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CONVENTIONAL AND PATENTED TECHNOLOGIES IN ORAL DISPERSIBLE TABLETS: A REVIEW

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ABSTRACT

Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. One such approach is oral disintegrating tablets (ODTs). ODTs are solid unit dosage forms, which disintegrates or dissolves rapidly in the mouth without the general requirement for swallowing, the chewing and water. An oral disintegrating tablet provides an advantage particularly for paediatric and geriatric populations and is who has difficulty in swallowing conventional tablets and capsules. This review depicts the various mechanisms, formulation aspects, patented technologies developed, ingredients used, evaluation tests and international and national marketed formulations.

Key words: Disintegration, Oro dispersible tablets (ODT), Fast disintegrating tablets (FDT), Super disintegrants

INTRODUCTION

Orally disintegrating tablets are also called as Oro dispersible tablets, fast disintegrating, and mouth dissolving tablets, fast dissolving tablets, rapid dissolving tablets and porous tablets. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing (Sastry, 2000).

This dosage form combines the advantages of dry and liquid formulation. Some novel ODT technology allow high drug loading, have an acceptable taste, offer a pleasant mouth felling, leaving minimal residue in the mouth after oral administration.ODT have been investigated for their potential in improving bio availability of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs. Super disintegrant is the key element in inducing fast disintegration of oral dispersible tablets.

Advantages:

1. As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients (Dobetti, 2003).

2. Easy to administer for paediatric, geriatric, and institutionalized patients (especially for mentally retarded and psychiatric patients) Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.

3. Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavours and sweeteners in ODTs.

4. Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased. Pre gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.

5. From the pharmaceutical industry's point of view, FDTs can provide new dosage forms as a life cycle management tool for drugs near the end of their patent life (Chang, 2008).

ODT disintegration mechanism: The super-disintegrant is the key element in inducing fast disintegration of the ODT. The super-disintegrant is a hydrophilic product that weakens the tablet by creating a hydrophilic tablet network upon swelling. The amount of saliva in the mouth is low (about 2ml), maximum amount of aqueous milieu should be available to allow super-disintegrant particle growth and quickly achieve optimal tablet disintegration. Therefore, the filler must have less affinity for water than the super-disintegrant. But to achieve a pleasant mouth-feel (to avoid grittiness), the filler should be water soluble. Mannitol is often used in ODTs since it has these two opposite characteristics: low affinity for water and high solubility. These characteristics facilitate fast water penetration through the channels to the super-disintegrant.

a. Swelling: General mechanism of action for tablet disintegration is Swelling, tablets through high porosity expression poor Disintegration due to lack of sufficient swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. (Bradoo, 2001)

b. Porosity capillary action (wicking): While we place the drug into appropriate aqueous medium, the Medium enters into the tablet and replaces the air absorbed on the particles, which softness the intermolecular bond and Breakdowns the tablet into fine particles. Water uptake by Tablet depends upon hydrophilicity of the drug/excipient and on tableting environments.

c. Heat of wetting (air expansion): When disintegrates through exothermic properties gets wetted, Localized stress is produced due to Capillary air expansion, this helps in breakdown of tablet.

d. Due to release of gases: Carbon dioxide released within tablets continuously wetting due to contact between Bicarbonate and carbonate with citric Acid or tartaric acid. The tablet disintegrates due to generation of pressure inside the tablet. As these disintegrates are highly Sensitive to small changes in humidity level and temperature, Strict control of environment is required during manufacturing of the tablets.

e. By enzymatic reaction: These enzymes destroy the binding action of binder and helps in disintegration. Actually due to Swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the Accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

f. Due to disintegrating particle repulsive forces (Secondary to wicking): The swelling of tablet made through 'non swellable' Disintegrates. The electric repulsive forces between particles are the mechanism of disintegration and Water is required for it.

