

MOUTH DISSOLVING DOSAGE FORMS: A NEW APPROACH TO DRUG DELIVERY

Introduction

Researchers throughout the world are focusing intensively on the methods for the development of new drug delivery systems to enhance patient's compliance. The oral route however still remained as the best administration route of therapeutic agents for its ease of ingestion, pain avoidance and versatility. Hence, fast dissolving tablets become an emerging trend in the pharmaceutical industry. Fast dissolving tablets are ideal for all types of people, including for people who have swallowing difficulties, paediatric, geriatric, and bedridden patients. It is also for active patients who are busy, travelling and may not have access to water. Fast dissolving tablets are also known as orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. This type of tablets disintegrates quickly once introduced into the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. In this review article, drug candidates suitable for fast dissolving drug delivery and the available marketed products have been listed

Many patient groups, such as the elderly, children, mentally retarded, uncooperative or nauseated, have difficulty in swallowing conventional dosage forms, like tablets. Swallowing conventional tablets will be further hindered by conditions such as unavailability of water, allergic reactions and episodes of coughing. These problems can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration, because they dissolve in saliva and does not require water for swallowing. Upon ingestion, the saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and oesophagus, as the saliva passes down in to the stomach. In these cases, the bioavailability of drugs is significantly greater than those observed from conventional dosage forms. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets.

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of

administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of conditions like:

1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water.

Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects.

Criteria for mouth dissolving dosages

The tablets should follow the following criteria:

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- 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.

Advantages of dosages

- No need of water to swallow the tablet.
- Can be easily administered to pediatric, elderly and mentally disabled patients.
- Accurate dosing as compared to liquids.
- Dissolution and absorption of drug is fast, offering rapid onset of action.
- Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down into the stomach
- Advantageous over liquid medication in terms of administration as well as transportation
- First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
- Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- Allows high drug loading.

Limitations of dosages

- These usually have insufficient mechanical strength. Hence, careful handling is required.
- Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Drugs with relatively larger doses are difficult to formulate into MDT e.g. antibiotics like amoxicillin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for MDT.

- Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Main ingredients used in preparation of dosages

Important ingredients that are used in the formulation of MDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients.

Disintegration and solubilization of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents. Excipients balance the properties of the actives in FDDTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Binders keep the composition of these fast-melting tablets together during the compression stage. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35°C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast-dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used. The most important ingredients of a mouth dissolving tablets are:

Super disintegrants:

Use of disintegrants is the basic approach in development of MDTs. Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. 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. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases.

List of Natural superdisintegrants :

1. Plantago Ovata husk
2. Lepidum Sativum
3. Plantago Ovata husk
4. Plantago ovate Mucilage,
5. Locust Bean gum
6. Treated Agar
7. Cassia fistula gum
8. Plantago ovata mucilage

List of synthetic superdisintegrant:

1. Cross Povidone Cross
2. Carmellose sodium
3. Sodium Starch glycolate
4. Crodpovidone
5. Cetric Acid
6. Sodium bicarbonate
7. kollidon CL(K)
8. Explotab(E)

Mechanism of action of disintegrants

a. By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into 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. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions.

For these types of disintegrants, 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.

b. By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

c. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

d. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

e. By enzymatic reaction

Here, enzymes present in the body act as disintegrants. 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/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with non-swelling disintegrants. Guyot- Hermann has proposed a particle repulsion theory based on the observation that nonswelling 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.

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 break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

Sugar based excipients:

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. And the basic requirement for designing MDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking. But not all sugar-based materials have fast dissolution rate and good compressibility or compactability. However technologies have been developed to make use of the sugar based excipients in the design of fast dissolving tablets. Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, binders, colors and flavors.

Approaches for preparation of dosages

Various technologies used in the manufacture of Mouth Dissolving

Tablets include:

1. Freeze-drying or lyophilization
2. Sublimation
3. Spray drying
4. Moulding
5. Mass extrusion
6. Direct compression

Freeze drying:

The tablets prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve rapidly when come in contact with saliva. In this process, water is sublimated from the product after freezing. First of all, the material is frozen to bring it below its eutectic point. Then primary drying is carried out to reduce the moisture to around 4% w/w of dry product. Finally, secondary drying is done to reduce the bound moisture to the required volume. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapsed temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature, instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva. However the use of freeze-drying is limited due to high cost of equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

Sublimation:

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method.

