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A Review on Recent Trends in Oral Drug Delivery-Fast Dissolving Formulation Technology

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Abstract: As pharmaceutical scientists are attaining a better understanding of biochemical and physicochemical properties related to the drug action, the drug delivery systems are becoming simple. Fast dissolving tablets (FDTs) have become popular due to better patient compliance and preferred over conventional capsules and tablets. When FDT is put on the tongue, it disintegrates or dissolves rapidly (in seconds) without chewing or water. Various FDT products entered into the market in 1980s. Their demand is progressively increasing and their product pipelines are speedily intensifying. Recent FDT production techniques have helped in management of convenient dosing in patients suffering with dysphagia. The aim of this review article is to give an overview on desired characteristics, preparation techniques and patented technologies of FDTs formulation.

Key words: Dysphagia · Fast Disintegrating · Fast Dissolving · Disintegration Time · Lyophilization · Direct Compression · Disintegrants

INTRODUCTION

Oral route is the most preferred route for administration of drugs, because it provides high patient compliance. Dysphagia is commonly found among all age groups [1-3]. Due to this problem, approximately 50% of population suffers. The difficulty in swallowing may be due to the taste, size and surface of dosage form. During journey, sometimes water is not easily accessible so a patient feels difficulty in swallowing solid dosage form [4]. Hence there is an urgent need to develop novel dosage form that improves patient compliance [2, 5, 6]. This may be achieved by development of a dosage form that can disintegrate or dissolve with saliva [1,7]. Furthermore, FDTs are beneficial for patient having swallowing problems usually during travelling and/or mentally retarded patients. There are various fast dissolving dosage forms such as FDTs, fast dissolving pellets and fast dissolving films. FDT is a type of solid dosage forms which disperse/dissolve/disintegrate in saliva within seconds without the aid of water [3, 6, 8]. The excipients employed in FDTs are always hydrophilic in nature whereas drug may be either hydrophilic or hydrophobic [9]. If the drug is hydrophilic, the dosage form is known as fast dissolving tablets otherwise if drug is hydrophobic it is known as fast disintegrating tablets. The various synonyms used for FDTs include mouth dissolving tablets (MDTs), orally disintegrating tablets (ODTs), melt-in-mouth tablets, porous tablets, oro-dispersible, quick dissolving and rapid disintegrating tablets [9, 10].

Advantages of FDTs: The advantages of FDTs include easy manufacturing, accurate dosing and easy handling by patients, no requirement of chewing and water for swallowing [5, 9-12]. It has advantages over other oral dosage forms including better shelf-life, more accurate dosing and lower volume and lower weight [9]. They help in easy administration of drug to psychiatric patients who refuse to swallow [13]. FDTs also offer merits over other oral dosage forms viz. effervescent tablets, extemporary preparations, chewing gum, or chewable tablets, which are commonly used to enhance patient compliance. Thus, the drugs with bitter taste and unpleasant odour can be masked by FDTs as prolonged time that they are in the mouth or as a result of leaching of the drug from chewed or broken microcapsules is decreased to great extent [8]. Bitter taste can be improved by using various technologies. FDTs may be absorbed in buccal region

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because they disintegrate or dissolve inside the mouth. Thus, increased bioavailability of drugs may be achieved. Additionally, it provides the benefits of liquid medication. Hence, first-pass metabolism may be avoided. There may be reduction of dose of drug as during hepatic metabolism, there may be loss of significant amount of drug. FDTs act as a management tool to promote among medical profession for the drugs having last or nearly last stage of product of conventional dosage form [1, 14].

Ideal Properties of FDTs: An ideal FDT should meet the following properties [1, 15]:

- It should allow high drug loading.
- It should require no water during oral administration as it dissolves/disintegrates in mouth within few seconds.
- It should have an acceptable taste.
- It should give a pleasing mouth feel.
- It should be less friable, but have good mechanical strength to withstand the post manufacturing handling.
- It should be stable in environmental conditions.
- Subsequent to oral administration, it should leave least or no residue in mouth.
- It should be compatible with other ingredients.

Desired Characteristics and Development Challenges of FDTs: The FDTs should maintain several unique properties, as given below:

Drug Properties: The tablet properties should not be affected by the drug properties. The FDTs properties like mechanical strength and disintegration time may be affected by drug characteristics such as particle size, solubility, crystal structure, hydrophilicity, compressibility and bulk density. The FDT formulation technique should be flexible to accommodate distinctive properties of a drug [1, 9].

