1 Introduction

Introduction of a therapeutic substance into the body to improve its efficacy and safety is known as a drug-delivery system which interfaces between the patient and the drug. Drug may be introduced into the human body by various routes, but oral route has been one of the most popular and used route for both conventional as well as novel drug delivery because of low cost of therapy, pain avoidance, self-medication, ease of ingestion, leading to high levels of patient compliance, and it did not require sterile conditions. However, this form of dosage has some limitations like motion sickness (kinetosis), sudden episodes of allergic attacks or coughing, and unavailability of water, but one important drawback is ‘Dysphagia’ or difficulty in swallowing. This is seen to afflict nearly 45% of the general population. Particularly, the difficulty is experienced by pediatric and geriatric patients.

To overcome these problems, mouth dissolving tablets (MDT) have been developed, which having good hardness, dose uniformity, easy administration and serves as the first choice of dosage form for pediatrics, geriatrics and travelling patients. Mouth Dissolving Tablet has a pleasing mouth feel, and it does not require water to swallow. MDT easily dissolved or disintegrates in saliva within a few seconds (15 s to 3 min) without the need of drinking water or chewing, leaves no residue in the mouth when administered and less sensitive to environmental conditions like temperature, humidity. Some MDT tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are called true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast-disintegrating tablets, as they may take about one minute to disintegrate completely.

2 Ingredients used in preparation of MDTs

Ingredients used in MDT formulation are help in quick release of the drug, resulting in faster dissolution.

2.1 Super disintegrants

The most important ingredients of a mouth dissolving tablets are Super disintegrants, which play a major role in the disintegration and dissolution of MDT. Sodium starch glycolate, Ac-di-sol (Crosscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised starch are some of the examples of disintegrants. Most of the MDTs consists certain super disintegrants and taste masking agents.
It is necessary to select a suitable disintegrant, in an optimum concentration (selected according to critical concentration of disintegrant) to ensure quick disintegration and high dissolution rates.

Although superdisintegrants primarily affect the rate of disintegration, high levels, they can also affect mouth feel, tablet hardness and friability. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.

2.2 Flavours

Flavours and taste_masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. For example, example Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, etc. Aspartame, Sugars derivatives are used as sweeteners.

2.3 Fillers

Selection of filler also had an important role in deciding the disintegration time. Some examples of fillers are directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium.

2.4 Surface active agents

The presence of esterase or bile salts (sodium doecyl sulfate, sodium lauryl sulfate, polyoxy ethylene sorbitan fatty acid esters) like surface active agents plays a role in drug release.

2.5 Lubricants

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach. Some examples are Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene.

2.6 Binder

Binders are added to tablet to add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet. Polyvinyl pyrrolidone, Polyvinyloxcohol, Hydroxy propyl methyl cellulose.

2.7 Colour

Sunset yellow, Amaranth, etc.

3 Conventional manufacturing techniques for MDTs

3.1 Lyophilization or freeze-drying

Freeze-drying, also known as lyophilization, lyophilization, or cryodesiccation, in this method water is sublimated from the product after freezing. This technique creates an amorphous porous structure that can dissolve rapidly. The active drug is dissolved in an aqueous solution of a carrier. Then the mixture is dosed by weight and poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through a 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.

The major disadvantage of lyophilization technique is high cost of equipment and processing. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms.

3.2 Moulding

Moulded tablets are designed to facilitate the absorption of active ingredients through mucosal linings of mouth. In this method, tablet disintegrates and dissolves rapidly due to the presence of water-soluble ingredients. Moistened powder blend is molded in to tablet using compression pressure lower than used in conventional tablet’s compression. Then the solvent is removed by air-drying. Molded tablets have a porous structure that enhances dissolution. The two major problems with molding are less mechanical strength and poor taste masking.

3.3 Sublimation

In this technique, highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, etc., are added that volatilize readily, to other tablet excipients and the mixture is then compressed in to tablets. Volatile material is then removed via sublimation, leaving behind a highly porous matrix. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

3.4 Direct compression

It is the easiest and most popular method to manufacture tablets by using conventional equipments. In this method, tablets are compressed directly from the mixture of the drug and excipients. This technique can now be applied to fast dissolving tablets.
because of the availability of improved tablet excipients (superdisintegrants) and sugar based excipients. This technology is cost-effective and easy to implement at the industrial level18, 19.

