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REVIEW ARTICLE

FAST DISSOLVING DRUG DELIVERY SYSTEMS: FORMULATION, PREPARATION TECHNIQUES AND EVALUATION

Satbir Singh¹, Tarun Virmani¹, Reshu Virmani¹, Pankaj Kumar², Geeta Mahlawat¹

¹School of Pharmaceutical Science, MVN University, Palwal, (Haryana), 121105, India.

²Advanced Institute of Pharmacy, Palwal, (Haryana), 121105, India.

ABSTRACT

The fast dissolving drug delivery systems sets a new benchmark was an expansion that came into existence in the early 1980's and combat over the use of the different dosage form like tablets, suspension, syrups, capsules which are the other oral drug delivery systems. Fast Dissolving Drug Delivery System (FDDS) has a major advantage over the conventional dosage forms since the drug gets rapidly disintegrated and dissolves in the saliva without the use of water. In spite of the downside lack of immediate onset of action; these oral dosage forms have valuable purposes such as self medication, increased patient compliance, ease of manufacturing and lack of pain. Hence Fast Disintegrating Tablets (FDTs) technology has been gaining importance now-a-days with wide variety of drugs serving many purposes. Fast Disintegrating Tablets (FDTs) has ever increased their demand in the last decade since they disintegrate in saliva in less than a minute that improved compliance in pediatrics and geriatric patients, who have difficulty in swallowing tablets or liquids. As fast dissolving tablet provide instantaneous disintegration after putting it on tongue, thereby rapid drug absorption and instantaneous bioavailability, whereas Fast dissolving oral films are used as practical alternative to FDTs. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action.

In present review article different aspects of fast dissolving tablets and films like method of preparations, latest technologies, and evaluation parameters are discussed. This study will be useful for the researchers for their lab work.

Keywords: Bioavailability, dysphagia, fast dissolving drug delivery systems, fast disintegrating tablet, geriatric, pediatric.

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Address for Correspondence:

Satbir Singh, School of Pharmaceutical Science, MVN University, Palwal, Haryana, 121105, India. Phone: +91-8816973242, E-mail: satbirpharma89@gmail.com

INTRODUCTION

At present scenario formulation research is modified in such a way that the active ingredients can be delivered to the target site with a level of convenience, performance and improved bioavailability¹. As the cost for developing a generic molecule is too expensive, the research is being done on the new dosage forms for having better patient compliance as compared to the different dosage forms of which the oral route serves to make a provenance. The oral route of administration is always considered to be the most preferred route because of its various advantages like ease of administration, pain avoidance, versatility and most important patient compliance².

Dysphagia and Fast-dissolving tablets-Dysphagia is the term used to describe difficulty swallowing. Dysphagia includes difficulty starting a swallow (called oropharyngeal dysphagia) and the sensation of food being stuck in the neck or chest (called

esophageal dysphagia)³. Tablet is the most popular and common dosage form. However some limitations are associated with it like, large size of dosage forms, and in some cases as of uncooperative, pediatric and dysphagia patients, it may create some problems. Moreover traveling patients suffering from motion sickness and diarrhea don't have easy access to water for oral drug administration. To overcome these problems, a new modified form of tablets is developed, which is known as fast dissolving tablet or mouth dissolving tablet⁴. Fast-Dissolving Tablets (FDTs) disintegrate and/or dissolve instantaneously in the saliva without the use of water. FDTs are best alternative for all of these patients. The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue⁵. The disintegration time of such tablets is very short because

of their highly porous structure and the high solubility of the sugar alcohol or saccharide present as the diluents.

Table 1: Various ingredients of FDTS.

Types of ingredients	%
Active pharmaceutical agent	1-25%
Water soluble film forming polymer	40-50%
Plasticizer	0-20
Sweetening agent	3-6%
Saliva stimulating agent	2-6%
Colors and Flavors	0-10%

Drug gets released after rapidly disintegration rapidly; drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach⁶. Most fast dissolving drug delivery system films consist of different substances to mask the bitter taste of active ingredient. This masked active ingredient is than swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called as melt-in-mouth tablets, repimelts or porous tablets.