g. Due to deformation: Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

Table.1.List of superdisintegrants and their mechanism of action

Superdisintegrants	Nature	Mechanism of action	Brand Names
Crosscarmellose	Modified cellulose or cross linked cellulose	Wicking due to fibrous structure swelling with minimal gelling	Ac-Di-Sol Nymce 25X Nymcel
Crosspovidone	Cross linked PVP	Water wicking,swelling and possibly some deformation recovery	Kollidon Polyplasdone
Alginic acid NF	Cross linked Aliginic acid	Wicking action	Satialgine
Soy polysaccharides	Natural disintegrant	EMCOSOY	EMCOSOY
Calcium silicate		Wicking action	
Sodium starch glycolate	Modified Starch	Rapid extensive swelling minimal gelling	Explotab Primogel
Ion exchange resin	Resins		Amberlite (IPR 88)
L-HPC	Low hydroxyl propyl cellulose	Both swelling and wicking	
Acrylic acid derivatives	Poly (Acrylic acid) Superporous	Wicking action	

Technologies used for manufacturing of orally disintegrating tablets:

Conventional technologies:

Freeze drying or lyophilisation: Freeze drying (lyophilisation) is a process in which solvent is removed from a frozen drug solution or a suspension containing structure-forming excipients. The resulting tablets are usually very light and have highly porous structures that allow rapid dissolution or disintegration. When placed on the tongue, the freeze dried unit dissolves almost instantly to release the incorporated drug. The entire process is done

at non elevated temperatures to eliminate adverse thermal effects that may affect drug stability during processing.The Zydis® technology is the most well known example of the freeze drying (Kaushik, 2004).

Direct compression: Direct compression is the simplest and most cost-effective tablet manufacturing procedure. This method can be applied by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility and sweetness, pleasing mouth-feel and good taste masking.

Disintegrants used in FDTs: Some patents use effervescent couples as their disintegrant, while others use a combination of disintegrants. Dobetti summarized different types of non-effervescent disintegrants used in the pharmaceutical area.

- Starch and modified starches: This group includes natural starches (such as maize starch and potato starch), directly compressible starches (such as starch 1500), modified starches (such as carboxy methyl starches and sodium starch glycolate), and starch derivatives (such as amylose).
- Cross-linked polyvinyl pyrolidone
- Modified celluloses such as cross-linked sodium carboxy methyl cellulose.
- Alginic acid and sodium alginate
- Microcrystalline cellulose
- Methacrylic acid-divinylbenzene copolymer salts

In addition, poly (acrylic acid) super porous hydro gel (SPH) micro particles were recently reported as super disintegrants possessing a unique porous structure. They were used as a wicking agent to decrease the disintegration time of FDTs.

Inorganic excipients used in FDTs: Dobetti has developed a formulation using insoluble inorganic excipients as the main component for FDTs. According to the patent, disintegration of a tablet depends on the quantity of the disintegrant and insoluble inorganic excipients used. The disintegration also depends on the relative weight ratio between the water insoluble and soluble excipients, if the water-soluble excipients are used. In the formulation, three major components were used:

- **Substantially water insoluble components:** This group includes water-insoluble excipients, water-insoluble drugs (either coated or uncoated), and water- insoluble lubricant and glidant. The water-insoluble excipients e.g., di- or tri-basic calcium phosphate or organic filler e.g., microcrystalline cellulose can be used.
- **Substantially soluble components:** This group includes compressible sugars, flavouring agents, sweeteners, binders, and surfactants.
- **Disintegrants:** Examples are maize starch or modified starch, cross-linked polyvinyl pyrrolidone, or sodium carboxy methyl cellulose. The disintegration time increased as the amount of insoluble component decreased. If the active ingredient was only a small portion of the whole formulation, the disintegration time could be optimized by including insoluble fillers (e.g., microcrystalline cellulose and silicon dioxide) or by increasing the amount from the pharmaceutical manufacturer's point of view.(Milovac, 2001; Khankari, 2000)

Molding: Molded forms have been prepared directly from a molten matrix, which the drug is dissolved or dispersed or by evaporating the solvent from a drug solution or suspension at a standard pressure. Usually molded tablets are compressed at a lower pressure than are conventional tablets. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Unfortunately, moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet soften occurs during tablet handling and when blister pockets are opened. Hardness agents can be added to the formulation, but then the rate of tablet solubility usually decreases (Sastry, 2000; Bogner, 2002).

