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Recent Trends of Oral Fast Disintegrating Tablets - An Overview of Formulation and Taste Masking Technology

Raja Shekhar S*, Vedavathi T

CMR College of pharmacy, Kandlakoya, Medchal Road, Hyderabad.

ABSTRACT

A solid dosage form that dissolves or disintegrates rapidly in the oral cavity, resulting in a solution or suspension without any need for the water is known as an oral fast- disintegrating dosage form. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Among them, the oral fast disintegrating tablet (OFDT) is one of the most widely employed commercial products to facilitate ease of medication. The development of fast dissolving tablets have been formulated for pediatric, geriatric, bedridden, mentally ill patients and for active patients who are busy on traveling and may not have access to water. But, oral pharmaceuticals often impart an unpleasant taste, primarily bitterness. The desire for improved palatability in these products has prompted the development of numerous methods for taste masking by complexation, micro encapsulation, particle coating etc. Many of these contributions have been successfully commercialized in oral pharmaceutical preparations that are available over the counter or by prescription. This article focuses on the methods, patented technologies available, additives used and the recent advances made so far in the field of fabrication of oral fast disintegrating tablets.

Keywords: Oral Fast Disintegrating tablets (OFDT), Oral route, patented technologies, improved bioavailability, Superdisintegrants.

***Corresponding author**
Email: s.rajashekhar2@gmail.com

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INTRODUCTION

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance [1]. The most popular solid dosage forms are being tablets and capsules, one important drawback of these dosage forms for some patients is the difficulty to swallow. [2] Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablets when water is not available, in motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only preferable for people who have swallowing difficulties, but also are ideal for active people.

Orodispersible tablets are those when put on tongue, disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. The faster the drug goes into solution, quicker the absorption and onset of clinical effect. [3] Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater and faster than those observed from conventional tablet dosage form. The advantages of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European Pharmacopoeia adopted the term “Orodispersible tablet” as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. [4]

CHARACTERISTICS OF ORAL FAST DISINTEGRATING TABLETS [5]

- Convenient and easy to administer as it does not require water for oral administration.
- Durable and sufficient strength to withstand the rigors of the manufacturing process and manufacturing handling.
- Pleasant mouth feel.
- Improved taste without any residue in the mouth after disintegration.
- Adaptable and amenable to existing processing and packaging machinery.
- Cost effective.
- Compatible with taste masking.
- Insensitive to environmental conditions such as humidity and temperature.

BENEFITS OF ORAL FAST DISINTEGRATING TABLET

- Suitable for administration without water, anywhere, any time.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative or are on reduced liquid intake plans or are nauseated.

- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets in the mouth itself.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.[6-9]

METHODOLOGY EMPLOYED FOR FAST DISINTEGRATION FORMULATIONS

Many techniques have been reported by various researchers for the formulation of FDT.

1. Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvent is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG – 6 – stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues.

2. Phase transition process

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

3. Three-dimensional Printing (3DP)

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

The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.[10]

4. 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 FDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated the improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that, it is expensive, time consuming and fragility. The conventional packaging is unsuitable for these products due to fragility and poor stability under stressed conditions.

5. Tablet Molding

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is than removed by air-drying. The tablets manufactured in this manner are less compact than the compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing by forming a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol, and an active ingredient, into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

6. Spray Drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking

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agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

7. Sublimation

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. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