Advantages of FDTS

1. No need of water and chewing.
2. Better taste masking properties.
3. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing.
4. Ease of administration to patients who cannot swallow like the bed-ridden, stroke victims and patients who refuse to swallow like geriatrics, pediatrics and psychiatrics.
5. Stability can be improved⁷.
6. Acceptable taste and pleasant mouth feeling.
7. Dissolution and absorption of drug is fast, offering rapid onset of action.
8. Bioavailability of drugs is increased by avoiding first pass metabolism.
9. High drug loading can be possible.
10. No specific packaging is required. It can be packaged in push through blisters.
11. Minimum risk of suffocation in airways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations⁸.

Disadvantages of FDTS

1. These tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2. Fast dissolving tablets requires special kind of packaging for proper stabilization and safety of stable product⁹.
3. Drugs with relatively larger doses are difficult to formulate into MDT e.g. antibiotics like amoxicillin with adult dose tablet containing about 500 mg of the drug.
4. Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
5. Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations¹⁰.
6. They are more susceptible to degradation by humidity and temperature. Fast dissolving tablets

are hygroscopic in nature so must be keep in dry place.

7. Drugs with short half-life and frequent dosing and those whom require controlled or sustained release are unsuitable candidates of FDTS.

Table 2: Composition of fast dissolving oral film.

Ingredients	Quantity
Active pharmaceutical agent	1-25%
Film forming polymer	40-50%
Plasticizer	0-20%
Saliva stimulating agent	2-6%
Sweetening agent	3-6%
Flavoring agent	10%
Colouring agent	1%

Challenges for development of FDTS

1. Taste masking

Undesirable taste is one of the important formulation problems that are encountered with many drugs. Bitter drugs in the form of FDTS can't be accepted by the patients. Administration of bitter drugs orally with acceptable level of palatability is the aim of all manufacturers. As most drugs are unpalatable, rapid 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. Taste-masking technologies are being used for bitter-tasting drugs like the macrolide antibiotics, non-steroidal anti-inflammatory drugs, and penicillins. However taste masking of water-soluble bitter drugs, with a high dose, is difficult to achieve by using sweeteners alone¹¹.

2. Hygroscopicity

It is the capacity of a product (e.g. cargo, packaging material) to react to the moisture content of the air by absorbing or releasing water vapor. Hygroscopicity is, of course, an important characteristic of a powder. It can be shown, roughly, for a fairly soluble compound that the hygroscopicity is related to its solubility. FDTS should have low sensitivity to humidity. This problem can be especially challenging because many highly water soluble excipients are used in formulation. Highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be followed to protect FDTS from atmospheric conditions¹².

3. Mouth feel

The particles generated after disintegration of the FDTS should be as small as possible in oral cavity for the good feeling. Moreover addition of flavors and cooling agents like menthol improve the mouth feel¹³.

4. Aqueous solubility

Water-soluble drugs pose various formulate ion challenges because they form eutectic mixtures, which result in freezing-point depression and the format ion of a glassy solid that may collapse upon drying because of loss of supporting structure during

the sublimate ion 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 composite¹⁴.

5. Amount of drug

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. The application of technologies used

for FDTS is limited by the amount of drug that can be incorporated into each unit dose¹⁵.

6. Mechanical strength and disintegration time

FDTS are formulated to obtain disintegration time usually less than a minute. FDTS dissolves or disintegrates quickly in the oral cavity upon the contact with saliva, resulting in solution or suspension of the administered medicine. It is obvious that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential. While doing so, maintaining a good mechanical strength is a prime challenge¹⁶.

Table 3: Comparison between fast dissolving, tablets and films.

Criteria	Fast Dissolving Tablets	Fast Dissolving Films
Form	It is a tablet	It is a film
Thickness	thickness 0.015-.05 inches	Same size as of conventional tablet
Dissolution	Less dissolution due to less surface area	Greater dissolution due to larger surface area
Durability	Less durable as compared with oral films	Better durable than oral disintegrating tablets
Patient compliance	Less patient compliance than films	More patient compliance
Dose size	Large dose can be incorporated	Small dose can only be incorporated
Chocking	Fear of chocking is present	No risk of chocking

7. Cost

The technology used for FDTS should be economical. Special technologies used may increase the cost of final products.

