The Pharma Innovation Journal 2018; 7(4): 1090-1094

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(4): 1090-1094

www.thepharmajournal.com
Received: 24-02-2018
Accepted: 28-03-2018

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Fast dissolving tablets: An overview of preparation techniques and evaluation

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Abstract
Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop Fast dissolving tablets (FDTs) with improved patient compliance and convenience. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes the various formulation aspects, and technologies developed for FDTs, along with various excipients, evaluation tests, and drugs explored in this field.

Keywords: Disintegration, fast dissolving tablets, lyophilization, superdisintegrants

Introduction
Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet (Kuchekar *et al.*, 2003) [15].

Fast dissolving tablets are also called as orally disintegrating tablets, orodispersible tablets, mouth dissolving tablets, fast disintegration tablets, rapid dissolving tablets, porous tablets and rapimelts. However, all of the above terms, United States Pharmacopoeia (USP) approved these dosage forms as FDTs. Recently, European Pharmacopoeia has used the term orodispersible tablets that disperse readily in and within 3 minutes in mouth before swallowing (Fu *et al.*, 2004) [11].

United States Food and Drug Administration (FDA) defined FDT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed on the tongue." The disintegration time for FDTs generally ranges from several seconds to about a minute. The basic approach used in development of FDT is the use of superdisintegrants like Cross linked carboxymethylcellulose (Croscarmellose), Sodium starch glycolate (Primogel, explotab), Polyvinyapyrrolidone (Polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva.

Advantages of fast dissolving drug delivery system
- Ease of administration to pediatric and geriatric patients and psychiatric patients.
- Convenience of administrate accurate dose as compared to liquids.
- No need of water to swallow the dosage from.
- Good mouths feel property.
- Rapid dissolution of drug and absorption, which may produce rapid onset of action.
- Rapid drug absorption through pre-gastric absorption from the mouth, pharynx and esophagus.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Free of the risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.

- New business opportunities like product differention (Kuchekar *et al.*, 2003) [15].

Formulation aspects in developing FDT

Fast dissolving tablets are formulated by utilizing several processes, which differ in their methodologies and the FDTs formed vary in various properties such as,

- Mechanical strength of tablets
- Taste and mouth feel
- Swallow ability
- Drug dissolution in saliva
- Bioavailability
- Stability

Various processes employed in formulating FDTs include freeze-drying, cotton candy process, molding, spray drying, mass extrusion and direct compression.

Freeze drying

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation.

The influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in freeze dried form was investigated by Corveleyn and Remon who concluded that maltodextrins are useful in the formulation of fast dissolving tablets made by freeze drying (Remon and Corveleyn, 2000) [20].

Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDT. This process can accommodate high doses of drug and offers improved mechanical strength. However, high-process temperature limits the use of this process (Meyers *et al.*, 1995) [17].

Moulding

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent; it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution. Cherukuri *et al.*, 1996 [5] have developed the method of preparing a comestible unit which disperses quickly in the mouth. The present invention also includes the product resulting from the method. The method includes initiating crystallization of shear form matrix and combining with an additive, either before or after initiating crystallization, to form flow able, compactible micro-particulates. The combination is then subjected to compacting to form a comestible unit having high structural integrity, good appearance, and excellent release characteristics.

Mizumoto *et al.*, 1996 [18] have done a Intra buccally dissolving compressed moldings comprising a saccharide having low mold ability having been granulated with a saccharide having high mold ability. The moldings of the present invention show quick disintegration and dissolution in the buccal cavity and have an adequate hardness. No-vacuum lyophilization is another process which involves the evaporation of a solvent from a drug solution or suspension at standard pressure.

Spray-drying

Highly porous and fine powders can be produced by spray drying process, as the processing solvent is evaporated rapidly during spray drying. For fast dissolving tablets, they developed formulation by using mannitol as bulking agent, hydrolysed and non-hydrolysed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (eg. citric acid) and/or alkali material (eg. $NaHCO_3$) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds. Spray drying technique has been employed to prepare fast dissolving tablet (Allen and Wang, 1997) [2]. They developed formulation by using mannitol as bulking agent, hydrolyzed or non hydrolyzed gelatin as support matrix, sodium starch glycollate as disintegrant citric acid and NaHCO3 to enhance the disintegration and dissolution.

Sublimation

Compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets exhibit good mechanical strength and dissolve quickly. Inert solid ingredients {eg: urea, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure. The highly porous mouth dissolving tablets of Domperidone was formulated by using meltable binder polyethylene glycol-4000, a diluent mannitol and a component which sublimes readily camphor/ ammonium carbonate and later is removed from the tablet by sublimation process after compression (Mane *et al.*, 2003) [16].

Mass-extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste. The mouth disintegrating tablets of ofloxacin using aspartame as sweetener, sodium starch glycolate disintegrant and isopropyle alcohol as granulating agent and by mass extrusion technique using eudragit E100 as taste masking agent along with avicel 102 and ethanol (Dandagi *et al.*, 2005) [8]. Rapidly disintegrating domperidone tablets were formulated byusing two methods as mass extrusion technique and treated agar (Dandagi *et al.*, 2006) [7]. In mass extrusion formulations sodium starch glycolate, eudragit E-100, low substituted hydroxyl propylcellulose, lactose and in treated agar formulations mannitol, treated

agar, lactose, aspartame was used as exciepients.

Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling, tablet rupture during the opening of blister alveolus all results from insufficient physical resistance (Wayne *et al.,* 2006) [22].

Disintegrants have major role in the disintegration and dissolution process of mouth dissolving Tablets made by direct compression. To ensure a high dis- integration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water-soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature. The understanding of disintegrant properties and their effect on formulation has advanced during last few years, particularly regarding so called super-disintegrants. Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrant concentration and above that disintegration time remains approximately constant or even increases.

Table 1: Drugs explored for fast dissolving tablets

Category	Drug	Category	Drug	Reference
NSAIDS	Ketoprofen	Anti depressants	Mitraxepine	(Ahmed *et al.,* 2006; Behnke *et al.,* 2003; Clarke *et al.,* 2003; Dollo *et al.,* 1999; Fu *et al.,* 2004; Gafitanu *et al.,* 1991; Gohel *et al.,* 2004; Shimuzu *et al.,* 2003) [1, 3, 6, 9, 11-13, 21]
	Piroxicam		Fluoxetine	
	Paracetamol	Antiparkinsonism	Selegilline	
	Rofecoxib	Antimigrane	Sumatriptan	
	Nimesulide		Rizatriptan benzoate	
	Ibuprofen		Zolmitriptan	
Anti-ulcer	Famotidine	Antiemetics	Ramosetoron Hcl	
	Lansoprazole		Ondansetron	
Anti-histamincs	Loratidine	Miscellaneous	Baclofen	
	Diphenhydramine		Hydrochlorthiazide	
	Meclizine		Spiranolactone	
Hypnotics and sedatives	Zolpidem Clonazepam Atenolol		Ethenzamide Tramodol Hcl Sildenafil	
Anti psychotics	Olanzepine			
	Resperidone			
	Pirenzepine			

New orally disintegrating dosage forms

Oral films and wafers

Oral films and wafers are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. They have the advantage of a large specific surface area for disintegration. One or a combination of the following processes like hot-melt extrusion, solid dispersion extrusion, rolling and solvent casting are used to manufacture these films. A major limitation of these dosage forms is low drug loading capacity and limited taste masking option (Borsadia *et al.,* 2003) [4].

Evaluation of orally disintegrating tablets

Evaluation parameters of tablets mentioned in the pharmacopoeia need to be assessed, but some, which require special concern or need to be modified, are discussed here.

Crushing strength

A significant strength of FDT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for an FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet may be measured using conventional hardness testers.

Friability of tablet

To achieve% friability within limits for an FDT is a challenge to the formulator since all methods of manufacturing of FDT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1 to 0.9%).

Wetting time

Wetting time of dosage form is related with the contact angle. Wetting time of the FDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet.

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Modified disintegration test

The time for disintegration of FDTs is generally less than one

minute and actual disintegration time that patient can experience ranges from 5-30 seconds. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for FDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted. The disintegration test performed using a texture analyzer instrument. In this test, a flat ended cylindrical probe penetrates into the disintegrating tablet immersed in water. As the tablet disintegrates, instrument is set to maintain a small force for a determined period of time. The plots of the distance traveled by the probe generated with the instrument's software provide a disintegration profile of the tablets as a function of time. The plot facilitates calculation of the start and end point of the tablet disintegration (Dor and Fix, 2000; Parakh and Gothoskar, 2003) [10, 19].

Dissolution test

The development of dissolution methods for FDTs is comparable to the approach taken for conventional tablets, and is practically identical.

Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent FDT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for FDT much in the same way as their ordinary tablet counter parts.

Klancke *et al.,* (2003) [14] have suggested the USP 2 Paddle apparatus which is the most suitable and common choice for orally-disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically the dissolution of FDT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles.

As with all oral solid dosage forms, dissolution serves as a control test. The same is true for taste-masked bulk drug. For batch-to-batch consistency can be assured, and dissolution data on the taste-masked drug is frequently predictive of dissolution of the tableted product. The USP 2 Paddle apparatus at 50-100 rpm is suitable for dissolution testing of taste-masked drug as well. The media used for the taste-masked drug should match that of the finished product to maximize the value of the test. HPLC is often required to analyze dissolution aliquots due to presence of UV absorbing components, specifically flavors and sweetener. Excipient to drug ratio may be higher since the formulation is designed to have good taste and mouth feel, decreasing the signal of the drug to background (excipient) in the UV spectrophotometric technique.

Moisture uptake studies

Moisture uptake studies for FDT should be conducted to have an insight into the stability of the formulation. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37 ˚C for 24 h. The tablets were then weight and exposed to 75% RH, at room temperature for two weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccators for three days. One tablet as control (without superdisintegrant) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Summary

Fast dissolving tablets are formulated to drug delivery system aims 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.

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