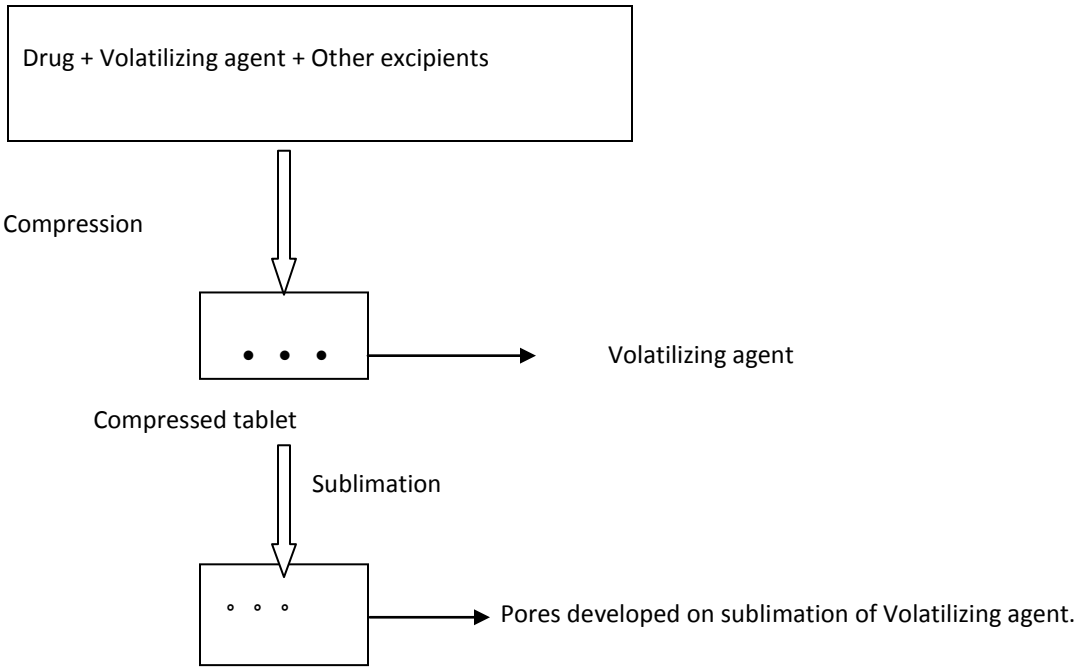

Fig 2: Steps involved in Sublimation.

8. Cotton Candy Process

The cotton candy process is also known as the “candy floss” process and forms on the basis of the technologies such as Flash Dose30 (Fuisz Technology). An ODT is formed using a candyfloss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candyfloss can then be milled and blended with active

ingredients and other excipients and subsequently compressed into ODT. However, the high processing temperature limits the use of this technology to thermostable compounds only.

9. Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion 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 achieve taste masking.

10. Nanonization

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

11. Fast Dissolving Films

It is a new frontier in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste. [11]

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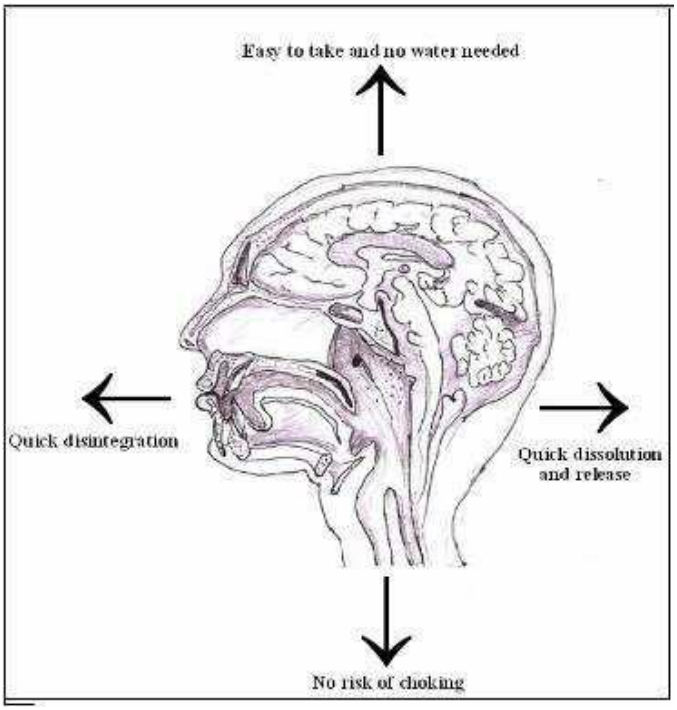

Fig.1: Mechanism of action of oral fast disintegration tablets

12. Direct Compression

It is the simplest and most cost-effective tablet manufacturing method. The preparation of FDTs by this method involves same processing steps as that of conventional solid dosage forms such as weighing, screening, mixing and compression. Hence, most of the pharmaceutical companies adopt this method for preparing mouth dissolving tablets.