3.5 Spray drying

In this technique, processing solvent is evaporated rapidly and can produce highly porous and fine powder, which was compressed into tablets. Hydrolyzed and non hydrolyzed gelatin used as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium20, 21.

3.6 Mass extrusion

This method 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 the heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking22, 23.

3.7 Nanonization

Nanonization technology has been recently developed method, which involves the reduction in the particle size of drug to nano size by wet-milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and 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 doses16.

3.8 Melt granulation

In this process, MDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate is a waxy material with a melting point of 33-37 °C and a hydrophilic-lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated into the formulation of MDTs by melt granulation method where granules are formed by the molten form of this material17.

4 Patented technologies for preparation of MDTs

4.1 Zydists technology

Zydists formulation was first marketed and fast disintegrating tablet preparation's technique in which the tablet dissolves in the mouth within seconds after placement of the tongue. It is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When Zydists units are put to the mouth, the freeze-dried structure disintegrates instantaneously. To provide strength and resilience to tablets: polymers such as gelatin, dextran or alginites are incorporated with it which also from glossyamorphous structure. Saccharides such as Mannitol or sorbitol are incorporated to obtain crystallinity, elegance and hardness. Water is used for the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles during the manufacturing process.

The major advantage of Zydists formulation is that Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydists formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. Zydists products are packed in blister packs to protect the formulation from moisture to the environment24.

Limitation of Zydists formulation is that the particle size of the insoluble drugs should not be less than 50 μm and not more than 200 μm to prevent sedimentation during processing, and the amount of drugs could be incorporated should generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs25. There are some disadvantages of Zydists technology. The process of freeze drying is a relatively expensive manufacturing process. The Zydists formulation has poor stability at higher temperatures and humidity. It readily absorbs water, and is very sensitive to degradation at humidity greater than65%.

4.2 Orasolv technology

Orasolv formulation has been developed by CIMA labs. In this system, active medicament is taste masked in two-fold. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique, low compression force in order to minimize oral dissolution time. Soft and friable tablets produced by Conventional blenders and tablet machine, and the tablet matrix dissolve in less than one minute.

The advantage of Orasolv Technology is that the formulations are not very hygroscopic, and it also provides a distinct, pleasant sensation of effervescence in the mouth. The major disadvantage of the Orasolv formulations is its Poor mechanical strength and
Manufacturing require a controlled environment at low relative humidity.

4.3 Durasolv technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. In this system, active medicament is taste masked. It also contains effervescent disintegrating agent. 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 tableting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner. 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.

4.4 Wowtab technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldable and high mouldable saccharides is used to obtain a rapidly melting, strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides) and compressed into the table.

Tablets formulated by Wowtab technology offers the superior mouth feel due to the smooth melt action and suitable for both conventional bottle and blister packaging.

4.5 Flash dose technology

Flash does technology has been patented by Fuisz. This technology is based upon the preparation of sugar based matrix known as floss, which is made from a combination of excipients either alone or in combination of drugs by flash heat processing. Tablets are made by direct compression technique. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed on the tongue. Interestingly, by changing the temperature and other conditions during production, the characteristics to the product can be altered greatly.

4.6 Flashtab technology

Ethpharm, Saint Cloud, France has patented the Flashtab technology. Tablets formulated by this technology consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusionspheronisation. Reticulated polyvinyl pyrrolidine or carboxy methylcellulose is used as disintegrating agents and carboxy methylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starches, etc are used as Swelling agents. All the processing utilized the conventional tableting technology, and the tablets produced have good mechanical strength and disintegration time less than one minute. All the processing utilized conventional tableting technology.

4.7 Oraquick technology

The OraQuick fast-dissolving/disintegrating tablet formulation is patented by K.V Pharmaceuticals. It utilizes taste masking microsphere technology called as micromaskin which does not utilize solvents of any kind, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product, therefore, leads to faster and more efficient production. Lower heat of production than alternative fast-dissolving/disintegrating technologies make OraQuick appropriate for heat-sensitive drugs.

