td>
<td>Accommodate high dose, disintegrates rapidly within a matter of seconds</td>
</tr>
<tr>
<td>Orasolv</td>
<td>Effervescent disintegrant compression</td>
<td>CIMA Labs, Inc.</td>
<td>Paracetamol (Tempra)</td>
<td>Unique taste masking, fast dissolution rate of tablets</td>
</tr>
<tr>
<td>Durasolv</td>
<td>Molding</td>
<td>CIMA Labs, Inc.</td>
<td>Hyoscyamine Sulfate(NuLev)</td>
<td>Good rigidity</td>
</tr>
<tr>
<td>Patented Technology</td>
<td>Technique Employed</td>
<td>Innovator Company</td>
<td>Active Ingredient &amp; Brand Names</td>
<td>Advantages</td>
</tr>
<tr>
<td>Wowtab</td>
<td>Compression molded tablets</td>
<td>Yamanouchi Pharma</td>
<td>Famotidine (Gaster D)</td>
<td>Adequate dissolution rate and hardness in tablets</td>
</tr>
<tr>
<td>Flashdose</td>
<td>Cotton Candy Process</td>
<td>Fuisz Technology Ltd</td>
<td>Tramadol Hcl (Relivia Flashdose)</td>
<td>Highly porous in nature, and tablets shows pleasant mouthfeel property</td>
</tr>
<tr>
<td>Flashtab</td>
<td>Effervescent Disintegrant</td>
<td>Prographarm Group</td>
<td>Ibuprofen (Nurofen FlashTab)</td>
<td>Conventional tableting technology and faster dissolution rate</td>
</tr>
</tbody>
</table>
### Superdisintegrants Used in FDTs

The basic approach in development of FDTs is use of disintegrant. Disintegrant play an important role in the disintegration and dissolution of FDTs. 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. Due to swelling of superdisintegrant, the wetted surface of the carrier increases this promotes the wetability and dispersibility of the system, thus enhancing the disintegration and dissolution. Superdisintegrante’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. Common disintegrants used in this formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmellose (NS-300), sodium starch glycolate etc [49]. Selection of Superdisintegrants primarily affect the rate of disintegration, but when used at high levels they can also affect mouth feel, tablet hardness and friability. Some of the superdisintegrants with mechanism of action are shown below in Table 3 [50-52]

<table>
<thead>
<tr>
<th>Superdisintegrants</th>
<th>Example</th>
<th>Mechanism of action</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-HPC</td>
<td>Low hydroxyl propyl cellulose</td>
<td>Both swelling and wicking</td>
<td>Promote disintegration</td>
</tr>
<tr>
<td>Croscarmellose Ac-Di-Sol</td>
<td>Crosslinked Cellulose</td>
<td>Swells 4-8 folds in &lt; 10 seconds. Swelling</td>
<td>Swells in two Dimensions, Direct compression</td>
</tr>
<tr>
<td>Crospovidone Kollidon Polyplasdone</td>
<td>Crosslinked PVP</td>
<td>Swells very little</td>
<td>Water insoluble and spongy in nature</td>
</tr>
<tr>
<td>Sodium Alginate</td>
<td>Sodium salt of Alginic acid</td>
<td>Swelling</td>
<td>By wicking and swelling disintegrate the tablets rapidly</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Crosslinked Starch</td>
<td>-Swells 7-12 folds in &lt; 30 seconds</td>
<td>Swells in three Dimensions</td>
</tr>
<tr>
<td>Acrylic acid</td>
<td>Poly</td>
<td></td>
<td>Capillary and wicking</td>
</tr>
</tbody>
</table>
Derivatives | (Acrylic acid) Superporous | Wicking action hydrogel | Increase the disintegration
---|---|---|---
Alginic acid | Crosslinked alginic acid | Rapid swelling in aqueous medium | Promote disintegration
Calcium silicate | | By Wicking | Highly porous
Soy polysaccharides | Natural Disintegrant | Swelling | EMCOSOY
Ion exchange Resin | | By ion exchange mechanism | Amberlite (IPR 88)
Effervescent Mixture | Citric acid, tartaric acid and sodium bicarbonate | Effervescence | Promote disintegration

**CONCLUSION**

Fast dissolving tablets are formulated to improve patient compliance and convenience. They are a very good alternative for drug delivery to geriatric and pediatric patients. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus, looking at the advances and advantages in this therapeutic approach, the pharmaceutical formulator need not restrict his choice in the development of conventional dosage forms but should also try to develop these fast dissolving drug delivery systems.

**REFERENCES**