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Fast Dissolving Tablet- An Overview of Formulation Technology

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ABSTRACT: In recent years, a variety of pharmaceutical research has been conducted to develop new dosage forms. Among the dosage forms developed to facilitate ease of medication, the rapid disintegrating tablet (RDT) is one of the most widely employed commercial products. As our society is becoming increasingly aged, 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 (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphasia. Swallowing problems also are common in young individuals because of their underdeveloped muscular and nervous systems. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled, and patients who are uncooperative, on reduced liquid-intake plans, or are nauseated. In some cases such as motion sickness, sudden episodes of allergic attack or coughing, and an unavailability of water, swallowing conventional tablets may be difficult. This paper summarizes the formulation methods and drug formulation coming in market.

KEYWORDS: Mouth Dissolving; Direct Compression; Superdisintegrants.

INTRODUCTION

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films [1]. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates 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. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients[2,3]. These are also called melt-in-mouth tablets,

rapid melts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets, Moth dissolving tablets, fast dissolving, rapid dissolve, fast melts, Effervescent Drug Absorption system, Orosolv, Zydus etc. Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets[14]. These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach used in development of MDT is the use of superdisintegrants like Cross linked carboxymethyl cellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab). Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets[5-8]. Another approach used in developing MD tablets is maximizing pore structure of the tablets. Different types of technologies have been employed for the formulation of mouth dissolving tablets viz freeze-drying, Tablet Molding, Direct Compression Method, spray drying and sublimation Technology etc. have been tried by researchers to maximize the pore structure of tablet matrix[9-13].

Requirements of Fast Dissolving Tablets an ideal FDT should [14]

1. Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
2. Have a pleasing mouth feel.
3. Have an acceptable taste masking property.
4. Be harder and less friable
5. Leave minimal or no residue in mouth after administration
6. Exhibit low sensitivity to environmental conditions (temperature and humidity).
7. Allow the manufacture of tablet using conventional processing and packaging equipments.

Advantages of Fast Dissolving Tablets [15]

1. Ease of administration to patients who cannot swallow, such as the elderly, strokes 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[16-17].
2. Patient's compliance for disabled bedridden patients and for travelling and busy people, who do not have ready access to water.
3. Good mouth feel property of MDDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients due to improved taste of bitter drugs.
4. Convenience of administration and accurate dosing as compared to liquid Formulations.
5. Benefit of liquid medication in the form of solid preparation.
6. More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action[17,18].

7. Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects[19].
8. New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension[17,18].

METHODOLOGY EMPLOYED FOR FAST DISSOLVING FORMULATIONS

1. Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin[20]. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder. Superpolystate is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues[21].

2. Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol[22].

3. Sublimation

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva[23]. Granules containing nimusulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure[24]. Conventional methods like dry granulation, wet granulation and direct compression with highly soluble excipients, superdisintegrants and/or effervescent systems can also be used.

4. Three-dimensional Printing (3DP)

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system[25]. It was found that rapidly disintegrating oral tablets with proper

hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume[26].

5. Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste[15,27].

6. 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 orcrosscarmellose 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. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution. Maximum drug release and minimum disintegration time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique

7. Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament[29, 30]. The Shear form technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F[31]. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermo labile drugs into the formulation[32]. The tablets manufactured by this process are highly porous in nature 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 as detailed below.

A) Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture[33].

B) Floss Processing

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in ‘cotton-candy’ formation which consists of a spinning head and heating elements. In the flash heat

process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature[34-36].

C) Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss[31].

D) Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form[37].

8. Tablet Molding

Molding process is of two type's 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.

9. Lyophilization or Freeze-Drying

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.

10. Direct Compression[38]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

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. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the superdisintegrant, Some important examples of superdisintegrants are given in **Table 1** with their mechanism of action.

b) Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture[38].

11. Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique[39]. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poor water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit)[15].

Table 1: List of Super Disintegrants

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
Soy polysaccharides Emcosoy®	Natural super disintegrant	-Does not contain any Starch or sugar. Used in nutritional products	-
Calcium silicate	-	-Wicking action	Highlyporous, Optimum concentration is between 20-40%

Table 2: List of Marketed Fast Dissolving Tablets[47-48]

SR. NO.	*TRADE NAME*	*ACTIVE DRUG*	*MANUFACTURER*
1.	Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
2.	Claritin redi Tab	Loratidine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
4.	Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merck and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7	Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
8.	Zeplar TM	Selegilline	Amarin Corp., London, UK
9.	Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
10.	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
11.	Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
12.	Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
13.	Olanex instab	Olanzapine	Ranbaxy lab. Ltd.New-delhi, India
14.	Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
15.	Benadryl Fastmelt	Diphenhydramine and pseudoephedrine	Warner Lambert, NY, USA
16.	Propulsid Quicksolv	Cisapride monohydrate	Janssen pharmaceutics
17.	Risperdal MTab	Risperidone	Janssen pharmaceutics
18.	Spasfon Lyoc)	Phloroglucinol Hydrate	Farmalyoc

19.	Nurofen FlashTab)	Ibuprofen	Ethypharm
20.	Tempra Quicklets	Paracetamol	Cima Labs,Inc.
21.	Zolmig Repimelt	Zolmitriptan	Cima Labs,Inc.
22.	(NuLev	Hyoscyamine Sulfate	Cima Labs, Inc.
23.	Gaster D)	Famotidine	Yamanouchi Pharma Tech. Inc.
24.	Cibalgina DueFast	Ibuprofen	Eurand International
25.	Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd.
26.	Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc.
27.	Abilify Discmelt	Aripiprazole	Otsuka America/Bristol-Myers Squibb
28.	Allegra ODT	Fexofenadine	Sanofi Aventis
29.	Aricept ODT	Donepezil	Eisai Co.
30.	Clarinex RediTabs	Desloratadine	Schering-Plough
31.	Alavert Quick Dissolving Tablets	Loratadine	Wyeth
32.	Clonazepam ODT	Clonazepam	Par Pharmaceutical
33.	FazaClo	Clozapine	AzurPharma
34.	Jr. Tylenol Meltaways	Acetaminophen	McNeil Consumer Healthcare
35.	Klonopin Wafers[26]	Clonazepam	Roche
36.	Loratadine Redidose	Loratadine	Ranbaxy
37.	Mirtazapine ODT	Mirtazapine	Teva Pharmaceuticals
38.	Niravam	Alprazolam	Schwarz Pharma
39.	Ondansetron ODT	Ondansetron	Teva Pharmaceuticals
40.	Orapred ODT	Prednisolone	Sciele Pharma
41.	Parcopa	Carbidopa/levodopa	Schwarz Pharma
42.	Prevacid SoluTab	Lansoprazole	Takeda Pharmaceuticals
43.	Remeron SolTab	Mirtazapine	Schering-Plough
44.	Risperdal M-Tab	Risperidone	Janssen
45.	UNISOM SleepMelts	Diphenhydramine	Chattem
46.	Zomig-ZMT	Zolmitriptan	AstraZeneca
47.	Zyprexa Zydis	Olanzapine	Eli Lilly and Company
48.	Citalopram ODT	Citalopram	Biovail
49.	Metoclopramide Zydis	Metoclopramide	Salix Pharmaceuticals
50	Reglan ODT	Metoclopramide	Schwarz Pharma[
51.	Tramadol/ Acetaminophen ODT	Tramadol/ Acetaminophen	Biovail
52.	Zolpidem ODT	Zolpidem	Biovail

CONCLUSION

The development of a fast-dissolving tablet also provides an opportunity for a line extension in the marketplace; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage form. 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.

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