ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

Fast disintegrating tablets: An overview of formulation, technology and evaluation

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ABSTRACT

Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Recently researcher developed the fast disintegrating tablets with improved patient compliance and convenience. Fast disintegrating tablets are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. Fast disintegrating tablets overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in paediatric and geriatric patients. Fast disintegrating tablets have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several fast disintegrating tablets technologies. This review includes requirements for fast disintegrating tablets, sailent features, advantages, limitations, challenges in formulation, various technologies developed for fast disintegrating tablets, patented technologies, evaluation methods and various marketed products.

Keywords: Fast disintegrating tablets, Superdisintegrants, Direct compression, wetting time.

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ISSN: 0975-8585

INTRODUCTION

Fast disintegrating drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. FDDDS offer the luxury of much more accurate dosing than the primary alternative oral liquids. This segment of formulation is especially designed for dysphagic, geriatric, paediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations [1, 2, 3].

Dysphagia or difficulty in swallowing is common among all age groups. Dysphagia is common in about 35% of the general population, well as an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and paediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms. During the last decade, fast disintegrating tablet (FDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention. The FDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and/or quick disintegrating tablet. All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute[3, 4].

Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction. Such a tablet disintegrates instantaneously when placed on tongue, releases the drug that dissolves or disperses in the saliva. This result to a rapid onset of action and greater bioavailability of the drug than those observed from conventional tablet dosage form.

During the last decade, several new advanced technologies have been introduced for the formulation of FDTs with very interesting features like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients. Various technologies utilized for fabrication of FDTs and these techniques are based on the principles of increasing porosity by addition of superdisintegrants or water soluble excipients in the tablets.

ISSN: 0975-8585

Requirements of fast disintegrating tablets

- Have a pleasing mouth feel.
- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).

Salient features of fast disintegrating tablets

- Does not require water for oral administration.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Allow high drug loading.
- Insensitive to environmental conditions such as humidity and temperature.
- Adaptable and amenable to existing processing and packaging machineries.
- Cost effective.
- Have a pleasant mouth feel.

Advantages [7-9]

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Limitations of fast disintegrating tablets [10]

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

ISSN: 0975-8585

Challenges in formulating Fast disintegrating tablets

Palatability [11, 12]

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength [13-15]

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wow tab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

Hygroscopicity [16]

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Amount of drug [11, 17]

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility [18, 19]

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet [20]

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Conventional methods used for the preparation of Fast disintegrating tablets

Addition of superdisintegrants [22, 23]

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are crosscarmellose, crospovidone and sodium starch glycolate, which are a cross linked cellulose, cross linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets.

Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch gycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants.

Direct compression [24]

It is one of the easiest way to manufacture tablets. conventional equipments, commonly available excipients and a limited number of processing steps are involved in direct compression. sawant k et al. prepared orodispersible tablets of ondansetron hcl by direct compression using superdisintegrants and they reported that *in vitro* dispersion time of these tablets has been found to be 5 minutes where as conventional tablets have shown 30-35 minutes.

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. 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.

Sublimation [25]

To 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. Ex: Ravikumar et al. prepared aceclofenac fast dissolving tablets by sublimation method using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants.

Mass extrusion

In this method active blend is softened using the solvent mixture of water-soluble polyethylene glycol and methanol and then subsequent expulsion of softened mass through the extruder or syringe is made to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

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 crosscarmellose 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.

Patented technologies for Fast disintegrating tablets

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 material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze-drying process or long-term

storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler 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 product requiring low amounts of active ingredients.

Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by biovail corporation. Flash dose tablets consist of self-binding shear form matrixtermed as “floss”. Shear form matrices are prepared by flash heat processing.

Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. 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 (eg. lactose, glucose, and mannitol) and granulatedwith a high mouldability saccharide eg. Maltose, oligosaccharides

Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.

ISSN: 0975-8585

Drugs to be promising in corporated in Fast Dissolving Tablets [15-17]

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient.

Analgesics and Anti-inflammatory Agents:

Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.

Anthelmintics

Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, Praziquantel, Pyrantel Embonate, Thiabendazole.

Anti-Arrhythmic Agents

Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate,

Anti-Epileptics

Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid.

Anti-Hypertensive Agents

Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin.

Anti Protozoal Agents

Benznidazole, Clioquinol, Decoquinate, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.

Anxiolytic, Sedatives, Hypnotics And Neuroleptics

Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam,

ISSN: 0975-8585

Clotiazepam, Clozapine, Droperidol, Ethinamate, Flunanisone, Flunitrazepam, Fluopromazine, Flupenuiixol Decanoate, Fluphenazine Decanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, Perphenazine Pimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone.

Table 2: Marketed products of Fast disintegrating tablets

Brand name	Drug Pharmaceutical	Company
Benadryl Fastmelt	Diphenhydramine	Pfizer
Benadryl Fast melt	Diphenhydramine	Warner Lambert
Rofaday MT	Rofecoxib	Lupin
Torrox MT	Rofecoxib	Torrent
Domray MD	Domperidone	Ray Remedies
Feldene melt	Piroxicam	Pfizer
Febrectol	Paracetamol	Prographarm
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Imodium Instant melts	Loperamide Hcl	Janssen
Kemstro	Baclofen	Schwarz Pharma
Klonopin Wafers	Clonaxepam	Roche
Maxalt-MLT	Rizatriptan Benzoate	Merck
Mosid MT	Mosapride	Torrent
Nulev	Hyoscyamine sulfate	Schwarz Pharma
Nimulid MD	Nimusulide	Panacea
Olanex Instab	Olanzepine	Ranbaxy
Pepcid ODT	Famotidine	Merck
Zotacet MD	Cetrizine Hcl	Zota Pharma
Zyprexa	Olanzapine	Eli lilly
Zofran ODT	Ondansetron	GSK
Zomig ZMT and Rapimelt	Zolmitriptan	Astra Zeneca
Claritin redi Tab	Loratidine	Schering plough Corp., USA
Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-Delhi, India
Romilast	Montelukast	Ranbaxy lab. Ltd. New-Delhi, India

Evaluation of Fast dissolving tablets

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation is given by the formula.

$$\% \text{ weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

ISSN: 0975-8585

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric
compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Friability (F)

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

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = r\gamma\cos\theta/(4\eta l)$$

Where l is the length of penetration, r is the capillary radius, ¡ is the surface tension, h is the liquid viscosity, t is the time, and q is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at370. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

In vitro drug release

Release of the drug *in vitro*, was determined by estimating the dissolution profile,
USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, phosphate buffer (PH 6.8) (900 ml) was used as a dissolution medium.

Mechanical Strength

Tablets should possess adequate strength to withstand mechanical shocks of handling in Manufacturing, packaging and shipping. Crushing strength and friability are two important parameter to evaluate a tablet for its mechanical strength.

Crushing Strength

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported.

Friability testing

The crushing test may not be the best measure of potential behavior during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measure in "Electro lab friabilator". Ten preweighed tablets were rotated at 25 rpm for 4 min, the tablets were then re weighed and the percentage of weight loss was calculated.

Rapidly Disintegrating Property

To evaluate the tablets for their rapid disintegration properties, following tests were carried out.

Modified disintegration test

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 ODT 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.

Disintegration in oral cavity

The time required for complete disintegration of tablets in oral cavity was obtained from six healthy volunteers, who were given tablets from the optimum formulation.

Water absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

$$R = 10(wa/wb)$$

Where,

Wb= weight of tablet before water absorption & wa is weight of tablet after water absorption.

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