Spray drying:

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet. Allen and Wang used this technique to prepare mouth-dissolving tablets, which disintegrated within 20 s.

Moulding:

Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on whether and to what extent it dissolves in the wetted mass. The drug can exist as discrete particles or micro particles in the matrix. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion. Different moulding techniques can be used to prepare mouth-dissolving tablets:

a. Compression moulding:

The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

b. Heat moulding:

A molten matrix in which drug is dissolved or dispersed can be directly moulded into Mouth dissolving tablets.

c. No vacuum lyophilization:

This process involves evaporation of solvent from a drug solution or suspension at a standard pressure. Moulded tablets possess porous structure, which facilitates rapid disintegration and easy dissolution. Moulded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But moulded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength.

Mass extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

Direct compression:

The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets due to certain advantages:

- a. High doses can be accommodated and final weight of the tablet can exceed that of other methods.
- b. Easiest way to manufacture the tablets.
- c. Conventional equipment and commonly available excipients are use
- d. A limited no. of processing steps are involved.
- e. Cost-effectiveness.

Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration and high dissolution rates. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.³⁵

Patented Technologies for preparation of dosages:

Several technologies are available for preparing Mouth dissolving tablets. But some commercially useful technologies are:

Zydis technology:

‘Zydis’ is the first mouth dissolving dosage form in the market. It is a unique freeze-dried tablet in which the active drug is incorporated in a water-soluble matrix, which is then transformed into blister pockets and freeze dried to remove water by sublimation. Zydis matrix is made up of a number of ingredients in order to obtain different objectives. Polymers such as gelatin, dextran or alginates are added to impart strength during handling. These form a glossy and amorphous structure. Mannitol or sorbitol is added to impart crystallinity, elegance and hardness. Various gums may be added to prevent sedimentation of dispersed drug particles. Water is used as a medium to ensure the formation of a porous dosage form. Collapse protectants like glycine may be used to prevent shrinkage of dosage form during freeze drying and longterm storage.³⁷ If necessary, suspending agents and pH adjusting agents may be used. Preservatives may also be added to prevent microbial growth. Zydis products are packed in blister packs to protect the

formulation from environmental moisture. A secondary moisture proof foil punch is often required as this dosage form is very moisture sensitive. When put into the mouth, Zydis unit quickly disintegrates and dissolves in saliva.

Orasolv technology:

It is CIMA lab's first mouth dissolving formulation. This technology involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet equipments are used for preparation of tablets. Less force of compaction is used for manufacturing so as to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system.

Durasolv technology:

This too has been developed by CIMA labs. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tableting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.

Wowtab technology:

Yamanauchi pharmaceutical company patented this technology. 'wow' means 'without water'. The active ingredients may constitute upto 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldability saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs.

Flashdose Technology:

This technology is patented by Fuisz. This system uses the combination of both Shearform and Ceform technologies in order to mask the bitter taste of the drug. A sugar based matrix, called

'Floss' is used, which is made up of a combination of excipients (crystalline sugars) alone or in combination with drugs. Nurofen meltlet, a new form of Ibuprofen, as a mouth-dissolving tablet is the first commercial product prepared by this technology and launched by Biovail Corporation.

Flashtab technology:

Prographarm labs. have a patent over this technology. In this technology, microgranules of the taste-masked active drug are used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusions pheronisation. All these processes utilize conventional tableting technology. These taste-masked micro crystals of active drug, disintegrating agent, a swelling agent and other excipients like soluble diluents etc are compressed to form a multiparticulate tablet that disintegrates rapidly.

Shearform Technology:

In this technology, a shearform matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. The flowing mass comes out through the spinning head that flings the floss. The produced floss is amorphous in nature. So by various techniques, it is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before recrystallising it.

Ceform technology:

This technology involves preparation of microspheres of the active drug. Drug material alone or in combination with other pharmaceutical substances, and excipients is placed into a precision engineered rapidly spinning machine. The centrifugal force comes into action, which throws the dry drug blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form a sphere, without affecting the drug stability. The microspheres thus formed are compressed into tablets. As the drug and excipients both can be processed simultaneously, it creates a unique micro-environment in which the materials can be incorporated into the microspheres that can alter the characteristics of the drug, such as enhancing solubility and stability.

Nanocrystal technology:

For MDT, 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 nanometers (nm) in diameter, which are produced by milling. For fast 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.