In this method tablets disintegration and solubilization are based on single or combined action of disintegrants, water soluble excipients and effervescent agents. The disintegration time is in general satisfactory, although the disintegrating efficacy is strongly affected by tablet size and hardness. Large and hard tablets have greater disintegration time than that of usually required for FDTs. 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, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of blister alveolus all result due to insufficient physical resistance.

Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of the tablet can easily exceed that of other production methods. This technique can now be applied to mouth dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar-based excipients.

Addition of disintegrants in FDTs, leads to quick disintegration of tablets and hence improves dissolution. Many FDT technologies are based on direct compression the disintegrants principally affect the rate of disintegration and hence the dissolution. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegration concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxy propyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of FDTs.

Sugar-based excipients: Another approach to FDTs by direct compression is the use of sugar based excipients (e.g., dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose and xylitol) which display high aqueous solubility and sweetness and hence impart taste masking and pleasing mouth feel. [12]

13. Method of addition of Disintegrants

Disintegrants are substances or mixture of substances added to the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally 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 crosscarmelose, crosspovidone, sodium starch glycolate which represent example of a cross linked cellulose, cross linked polymer and a cross linked starch respectively.

The ideal characteristics of disintegrant are:

- Poor solubility.
- Poor gel formation.
- Good hydration capacity.
- Good molding and flow properties.
- No tendency to form complexes with the drugs.

There are three methods of incorporating disintegrating agents into the tablet:

- Internal addition (Intragranular).
- External Addition (Extragranular).
- Partly Internal and External

In external addition method, the disintegrant is added to the sized granules with mixing prior to compression. In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When a part of disintegrant can be added internally and a part externally, this provides immediate disruption of the tablet into previously compressed granules, while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

14. Wet Granulation

Wet granulation is widely employed method for the production of compressed tablets. Granulation is the process in which primary powder particles adhere to form larger, multi particle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm. Granules are used in the production of tablets or capsules. Granules in such cases are made as an intermediate product and have a typical size range between 0.2 and 0.4 mm

Reasons for Granulation

- To prevent segregation of the constituents of the powder mix.

Segregation (or demixing) is due primarily to differences in the size or density of the components of the mix. The smaller and/or denser particles concentrating at the base of a container and the larger and/or less dense ones will be above them. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of the ingredients will not occur.

- To improve the flow properties of the mix.

Many powders may not flow well because of their small size, irregular shape or surface characteristics. Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc

- To improve the compaction characteristics of the mix.

Some powders are difficult to compact even if a readily compactable adhesive is included in the mix and some are compacted easily. This is associated with the distribution of the adhesive forces within the granule and is a function of the method employed to produce the granule. Solute migration occurring during the postgranulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder–binder bonding, which assists the consolidation of weakly bonding materials

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Other Reasons

- The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders.

- Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard, as the granules will be able to absorb some moisture and retain their flow ability because of their size.

- Granules are denser than the parent powder mix and occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING TABLETS

1. Zydis Technology.
2. Durasolve Technology.
3. Orasolve Technology.
4. Flash Dose Technology.
5. Wow Tab Technology.
6. Flash Tab Technology.
7. Oraquick Technology.
8. Quick –Dis Technology.
9. Nanocrystal Technology.
10. Shearform Technology.
11. Ceform Technology.
12. Pharmaburst technology.
13. Frosta technology.
14. Ziplet technology.
15. Humidity treatment.
16. Sintering.

1) Zydis Technology

Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pre-gastric absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. There are some disadvantages to the Zydis technology. As mentioned earlier, the Zydis formulation is very lightweight and fragile and

therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidities. It readily absorbs water and is very sensitive to degradation at humidities greater than 65%.