Technologies for preparation of FDTS

A. Non-patented Technologies

1. Direct Compression

Direct compression is the easiest way to manufacture tablets. Direct compression is viewed as the technique of choice for the manufacture of tablets containing thermolabile and moisture-sensitive drugs. The great advantage of direct compression is the low manufacturing cost. It uses conventional equipment, commonly available excipients, and a limited number process steps. Single or combined action of disintegrants, water soluble excipients and effervescent agents depends on the disintegration and solubilization of directly compressed tablets. Breakage of tablet edges during handling and tablet crack during the opening of blister alveolus, all result from insufficient physical resistance protection¹⁷.

2. Tablet Moulding

Tablets prepared by this method are solid dispersions. Molded tablets are less compact than compressed tablets, with a porous structure that facilitates rapid disintegration and easy dissolution. Molded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. Moulding technique is of two types¹⁸.

a. Solvent method

In this technique damping the powder blend is done by an alcoholic solvent and then compressing at low pressure in molded plates to form a wet mass. After air drying tablets prepared by this technique are less compact than compressed tablets and posses a porous structure that accelerates the dissolution¹⁹.

b. The heat process

It involves preparation of a suspension that contains a drug, agar and sugar and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is to be notified and hence binding agents are mixed to give strength. 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 form²⁰.

3. Spray Drying

For producing porous and fine powders that dissolve rapidly spray drying technique is used. The formulations are included by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and/or alkali material (e.g. sodium bicarbonate) to improve disintegration and dissolution. This formulation technique gives porous powder and disintegration time < 20 sec¹⁷.

4. Sublimation

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, menthol, camphor, naphthalene, urea, urethane or phthalic anhydride could be compressed along with other excipients into a tablet. Tablets manufactured by this technique are reported to usually disintegrate in 10-20 sec. and exhibit sufficient mechanical strength¹⁶.

Table 4: Commercially available fast dissolving tablets .

Brand name	Active ingredient	Company
Benadryl Fastmelt®	Diphenhydramine Citrate	Pfizer
Childrens Dimetapp® ND	Loratadine	Wyeth consumer Healthcare
Claritin® Reditabs®	Loratadine	Scherig corporation
Domray MD	Domperidone	Ray remedies
Dolib MD	Rofecoxib	Panacea
Excedrin®QuickTabs	Acetaminophen	Bristol-Myers Squibb
Felden FM	Piroxicam	Pfizer
Gaster D	Famotidine	Yamanouchi
Imodium Istant Melts	Loperamide HCL	Janssen
Klonopin® wafer	Clonazepam	Roche
Kozicold	Nimesulide	Kaizen Drugs
Lonazep MD	Olnazepine	Sun Pharma
Maxalt –MLT	Rizatriptan benzoate	Merck
Mosid MT	Mosapride	Torrent Pharma
Nasea OD	Ramosetoron HCl	Yamanouchi
Nimulid MD	Nimesulide	Panacea
Olanex Instab	Olanzapine	Ranbaxy Labs Ltd
Ondem MD	Ondansetron	Alkem Pharma
Pepcid RPD	Famotidine	Merck Pharma
Propulsid®Quicksolv ®	Cisapride Monohydrate	Janssen
Remeron® Soltab®	Mirtazapine	Organon Inc.
Resperdal®MTabTM	Resperidone	Janssen
Rofixx MD	Rofecoxib	Cipla Ltd.
Romilast	Montelukast	Ranbaxy
Tempra Quicksolv	Acetaminophen	Bristol-Mters squibb
Torrox MT	Rofecoxib	Torrent
Triaminic® Softchews®	Various combination	Novartis consumer Health
Valus	Valdecocix	Galen Mark
Vomidon MD	Domperidone	Olcare Lab
ZelaparTM	Selegiline	Elanl Amarin corporation
Zofer MD	Ondansetron	Sun Pharma
Zofex-25 MD	Rofecoxib	Zota pharma
Zontacet MD	Cetirizine	Zosta Pharma India
ZubrinTM (Pet drug)	Canine Tepoxelin	Scherig corporation
Zyperxa®	Olazepine	Eli Lilly

5. Lyophilization or 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 tablets are very porous in nature and dissolve quickly when come in contact with salivary the lyophilization technique. The active drug is dispersed in an aqueous solution of a carrier which is a polymer¹⁵. First the trays having sample are freeze in blister packs by passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. First of all, the material is frozen to bring it below its eutectic point. This primary drying is done to decrease the moisture to about 4% w/w of dry product. By repeating secondary drying which reduce the bound moisture to the required volume of the drug product. However the use of freeze-drying is restricted due to high cost of equipment and processing. The freeze- drying technique has demonstrated improved absorption and

increase in bioavailability. A major limitation of the final dosage form comprises lack of physical resistance in standard blister packs²¹.