Mass extrusion: T Mass extrusion was the technique used for preparing taste masked granules. In this technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat

granules of bitter drugs to mask their taste. The tablet was prepared with different super disintegrate e.g. sodium starch glycolate, cross carmellose sodium and cross povidone etc.

Melt granulation: Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. A new approach of preparing FDTs with sufficient mechanical strength, involving the use of a hydrophilic waxy binder (Superpolystate R, PEG-6-stearate) by melt granulation or wet granulation was reported. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate).

Phase transition process: Another novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, ODT were produced by compressing powder containing erythritol (M.P: 122 °C) and xylitol (M.P: 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. Heating process enhances the bonding among particles leading to sufficient hardness of tablets which was otherwise lacking owing to low compatibility.

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

Patented technologies:

Zydis® technology: Zydis, the best known of the fast dissolving /disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin. The product tablet is very light weight and fragile and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self preserving because the final water concentration in a freeze dried product is too low to allow for microbial growth. A major claim of 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.

Orasolv® Technology: Orasolv was cima's first dissolving dosage form. The orasolv technology unlike zydis disperses in saliva with the aid of almost imperceptile effervescence. The orasolv technology is best described as a fast dissolving tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the orasolv formulation is twofold. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste masking in orasolv. This technology is frequently used to develop over the counter formulations. Ora Solv® technology (Cima Labs) produces tablets by low compression pressure. It uses an effervescent disintegration pair that releases gas upon contact with water. The widely used effervescent disintegration pairs usually include an acid source and a carbonate source. The acid sources include citric acid, tartaric acid, malicacid, fumaric acid, adipic acid, and succinic acids. The carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. The carbon dioxide evolved from the reaction may provide some "fizzing" sensation, which is a positive organoleptic sensation. The amount of effervescent agent is in general about 20–25% of the total weight of the tablet. Because of the soft and fragile nature of OraSolv® tablets, a special packaging system, known as PakSolv®, was developed to protect the tablets from breaking during transport and storage. PakSolv® is a "dome-shaped" blister package that prevents the vertical movement of the tablet within the

depressions, because the diameter of the lower portion of the dome is too narrow to accommodate the tablet. PakSolv® also offers light, moisture, and child resistance.

Durasolv® technology: It is the second generation technology, the DuraSolvR technology was developed by Ciba to provide stronger tablets for packaging in blisters or bottles. The key ingredients in this formulation are non direct compression filler and lubricant. The particle size of the nondirect compression filler is preferably between about 20 and 65 μm, while for direct compressible fillers at least 85% of the particles are over 100 μm in size. These nondirect compression fillers, such as dextrose, mannitol, sorbitol, lactose, and sucrose, have the advantage of quick dissolution and avoid some of the gritty or sandy texture usually present in direct compressible versions of the sugar. The amount of a nondirect compression filler is usually about 60–95% of the total tablet weight. The tablets have low friability, which is about 2% or less when tested according to the USP, and the hardness of the tablets is at least about 15–20 N. The disintegration time is less than 60 seconds. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters.

Wow Tab®Technology: Wow means "without water". Wow tab is an intra buccally soluble, compressed tablets consisting of granules made with saccharine of low and high moldability. When low- and high-moldable saccharine are used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. Low moldability saccharides produce tablets with hardness between 0 and 2 kg, when 150 mg of such a saccharide is compressed under pressure of 10–50 kg/cm2 using a die 8 mm in diameter. The typical low-moldability saccharides include lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides produce tablets with hardness above 2 kg when prepared under the identical conditions. The typical high-moldability saccharides are maltose, manitol, sorbitol, and oligosaccharides. It is used to obtain a tablet of adequate hardness and fast dissolution rate. The wow tab formulation is stable to environment due to its significant hardness than zydis and Orasolv. Wow tab product is suitable for both conventional, bottle and blister package.