2) Orasolv Technology

OraSolv was Cima's first mouth-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolv formulations are not very hygroscopic.

3) Durasolv Technology

DuraSolv is Cima's second-generation mouth-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a mouther and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.

4) Flash Dose Technology

The Flash Dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self–binding shear form matrix termed as “floss”. Shearform matrices are prepared by flash heat processing.

5) Wowtab Technology

The Wowtab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market from a number of years. The WOW in Wowtab signifies the tablet is to be given "With Out Water". The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and mouth dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The Wowtab product dissolves quickly in 15 seconds or less.

6) Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the process utilized is same as that of conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

7) Oraquick Technology

The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable (tablets can be compressed to achieve significant mechanical strength without disrupting taste masking) Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

8) Quick –Dis Technology

Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked as Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. When 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. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. [13]

9) Nanocrystal Technology

For mouth dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds.

10) Shearform Technology ™

The Shearform technology is based on preparation of floss that is also known as 'shearform matrix', which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystalised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystalised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallisation. The shearform floss, when blended with the coated or uncoated microspheres, is compressed into Flashdose or EZ chew tablets on standard tabletting equipment. [14]

11) Ceform Technology ™

In Ceform technology microspheres containing active pharmaceutical ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly-spinning machine. The centrifugal force of the rotating head of ceform machine throws the dry drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquifies the drug blend to form a sphere without adversely affecting drug stability. The microspheres are then blended and/or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into

the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microspheres can be incorporated into a wide range of fast dissolving tablets such as Flashdose, EZ chew, Spoon Dose as well as conventional tablets.

12) Pharmaburst technology

SPI Pharma, New castle, patents this technology. It utilizes the coprocessed excipients to develop ODT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

13) Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and coprocessing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

1. Porous and plastic material
2. Water penetration enhancer, and Binder

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30s depending on size of tablet. [15]

14) Ziplet technology

In ziplet technology water insoluble drug(s) as coated microparticles are used. The addition of suitable amount of water soluble inorganic excipients combination with disintegrants are impart an excellent physical resistance to the FDT and simultaneously maintained optimal disintegration. The use of water soluble inorganic excipients offer better enhancement of disintegration in comparison to the most commonly used water soluble sugars or salts. Tablets primarily contain water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed reduces the rate of water diffusion into the tablet core. [16]

15) Humidity treatment

The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase mechanical strength is due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. When an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially. In a patent by Mizumoto et al a drug, a sugar, and an amorphous sugar capable of

transforming from amorphous to crystalline state were mixed and compressed into tablets. The "amorphous sugar" is that which can form an amorphous state by spray drying, freeze drying, or other granulation methods. These amorphous sugars include glucose, lactose, maltose, sorbitol, trehalose, lactilol, and fructose. The relative humidity is determined by the apparent critical relative humidity of the mixture of a drug and an amorphous sugar. A relative humidity is greater than or equal to the critical relative humidity of this mixture which is to be chosen for the humidity condition. The advantage of using amorphous sugar is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems.

16) Sintering

When thermal energy is applied to a powder compact, the compact is densified and the average grain size increases. The basic phenomena occurring during this process is called sintering or densification and grain growth. Lagoviyer et al disclosed a process that tablet strength can be increased by sintering the tablet components at high temperatures and then resolidifying them at lower temperatures. A bulk agent in this formulation is used to provide bulk volume to the overall tablet and suitable agents include carbohydrates, calcium carbonate, and magnesium carbonate. Solvents can be chosen from water, ethyl alcohol, isopropyl alcohol or a mixture thereof. Binders are water soluble polymers such as polyethylene glycol (PEG), with a molecular weight of approximately 1000 to 1,000,000 Dalton. The granules are then lightly compressed to form tablets. These tablets are heated for a sufficient time and temperature to allow the binding agent to melt. The heating step is intended to melt the binding agent to create intra tablet bonds and helps to weld the product in to shape. Typically, a laboratory oven is set at around 50-100ºC. The heating time ranges from 3 to 45 minutes. The binding agents are resolidified as the temperature is reduced to ambient temperature. The disintegration time is generally within 3-60 seconds. [17]