4.8 Ziplets/Advatab technology

This technology is patented by passano con Barnago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants. AdvtaTab tablets disintegrate rapidly in less than 30 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. AdvtaTab 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 packs.

4.9 Lyotechnolgy

Lyoc technology is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

4.10 Pharmaburst technology

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

4.11 Nanocrystal technology

Nanocrystaltechnology is patented by Elan, King of Prussia. Nanocrystal Technology which includes lyophilization of colloidal
dispersions of drug substance and water soluble ingredients filled into blister pockets. This method avoids the manufacturing process such as granulation, blending and tableting which is more advantages for highly potent and hazardous drugs.

5 Evaluation of mouth dissolving tablet

5.1 Size, shape, thickness and diameter

The size and shape of the tablet can be dimensionally described, monitored and controlled. Tablet thickness is counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken, and their thickness was recorded using micrometer (digital vernier calipers). The pressure required to break the tablets is measured as a function of hardness (kg/cm²). The values obtained must meet the standard value.

5.2 Uniformity of weight

Weight of the tablets determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

5.3 Tablet hardness

Hardness of tablet is defined as for ceapplied across the diameter of the tablet in the order to break the tablet. Hardness of the tablet of each formulation was determined using the conventional hardness tester (Monsanto Hardness tester, Pfizer hardness tester, etc.). It is expressed in Kg or pound. The pressure required to break the tablets is measured as a function of hardness (kg/cm²). The values obtained must meet the standard value.

5.4 Friability

Friability of the tablet was determined using friability test apparatus (Campbell Electronics, India). Friability is to measure the extent of tablet breakage during physical stress conditions like Packing, transportation, etc. A sample of randomly selected 6 tablets was evaluated for friability using Roche friabilator at 25 rpm for 4 minutes. The % weight loss is calculated by measuring the total weight of 6 tablets before and after operation.

5.5 Wetting time

The significant parameters for mouth dissolving tablets are the ratio of Wetting time and water absorption reported by Yunixia et al. A piece of filter paper folded twice (circularly cut) was placed in a small petri plate containing water soluble dye solution (Sorenson’s buffer pH 6.8). Tablet was placed in the paper, and the time required for complete wetting of the tablet was determined. Three trials for each batch and the standard deviation were also determined.

5.6 Disintegration time

Disintegration time for randomly selected 6 tablets was measured using the disintegration test apparatus (specified in I.P.-1996). The average time required for disintegration was calculated and compared with standards.

6 Mechanism of action of MDTs

There are various mechanisms for tablet’s disintegration as follows:

6.1 Swelling

Swelling is most widely accepted general mechanism of action for tablet disintegration. Water penetration is a necessary in first step of swelling for disintegration of tablet. Due to lack of adequate swelling force tablets with high porosity show poor disintegration while low porosity exerted sufficient swelling force in the tablet. If the packing fraction is very high, fluid is unable to penetrate into the tablet and disintegration again slows down.

6.2 Porosity and capillary action (Wicking)

The first step of Disintegration is by capillary action. When we put the tablet into the suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Uptake of water by tablet depends upon hydrophilicity of the drug/exipients and on tableting conditions. For these types of disintegrant’s maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary, which helps in disintegration by creating a hydrophilic network around the drug particles.

6.3 Repulsive forces

Particle repulsion theory proposed by Guyot-Hermann based in the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration, and water is required for it. Researchers found that repulsion is secondary to wicking.

6.4 Deformation

In this mechanism, during tablet compression, disintegrated particles get deformed inside the tablets and when they come in contact with aqueous media or water these deformed particles get into their normal structure. 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. Starch grains are generally thought to be “elastic” in nature meaning that grains that are deformed under pressure will return to their original shape when
that pressure is removed. However, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water.

6.5 Heat of wetting

This mechanism is limited to only in few disintegrants not for all. When disintegrants with exothermic properties get wetted, localized stress is created due to capillary air expansion, which aids in disintegration of tablet.

6.6 By enzymatic reaction

Enzymes also play a role as disintegrants. These enzymes present throughout the body, a dearth the binding action of binder and help in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or accelerated absorption of water leads to disintegration. Examples as amylase, protease, cellulase and invertase”.

References