Taste of Drug: An ideal taste-masking technology should produce drugs with a pleasant mouth feel. In order to enhance patient compliance for the unpleasant taste drugs [1, 9].

Fast Disintegration: Usually “fast disintegration” means tablets disintegrate rapidly. Saliva of the patient act as disintegration fluid. The disintegrated particles of tablet help in smooth swallowing [1, 9].

Sensitivity to Moisture: There is requirement of specialized product packaging as several fast dissolving dosage forms are hygroscopic due to which it cannot maintain physical integrity. FDTs should have low sensitivity to humidity. To protect FDTs from manufacturing and external environmental conditions a high-quality packaging or other approach should be created [1, 9].

Hardness and Porosity: For fast dissolving, the tablets are made by compression at very low compression force. But the tablets become more friable during handling, hence require humidity controlled environment. The tablets are required to be packed in aluminium packaging [1, 9].

Excipients for FDTs: FDTs are usually composed of both water-soluble and water-insoluble excipients [1- 9, 16-22]. The various ingredients used in FDTs are listed in Table 1.

Mechanism of Rapid Disintegration of Superdisintegrants: Various proposed mechanism of action of superdisintegrants is as follows:

Deformation Mechanism: According to this, during compression disintegrants may get deformed but regain their normal shape on contact with aqueous medium. So that the disintegrant particles swell to precompression size and breaking of tablet matrix occurs [23].

Swelling Mechanism: Swelling of disintegrant may cause break-up of the tablet [23].

Wicking Mechanism: When tablet comes in contact with aqueous medium, due to penetration of water there may be weaking of bonding force between drug particles. Finally tablet breaks into fine particles [23].

Repulsive Force Mechanism: In aqueous medium, water penetrates into tablet and there may be generation of electrical force. Due to which the drug particles may repel each other and finally tablet breaks into fine particles [23].

The examples of various superdisintegrants along with their mechanism are given in Table 2.

Preparation Techniques of FDT: The various approaches to prepare FDT including the following:

Table 1: Various ingredients for FDTs

Component	Example
Water-soluble excipients	Compressible sugars, binders, surfactants, flavouring agents
Water-insoluble excipients	Microcrystalline cellulose, di- or tri-basic calcium phosphate
Disintegrants	Modified celluloses (such as cross-linked sodium carboxy methyl cellulose), cross-linked polyvinyl pyrrolidone (PVP), microcrystalline cellulose, starch and modified starch (including potato starch, maize starch, starch 1500, sodium starch glycolate and starch derivatives), alginic acid and sodium alginate.

Table 2: Mechanism of superdisintegrants

Mechanism of disintegration	Example of super disintegrants
Wicking	Cross linked cellulose, cross linked PVP, calcium silicate [9]
Swelling	Cross linked starch [9]
Both wicking and swelling	Cross linked PVP, Cross linked aliginic acid [9]

Moulding Method: In this method, the ingredients blend is moistened with hydro alcoholic or aqueous solvent. Using low compression pressure, the blend is moulded into tablets. The pressure used here is lower than the pressure used for preparation of conventional tablets. Air drying is used to remove solvent. The tablets possess poor mechanical strength. Water-soluble ingredients are the main constituents of moulded tablets [8, 10].

Sublimation Method: By this technique, the active drug, volatilizing substance and other ingredients are compressed to form a tablet. Then sublimation of volatilizing substance is done. This result in development of pores in tablet [9, 10]. Volatile substances that may be used include camphor, hexamethylene tetramine, ammonium bicarbonate, urea, ammonium carbonate etc.

Direct Compression Method: This is the common and widely used method for FDT production. The blend prepared from excipients and drug is directly compressed [8-10, 24-25]. Commonly used excipients include diluents, directly compressible disintegrants, effervescent agents, lubricants, etc. Superdisintegrants are used in optimum quantity. This help in the rapid disintegration of tablet. The various superdisintegrants include cross povidone, sodium starch glycolate, microcrystalline cellulose, D-mannitol, etc [1, 9].

Phase Transition Process Method: In this method two sugar alcohols are used. The one sugar belongs to high melting point sugar category whereas the second belong to the low melting sugar category. They are heated to their melting point and finally compressed to produce tablets [9].

Effervescent Agent Addition Method: In this method a mixture containing tartaric acid and an alkaline substance such as sodium bicarbonate is prepared by mortar and pestle and preheated at 80°C. It is helpful in removing the residual or absorbed moisture. The mixture is then mixed with superdisintegrants and finally compressed to form tablets [1].