APPROACHES FOR TASTE MASKING OF MOUTH DISSOLVING TABLETS

Mouth dissolving tablet, which disintegrate or dissolve in the saliva produce a positive or negative taste sensation. Most of the drugs have unpalatable taste in which taste masking plays critical role in formulating OFDT. The negative taste sensation of drugs can be reduced or eliminated by various approaches which include:

- Taste masking with flavors and sweeteners.
- Taste masking by polymer coating.
- Taste masking with ion-exchange resins.
- Taste masking by formation of inclusion complexes with cyclodextrins.
- Miscellaneous Taste-masking approaches.

Taste masking with flavors and sweeteners

Maximum patient acceptability with FDT is seen if they provide pleasant taste and mouth feel. To provide this property in tablets various sweeteners and flavors are employed. Usually sugar-based excipients are used as they are highly water soluble and dissolve quickly in saliva and provide pleasant taste and mouth feel to the final product. Mannitol is most widely used excipient in formulating OFDT. Aspartame and citric acid are most commonly used along with various flavorants such as mint flavor, orange flavor, strawberry flavor, peppermint flavor to produce pleasant taste and mouth feel.

Taste masking by polymer coating

Some of the unpleasant drugs cannot be masked by incorporation of sweeteners and flavors, in such cases alternative method of masking the taste is by coating the drug. In fact this process retards or inhibits dissolution and solubilization of drug, which allows time for particles to pass from mouth before taste is perceived in mouth.

Taste masking by ion-exchange resins

Ion-exchange resins are high molecular weight polymers with cationic and anionic functional groups. The most frequently employed polymeric network is a copolymer of styrene and divinylbenzene. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets and mask the taste. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution.

Drugs are attached to the oppositely charged resin substrate, forming insoluble substance or resonate through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs.

Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecules.

Ion-Exchange Resins can be classified into four major groups:

- Strong acid cation-exchange resin.
- Weak acid cation-exchange resin.
- Strong base anion-exchange resin.
- Weak base anion-exchange resin.

Taste masking complexation

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. Vander waals forces are mainly involved in inclusion complexes. β-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch.

Miscellaneous taste-masking approaches

By effervescent agent

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide and optionally a taste bud desensitizing composition and other nonactive materials, such as sweeteners, flavouring components and fillers. The formulations contain the drugs in combination with effervescent agents to promote their absorption in the oral cavity and to mask their bitter taste.

Salt preparation

Salt preparation is one of the classical approaches to mask the bitter taste of drug by either decreasing solubility or by increasing hydrophobicity and thereby reducing contact of bitter drugs with taste buds. This approach differs from others to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thereby less stimulating to the taste buds, or to obtain a tasteless or less bitter form. Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid and tartaric acid.

Solid dispersion systems

Solid dispersion can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.

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Freeze drying process

This method is used to develop fast-dissolving oral technologies such as Zydis and Lyoc (Lyophilized) Technology. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the high porosity produced by the freeze drying process.

The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze dried. The two most commonly used structural excipients are gelatine and mannitol, although other suitable excipients can be used. This process is ideally suited to low solubility drugs such as these are more readily freeze dried. [18]

Table0: Excipients and their uses in the manufacture of FDT using freeze drying technique.

Excipient	Use	Example
Polymer	Strength and rigidity	Gelatine, alginate and dextrin
Polysaccharides	Crystallinity, hardness, and palatability	Mannitol and sorbitol
Collapse protectants	Prevents shrinking	Glycerin
Flocculating agents	Uniform dispersion	Xanthum gum and acacia
Preservatives	Prevent microbial and fungal growth	Parabens
Permeation enhancer	Tran mucosal permeability enhancer	Sodium lauryl sulphate
pH adjusters	Chemical stability	Citric acid and sodium hydroxide
Flavors and sweeteners	Patient compliance	-
Water	Porous unit formation	-

Table 2: List of Super Disintegrants

Superdisintegrants	Example	Mechanism Of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little andreturns to original size aftercompression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation

Soy polysaccharides Emcosoy®	Natural super disintegrant	-Does not contain any starch or sugar. Used in nutritionalproducts	-

Table 3: Marketed products of oral fast disintegrating tablets.