6. Melt Granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. It is a technique useful to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. There is no need of drying that is main benefit of the melt granulation technique benefit is compared to a conventional granulation is that no water or organic solvents is required. Since there is no drying step, the process is less time consuming and requires less energy than wet granulation²².

7. Mass extrusion

In mass extrusion technique solvent mixture of water-soluble polyethylene glycol and methanol are used for softening the blend of drug and consequent removal of softened mass through the extruder or syringe 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 achieving taste masking^{22,25}.

8. Cotton candy process/candy floss process

In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shear foam process. This technique makes use of a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy that's why this is called Cotton candy process involves the formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning²³.

B. Patented Technologies

1. Lyoc

Lyoc technology is patented by Pharmalyco. Lyoc utilizes a freeze drying process but it differs from Zydis in that the product is frozen on the freeze dryer shelves. In order to prevent homogeneity by sedimentation during this process, these formulations also require a large proportion of undissolved inert filler such as mannitol, to increase the viscosity of the in process suspension. The high proportion of filler used reduces the potential porosity of the dried dosage form and hence results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations²⁴.

2. Wow tab Technology

Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "With Out Water". It consist of combination of low- moldability saccharides like lactose, mannitol, glucose, sucrose, and xylitol and high-moldability saccharides like maltose, sorbitol, and oligosaccharides in order to produce fast dissolving tablets using conventional granulation and tableting techniques^{4,6,9}.

3. Flash dose technology

Flash dose technology has been patented by Fuisz Technologies Ltd. It uses a unique spinning mechanism so as to produce a floss-like crystalline structure, much like cotton candy. The Flash dose tablets consist of self-binding shear form matrix termed as "floss. This crystalline sugar can then incorporate the drug and be compressed into a tablet. The final product which is being produced has a very high surface area for dissolution. It disperses and dissolves quickly once placed on the tongue²⁵.

4. DuraSolv technology

DuraSolv R technology was developed by Ciba to provide stronger tablets for packaging in blisters or bottles. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. The key ingredients in this formulation are filler and lubricant. The tablets have low friability (about 2%). The disintegration time is less than 60 seconds. This method can produce tablets by using the direct compression method, conventional tableting methodologies and conventional package equipment. Thus, the production cost is significantly reduced²⁶.

5. Quicksolv technology

Quicksolv technology is patented by Janssen Pharmaceutica, Beese, Belgium. This method claimed to prevent or to reduce the incidence of cracking during the final preparation, having uniform porosity and also the adequate strength for handling.

In this technology, the matrix compositions are dissolved in the solvent (usually water), and then this solution is frozen^{3,7}. The first solvent will remain in the solid form, and then the frozen solution contacts the second solvent which is usually, ethanol, menthol, or acetone. Thus, the first solvent is removed after a few hours of contacting the second solvent to result in a usable matrix. The final product disintegrates almost instantly²⁷.

6. Zipllets/Advatab

This technology is patented by Passano con Barnago, Italy. In this technique water-insoluble ingredient are merged with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force²⁸.

7. Nanocrystal technology

This is patented by Elan, King of Prussia. In this technique, crystal colloidal dispersions of the drug substances are combined with water soluble ingredients, followed by filling into blister and lyophilization. This technique avoids manufacturing processes such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous²⁹.

8. OraSolv technology

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. This includes the use of effervescent disintegrating agents which is compressed with low pressure to produce the fast dissolving tablets. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. The evolution of carbon dioxide from the tablet produces a fizzing sensation, which is a positive organoleptic property. The limitation associated is that the tablets produced are soft and friable⁹.

9. Pharmaburst technology

Pharmaburst technology is being patented by SPI pharma. By this methodology tablets have sufficient strength and can be packed in blister packs and bottles. The tablet manufactured by this process involves a dry blend of a drug, flavors, and lubricant then followed by compression into tablets which then dissolve within 30-40 seconds⁵.