Spray Drying Method: This method involves spray drying of a blend containing drug, bulking agents, effervescent and disintegrating agents. It results in production of a porous powder which gets rapidly dissolved in water. Finally the porous powder is compressed to produce tablet [10].

Taste Masking Method: Usually, microencapsulation is used to mask the bitter taste of drug. The active drug is encapsulated in an immediate release matrix. In FDTs, the rapid disintegration is achieved by using effervescent agents. The taste masking method involves the compression of taste masked microcrystal of active drug compound along with swelling and disintegrating agents [1].

Freeze Drying or Lyophilization Method: This method is generally used for drying the heat sensitive drugs. Drying is done at low temperature and water is removed by sublimation process. Through lyophilization the highly porous tablet may be formed [8, 10]. The tablet formed by lyophilization are more fragile, hence require special packaging. The disadvantage of lyophilized drug is that they have poor stability when stored under stressed conditions.

The various superdisintegrants and preparation technologies used for formulating FDTs of several drug are given in Table 3.

Table 3: Name of drugs formulated as FDTs

Name of drug	Superdisintegrant	Preparation method
Prednisolone [26]	Croscarmellose sodium	Direct compression
Flurbiprofen [27]	β-Cyclodextrin	Direct compression
Ketoprofen [28]	Mixture of gelatin, glycine and sorbitol.	Blister technique
Glyburide [29]	Sodium laurylsulphate	Direct compression
Granisetron HCl [30]	β-Cyclodextrin	Direct compression
Terfenadine [31]	Crospovidone, Ac-Di-Sol, Primojel, low substituted hydroxyl propylcellulose	Direct compression
Perphenazine [32]	Polyethylene glycol 8000	Freeze-drying
Ondansetron HCl [12]	Crospovidone	Direct compression
Epinephrine bitartrate [25]	Mixture of microcrystalline cellulose and low substituted hydroxyl propylcellulose (9:1)	Direct compression
Glyburide [33]	Binary system of cyclodextrin and polyvinyl pyrrolidone (PVP)	Direct compression
Nimesulide [34]	Crospovidone	Vacuum drying
Ketoprofen [35]	Poly(acrylic acid) superporous hydrogel microparticles	Direct compression
Metoclopramide HCl [36]	Crospovidone	Direct compression
Fenoverine [37]	Sodium starch glycolate	Direct compression
Meloxicam [38]	Sodium starch glycolate	Direct compression
Rofecoxib [22]	Crospovidone	Direct compression
Ibuprofen [39]	26% Galactomannan and 5% crospovidone	Direct compression
Meclizine [40]	Mannitol and camphor	Direct compression
Hydrochlorothiazide [41]	Hydroxyl ethyl cellulose	Freeze-drying
Promethazine HCl [42]	Ac-Di-Sol	Direct compression
Lansoprazole [43]	Microcrystalline cellulose, low-substituted hydroxypropyl cellulose	Direct compression
Cetirizine HCl [44]	Sodium croscarmellose	Direct compression

Patented Technologies for Preparation of FDT: There are various patented techniques for the preparation of FDT and includes:

Zydis Technology: This technology utilizes a unique freeze-drying method. This technology involves preparation of drug solution or suspension, by employing vacuum mixer. This mixture is placed in a holding vessel and filled into blister pockets and lyophilized. The porous matrix is packed into the pockets by lidding foil [1, 10].

Advatab Technology: During the production process of FDTs, the lubricant is coated on each tablet surface by a spray. The produced tablets are stronger and harder than conventional due to which saliva cannot penetrate easily [10]. High drug loading is possible in this technology. Additionally, there is no requirement of special packaging and, also, the tablet can be packaged in both push-through blisters and standard bottles. It is reported that AdvaTab tablets disintegrate within less than 30 seconds due to quick penetration of saliva in pores of tablet in mouth.

Pharmaburst Technology: A blend of drug, lubricant and flavour is prepared and compressed to produce tablets. These are then packed in special packaging. In this technology mainly co-processed excipients are used [1].

Frosta Technology: In this technology, a plastic material which is porous is used. It should be water-soluble. The highly plastic granules composed of binder; surfactant and a plastic material are compressed at low pressure. This lead to the formation of a fast melt tablet having good mechanical strength and more porous [1].

Lyoc Technology: It involves the preparation of oil-in-water emulsion of drug. Then it is placed in blister pockets and lyophilized. This product is able to hold high dose and disintegrates quickly but own poor mechanical strength. In this technology, to prevent sedimentation, the filler are used to enhance the viscosity of the suspension [8, 10].

