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Orally disintegrating tablets: A Review

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Abstract

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as over-the-counter products for the treatment of allergies and cold and flu symptoms. Technologies used for manufacturing of orally disintegrating tablets are either conventional technologies or patented technologies. In conventional freeze drying, tablet molding, sublimation, spray drying etc. and in patented Zydis technology, Orasolv technology, Durasolv technology, Wowtab technology, Flashdose technology are important. Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. Evaluation of these tablets are done by following weight variation, friability, tensile strength, wetting time, water absorption ratio,

Keywords: ODT, Technology, Patients compliance

Introduction

This is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient[1]. Orally Disintegrating Tablet (ODT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60seconds or less. Drug absorption through local oral–mucosal and through pre and post gastric parts of G.I.T. ODTs are also called as Oro-disperse, mouth dissolving, rapidly disintegrating, fast melt, quick dissolve and freeze dried wafers[2].

Oral dosage forms like tablets and capsules possessing great problem of swallowing mainly for pediatrics, geriatrics, and bedridden, nauseous or non-compliant patients'. Orally disintegrating dosage forms has to be placed in mouth and then get dispersed in saliva without the need of water[3,4]. Orally disintegrating tablets are also called as oral disperse, mouth dissolving, rapidly disintegrating, fast melt, and quick dissolve system. From past decade, there has been an increased demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing day by day[5]. US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book'an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually with a matter of seconds, when placed upon the tongue"[6]. United States Food and Drug Administration (FDA) define orally disintegrating tablets as "A solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue"[7]. European Pharmacopoeia described orally disintegrating tablets as 'uncoated tablets intended the placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 min[8].

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Advantages Of Orally Disintegrating Tablets[9, 10]

- Convenient and easy to administer as 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
- Insensitive to environmental conditions such as humidity and temperature.
- 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
- Rapid drug therapy intervention.

Benefits Of Orally Disintegrating Tablets

- Administered 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.
- 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.

Selection of Drug[11]

The ideal characteristics of a drug for in vivo dissolution from an ODT include

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (log p>1, or preferably>2)
- Ability to permeate oral mucosal tissue

Unsuitable drug characters tic's for Orally Disintegrating Tablets;

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release.

Techniques Used For the Formulation of Orally Disintegrating Tablets

Many techniques have been reported by various researchers for the formulation of orally disintegrating tablets.

1. Freeze-Drying or Lyophilization[12, 13, 14]

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 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 aluminum foil backing is applied on a blister-sealing machine . Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

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2. Tablet Molding [15, 16]

Molding process is of two type 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, 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.

3. Spray Drying[17, 18]

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 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.

4. Sublimation[19, 20, 21]

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.

5. Direct Compression[22, 23]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

6. Cotton Candy Process[24]

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

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

7. Mass-Extrusion[25, 26]

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.

Patented Technologies For Orally Disintegrating Tablets[27, 28, 29, 30, 31]

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.

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) Durasolv 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) Orasolv 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

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The FlashDose 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 Shear form. 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". Shear form matrices are prepared by flash heat processing and are of two types.

5) Wowtab Technology

The Wowtab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market for 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 processing utilized the conventional tableting 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, meaning 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 Quick-Dis™, is Lavipharm's proprietary patented technology and 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. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time is around 30 seconds for Quick Dis™ film with a thickness of 2 mm.

9) Nanocrystal Technology

For orally disintegrating 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.

Conclusion

Orally disintegrating tablets (ODTs) have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms.

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Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric, and psychiatric patients with dysphagia. Orally disintegrating dosage forms had satisfactorily solved the major problem of non-compliance for pediatrics and geriatrics which occur mainly because of swallowing difficulty. This dosage form has been formulated for existing drugs for extending the patent life of the drug and also for granting the new patent. The safety and efficacy profile of drugs in orodispersible tablet is same like their conventional tablet dosage form. Based on conventional techniques, new techniques are developed like Zydis, WowTab, Orasolv and many more, which leads to getting a patent and new market strategy for orodispersible tablets. Future possibilities for improvements in ODTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from ODTs have yet to be fully realized.

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