Oraquick: This technology is patented by K.V.Pharmaceuticals. It utilizes taste masking microsphere technology called as micro mask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of micro particles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in accommodates high doses of drug and offers improved mechanical strength.

Nano Crystal technology: Elan's proprietary Nano Crystal technology (Nanomelt TM) can improve compound activity and final product characteristics. Decrease in particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nano Crystal technology. Nano Crystal 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.

Pharmaburst technology: SPI Pharma, New castle, patents this technology. The Pharmaburst ODT uses a proprietary disintegrate (Pharmaburst) that is based on mannitol blended with conventional tableting aids. It utilizes the co processed 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.

Flash Tab Technology: Ethypharm, Saint Cloud, France has patented the Flash tab technology. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. This technology relays on the use of super disintegrates. Flash tab is a combination of wet and dry granulation before compression. Micro particles of taste-masked API are blended with conventional tableting aids and disintegrate such as pvp or crospovidone, cross-linked sodium carboxy methylcellulose and swelling agents such as starches or microcrystalline cellulose. Disintegration times are typically less than 1 min.

Frostatechnology: Akina patents this technology. The frostatechnology is based on the compression of highly plastic granules at low pressure to prepare fast melting tablets. The highly plastic granules are composed of three components: a plastic material, (Maltrin QD M580 and MaltrinM180 are maltodextrin and corn syrup solids) a water penetration enhancer (Mannogem EZ Spray) and a wet binder (sucrose, poly vinyl pyrolidone and hydroxyl propyle methylcellulose). Each of the three components plays an essential role in obtaining tablets with higher strengthened faster disintegration time.

Advantol™ 20053: Advantol™ 200 is a directly compressible excipient system offering "Soft-Melt" functionality and specially formulated for nutraceutical applications. SPI Pharma's Advantol platform uses proprietary co-processing technology. Advantol requires no special manufacturing equipment or tooling. Advantol formulations utilize a standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions to make robust "soft-melt" tablets.

Advatab53: AdvaTab tablets disintegrate rapidly in less than30 seconds. These tablets are prepared using polymer-coated drug particles that are uniformly dispersed in an ultra-fine, low-water content, rapidly disintegrating matrix with superior organoleptic properties. AdvaTab tablets are compressed using a proprietary, patented, external lubrication system in which the lubricant is applied only to the tablet surface, resulting in robust tablets that are hard and less friable and can be packaged in bottles or blister.

Quicksolv technology: This technology is patented by Janssen Pharmaceuticals. It uses two solvents in formulating a matrix which disintegrates instantaneously. Methodology includes dissolving medium components in water and the solution or suspension is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

Ziplettechnology: In ziplet technology water insoluble drugs or drugs as coated micro particles are used. The addition of a suitable amount of water-insoluble inorganic excipients combined with Disintegrants imparted an excellent physical conflict to the oral dissolving tablet (ODT) and the simultaneously maintained optimal disintegration. The use of water-insoluble inorganic excipients offer better enhancement of disintegration incomparison to the most commonly used water soluble sugars or salts. Tablets primarily of water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed which reduces the rate of water diffusion into the tablet core.

Oraquick: The oraquick fast-dissolving tablet preparation utilizes a patented taste masking technology. The taste masking method does not develop solvents ofany kind, and consequently leads to faster and additional efficient production. Also, lower heat of manufacture than alternative fast dissolving/ disintegrating technologies makes Oraquick suitable for heat-sensitive drugs.

CONCLUSION

Orally disintegrating tablets have potential advantages over conventional dosage forms, with improved patient compliance, convenience, bioavailability and rapid onset of action. They are a very good alternative for drug delivery to geriatric and paediatric patients. They have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus ODT has tremendous scope for being the delivery system for most of the drugs in near future.

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