10. Zydis technology

Scherer has patented the Zydis technology. In this the drug is produced by freeze drying or lyophilizing the drug in gelatin matrix. The product thus produced is very light weight and packed in blister packs. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. This technique mask the bitter taste of drug by means of microencapsulation using specialized polymers and resins. This technique is quite expensive. Zydis formulation should be used within six month after opening. This technology claims for increased bioavailability as compared to other conventional tablets. The main advantage of this technology is

convenience and disadvantage is that the freeze drying process is quite expensive manufacturing process³⁰.

11. Quick-dis technology

This technology is a proprietary patented technology of Lavipharm Laboratories. It is a thin, flexible, and quick dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.

12. Flash tab technology

Prographarm laboratories has patented the Flash tab technology. This technology engages in the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. To

prepare drug microgranules all the processing utilized conventional tableting technology like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. Disintegration time of these tablets is less than one minute³¹.

13. Frosta technology

This technology is patented by Akina. Plastic granules are prepared and compressed at low pressure to produce strong tablets with high porosity. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet³².

Table 5: Examples of commercially available fast dissolving oral films.

Brand name	Active ingredient	Company
Benadryl	Diphenhydramine HCl	Pfizer
Chloraseptic	Benzocaine: Menthol	Prestige
Donepzil	Donepzil HCL	Labtec GmbH
Eclipse3	Sugarfree mints	Wringley's
Gas-X	Simethicone	Novartis
Listerine	Cool mint	Pfizer
Little Colds	Pectin	Prestige brands
Ondansetron	Ondensteron	Labtec GmbH
Orazel	Menthol/Pectin	Del
Sudafed PE	Phenylephrine HCl	Pfizer
Suppress	Dextromethorphan	InnoZen
Theraflu	Dextromethorphan HBr	Novartis
Triaminic	Diphenhydramine HCl	Novartis

Evaluation of fast dissolving tablets

1. Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Deviation of $\pm 10\%$ is allowed for tablet of less than or equal to 80mg, $\pm 7.5\%$ deviation is allowed for tablet in between 80 to 250 mg. For a tablet of more than 250 mg, $\pm 5\%$ deviation is allowed³³.

2. Tensile Strength

Tensile strength is the measure of force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. The plunger of the hardness tester is driven down at a speed of 20 mm/min for measuring the hardness of the tablets³⁴.

3. Friability

The friability test for a tablet is carried out and the limit is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). Big challenge for a formulator is that how to achieve friability within this limit for FDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flash dose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques^{11,15}.

4. Moisture Uptake Study

Mouth dissolving tablets have high concentration of hydrophilic excipients with the minimum possible hardness which together contributes to their increased susceptibility to moisture uptake hence special attention is required during the storage and packaging

of these dosage forms. The test can be carried out by keeping ten tablets along with calcium chloride in a dessicator maintained at 37°C for 24 hr to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. For achieving the required humidity keep saturated sodium chloride solution in the dessicator for 24 hr. The tablets are reweighed and the percentage increase in weight is recorded³⁵.

5. Tablet Porosity

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration^{9,16}.

6. Wetting Time and Water Absorption Ratio

This study is carried out by using a piece of double folded tissue paper placed in a petri dish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined according to equation.

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where W_b and W_a are the weights of tablet before and after water absorption respectively. Where R is water absorption ratio²⁸.

7. In-vivo disintegration time

The time for disintegration of Orally Disintegrating tablets is less than one minute and in actual it is just 5 to 30 seconds time duration for the disintegration^{25,26}.

8. Dissolution Test

The development of dissolution methods for orally dissolving tablets and conventional tablet are similar. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent orally dissolving tablets. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for orally dissolving tablets much in the similar way as conventional tablets. USP dissolution apparatus 1 and 2 can be used for this study. 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. USP 2 Paddle apparatus, which is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of tablets is very fast when using USP monograph conditions; hence, slower paddle speeds may be utilized to obtain a profile. The USP 2 Paddle apparatus at 50 to 100 rpm is suitable for dissolution testing of taste-masked drug as well^{36,37}.