Ora Solv Technology: Effervescent agent is the main ingredient used in this technology. The drug microparticles are lightly compressed along with the effervescent agent [1, 8, 10]. The formulated tablets have the appearance of a traditional compressed tablet. But they are weaker and more fragile than the conventional tablets. Thus, there is a requirement for a special packaging. The particle coating which is used for taste masking purpose is not cracking at the time of compression because of low compression force.

WOW Tab Technology: Combinations of two different types of saccharides are used to obtain a tablet. One is low mouldability saccharide another is high mouldability

saccharide, thus produces a formulation having adequate hardness and rapid dissolution [8]. Because of hardness, the tablet is more stable in the environmental conditions than the Zydis or Orasolv and is fit for both usual bottle and blister packaging [1, 10].

Dura Solv Technology: Non direct compression filler (particle size between 20 to 65ìm) and lubricant are the main component of the tablet prepared by this technology. Usually mannitol, sucrose, sorbitol, dextrose and lactose are used as fillers because they show rapid dissolution. The tablets have disintegration time less than 60 seconds. In this technology more amounts of hydrophobic lubricants, can be used in the formulation. Low compressive force is required to compress the tablet. The production cost is significantly less because direct compression method and conventional package equipment are employed [10].

Flashtab Technology: Coated crystals of drug along with granular excipients are compressed to produce tablets. In this technology swelling and disintegrating agents are usually two main components. The tablet disintegrates in the mouth within one minute [1, 10].

Quicksolv Technology: Both the drug and excipients are dissolved in water and frozen. Add second solvent to the frozen mixture. And finally after a few hours, the second solvent is removed, which results in formation of a porous matrix. The second solvent may be acetone or ethanol. Always the matrix composition should be immiscible to the second solvent. The drug should be in fine size and have good stability in aqueous medium [1, 5, 8].

Nanocrystal Technology: The colloidal dispersion of drug along with other water-soluble ingredients mixes thoroughly. This mixture is then placed in blister pockets and freeze dried. It is considered that this technology reduces the particle size, which is beneficial to enhance the dissolution, hence bioavailability [1, 45, 46].

Flashdose Technology: It utilizes Shearform technology along with Ceform TI technology to avoid the bitter taste of the drug. Shearform technology prepares the floss matrix. Matrix is composed of drug and excipients. Floss refers to fibrous material, which is similar to cotton-candy fibres. These cotton-candy fibres are prepared by saccharides such as lactose, sucrose, fructose and polydextrose. Tablets prepared by this technology possess high porousity. Also, as tablets contain sugar, it shows fast salvation in mouth and offer a very pleasant mouth feel. The general manufacturing method of tablets by this technology involves preparation of sucrose solution (80%) and addition of 1 % surfactant. Surfactant helps in maintaining the structural integrity of the floss fibres. Then this whole product is subjected to the flash heat process. In this process, the heat provokes an interior flow state of the carrier substance. Then this processed material is passed through an exit, where a spinning head operated at 2000-3600 rpm. The role of spinning head is to throw the floss under centrifugal force and produce long floss fibres. These fibres are generally amorphous in nature. Mix the drug and required excipients with floss fibres and finally compressed [8, 10].

Future Research Developments in FDTs: Although the FDT technologies has passed through a lot of developments, as shown by a large number of commercial products in the market, but there are still many characteristics features to improve the formulations. Despite progress in the FDT technologies, formulation of FDT of lipophilic drugs is still a challenge, particularly when the amount of drug is more. So there is need to develop a new FDT technology to overcome this problem. Additionally, the hope of using FDTs too lies in the improvement of taste-masking properties. The coating of bitter taste drugs are commonly used, but it increases the total bulk volume of the formulation. As there is no solution to this problem, but use of more effective taste masking technologies can avoid the problems. Generally in the FDT formulations there is requirement of more amounts of excipients, which results in making big formulation. Hence, there is need to develop a FDT formulations that would require fewer excipients than the drug itself.

CONCLUSION

The FDTs have received paramount popularity over the last decade. There are numerous drugs that have been marketed as FDT formulation. The key feature of a FDT formulation is fast disintegration, dissolution in the mouth in presence of saliva. This can be attained by formulating a porous structure of the tablet matrix or by addition of effervescent agents and/or superdisintegrants. FDTs formulated by direct compression method usually possess good mechanical strength. This strength can be further improved by subsequent treatment, such as moisture

treatment. FDTs provide a rapid onset of drug action, finally enhance bioavailability. Various clinical studies have shown that they can help in improvement of patient compliance. However, future developments are required for cost reduction and broadening the use of the new manufacturing techniques.

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