S.No.	Trade Name	Active Drug	Manufacturer
1.	Felden fast melt	Piroxicam	Pfiser Inc., NY, USA
2.	Claritin redi Tab	Loratidine	Schering plough Corp., USA
3.	Maxalt MLT	Rizatriptan	Merck and Co., NJ, USA
4.	Zyprexia	Olanzapine	Eli lilly, Indianapolis, USA
5.	Pepcid RPD	Famotidine	Merck and Co., NJ, USA
6.	Zofran ODT	Ondansetron	Glaxo Wellcome, Middlesex, UK
7.	Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
8.	Zeplar TM	Selegilline	Amarin Corp., London, UK
9.	Tempra Quiclets	Acetaminophen	Bristol myers Squibb, NY, USA
10	Febrectol	Paracetamol	Prographarm, Chateauneuf, France
11	Nimulid MDT	Nimesulide	Panacea Biotech, New delhi , India
12	Torrox MT	Rofecoxib	Torrent pharmaceuticals , India
13	Olanex instab	Olanzapine	Ranbaxy lab. Ltd. New-delhi, India
14	Romilast	Montelukast	Ranbaxy lab. Ltd. New-delhi, India
15	Propulsid Quicksolv	Cisapride Monohydrate	Janssen pharmaceutics
16	Risperdal MTab	Risperidone	Janssen pharmaceutics
17	Spasfon Lyoc)	Phloroglucinol Hydrate	Farmalyoc
18	Nurofen FlashTab)	Ibuprofen	Ethypharm
19	Tempra Quicklets	Paracetamol	Cima Labs,Inc.
20	Zolmig Repimelt	Zolmitriptan	Cima Labs,Inc.
21	(NuLev	Hyoscyamine Sulfate	Cima Labs, Inc.
22	Gaster D)	Famotidine	Yamanouchi Pharma Tech. Inc.
23	Cibalgina DueFast	Ibuprofen	Eurand International
24	Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd.
25	Hyoscyamine Sulfate ODT	Hyoscyamine Sulfate	KV Pharm.Co.,Inc.
26.	Abilify Discmelt	Aripiprazole	Otsuka America/Bristol-Myers Squibb
27	Allegra ODT	Fexofenadine	Sanofi Aventis
28	Aricept ODT	Donepezil	Eisai Co.

EVALUATION OF OFDTs

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here.

Hardness. [19]

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

Friability [20]

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

Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the OFDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution 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 the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (W_b). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio,

R can be the determined according to the following equation.

$$R = 100 (Wa- W_b) / W_b \quad [21]$$

Moisture uptake studies

Moisture uptake studies for OFDT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a dessicator over calcium chloride at 37^0C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity (75% RH) was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One of the tablet is control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded. [22]

Disintegration test

The time for disintegration of OFDTs is generally <1min and actual disintegration time that patience can experience ranges from 5 to 30s. 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 test for ODT should mimic disintegration in mouth with in salivary contents.

Dissolution test

The development of dissolution methods for OFDT is comparable to approach taken for conventional tablets and is practically identical when OFDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N Hcl, pH 4.5 and pH 6.8 buffers should be used for evaluation of OFDT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of OFDT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of OFDTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for OFDT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile. [23]

CONCLUSION

Orally fast disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. OFDT products were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients and patients with dysphagia. Moreover now, they are widely available as OTC products for the treatment of allergies, cold, and flu symptoms. These can be taken anywhere, anytime, without water. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand. The future prospects of OFDT may include the oral delivery of drugs such as protein and peptide based therapeutics that has limited bioavailability when administered by conventional tablets.

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