FAST DISSOLVING ORAL FILMS

Fast dissolving oral films (FDOFs) are the most highly developed form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of drugs by dissolving within 60 seconds in oral cavity after the contact with saliva without chewing and no need of water for administration³⁸. It gives rapid absorption and instant bioavailability of drugs due to high blood flow and permeability. Fast dissolving oral films are based on the technology of the transdermal patch. Sometimes taste masking agents are also added to mask the taste of the active ingredient³⁴. Fast dissolving oral films have advantages like:

1. Thin film is more stable, durable and quick dissolving than other conventional dosage forms.
2. Improved dosage accuracy as compared to liquid formulations.
3. No need of water with improved patient compliance. Does not interfere with normal function like talking, drinking etc¹¹.
4. Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds.
5. No first-pass hepatic metabolism thus improved bioavailability²⁵.
6. Ease of handling and transportability.
7. Pleasant mouth feel

Formulation methodology for fast dissolving films

1. Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate dried and cut in to uniform dimensions³⁸.

2. Semisolid casting

In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid

insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4³⁹.

3. Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies.

4. Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies

5. Rolling method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and sizes^{16,17}.

Technologies for fast dissolving films

1. Wafer Tab

Wafer Tab is a drug delivery system which incorporates pharmaceutical actives into an ingestible film strip. It provides rapid dissolution and release of active pharmaceutical ingredient when the strip comes into contact with saliva in the mouth. The WaferTab film strip can also be flavoured for additionally improved taste-masking. The film can be prepared in a variety of shapes and sizes and is an ideal method for delivering medicines which require fast release and also for use by patients who have difficulty swallowing⁴⁰.

2. XGEL

XGel film Technology developed by BioProgress was causing a revolution in the product offerings and manufacturing methods. It is nonanimal-derived, approved on religious grounds and is suitable for vegetarians. These films can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water⁴¹.

3. Foamburst

In this technology gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt-in-the mouth sensation⁴².

4. Soluleaves

This technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. In this technology the film is produced in order to release the active ingredients on coming in contact with saliva. These are designed in such a way that they adhere to mucous

membrane in order to release the drug slowly in 15 mins⁴³.

Evaluation parameters

1. Thickness

The thickness of the patch is measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated⁴⁴.

2. Weight variation

A particular centimeter square of the film is cutted at different places from the casted film. The weight of each film is taken and weight variation is calculated²².

3. Folding endurance

Folding endurance is determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value²⁵.

4. Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks⁴⁵. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Film thickness} \times \text{film width}} \times 100$$

5. Percent elongation

A film sample stretches when stress is applied and it is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Elongation of film increases as the plasticizer content increases.

$$\% \text{ Elongation} = \frac{L}{L_0} \times 100$$

Where, L = Increase in length of film, L₀ = Initial length of film.

6. Surface pH

The film to be tested was placed in a petri dish and is moistened with 0.5 ml of distilled water and kept for 30sec. The pH is noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min³⁵.

7. Uniformity of drug content

This parameter is determined by dissolving one film of dimension 2x2 cm by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking. The absorbance was measured using an UV spectrophotometer³⁷.

8. In vitro dissolution studies

Dissolution profile of fast dissolving films is carried out using USP type II (paddle apparatus) with 300 mL of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37±0.50C. Medium was stirred at 100 rpm. Samples were withdrawn at every 30sec interval, replacing the same amount with the fresh medium. Amount of drug in the withdrawn samples was determined by UV spectrophotometer.

9. Ex vivo permeation studies through porcine oral mucosa

Permeation studies were carried using the modified Franz diffusion cell of specific internal diameter. The buccal pouch of the freshly sacrificed pig was procured from the local slaughter house. The buccal mucosa of the freshly sacrificed pig or mouse is used for this

purpose and washed in isotonic phosphate buffer of pH 6.6 and used immediately. Samples obtained are studied by UV spectrophotometer⁴⁶.

CONCLUSIONS

Due to decline in dysphagia swallowing ability with age, many elderly patients complain that it is difficult for them to take some currently used dosage forms such as tablets, capsules, or powders, fast dissolving tablets are thus a best alternative of these dosage forms. Fast dissolving tablets formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth. An extension of market monopoly, which can be provided by a fast-dissolving tablets or oral, films/disintegrating dosage form, leads to increased revenue of the pharmaceutical company which is also leads to target underserved and undertreated patient populations. Their unbeatable advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients.

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AUTHOR'S CONTRIBUTION

Singh S: designed the study. **Virmani T:** acquired the data. **Virmani R:** analyzed the data and interpreted the results. **Kumar P:** drafted the article. **Mahlawat G:** writing, review, and editing.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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