
RECENT TRENDS IN FORMULATION TECHNOLOGY FOR MOUTH DISSOLVING TABLET: AN OVERVIEW

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ABSTRACT

Now day's formulation research is breaking barriers of conventional methods. Recently, MDTs have take over an important position in the market by overcoming previously administration problems and contributing to extension of patient life, which have difficulty in swallowing tablets and capsules. Upon introduction into the mouth, these tablets dissolve/ disintegrate in the mouth without additional water for easy administration of pharmaceutical ingredients. These dosage forms are also used to attain instant a higher concentration of drug in body for immediate actions. These are novel dosage forms which dissolve in mouth cavity within a few seconds. This article attempts at discussing the ideal properties, advantages, limitation, choice of drug candidates, need of formulation, approaches for preparation of MDTs, Patented technologies on MDTs and Evaluation tests of MDTs.

Key Words: Mouth dissolving tablets, fast Dissolving Tablets, Superdisintegrants, patented technology, MDT's, FDT, MD

INTRODUCTION

The concept of Mouth dissolving dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for MDT's has enormously increased during the last decade, particularly for geriatric and pediatric patients who

experience difficulty in swallowing conventional tablets and capsules [1].

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms. Among the dosage

forms developed for facilitating ease of medication, the mouth disintegrating systems have been the favorite of product development scientists [2].

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms [3]. Mouth Dissolving tablets are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Mouth dissolving tablets are also known as "Orodispersible tablets", "Orally disintegrating tablets", "Melt-in-mouth", "Fast dissolving drug delivery", "Rapimelts tablets", "Porous tablets", "Quick dissolving tablets" etc. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia, and Centre for Drug Evaluation and Research (CDER) [4].

Mouth dissolving tablet (MDT)

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3

min. Most of the MDTs include certain super disintegrates and taste masking agents [5].

Ideal properties of Mouth Dissolving Tablets

The MDTs performance is depends on the manufacturing technology and the most necessary property of such a dosage form is the ability of rapidly disintegrating and dispersing or dissolving in the saliva, Therefore there is no need to take water along with MDTs. Important desirable characteristics of these dosage forms includes;

- Should dissolve or disintegrate in the mouth within a few seconds.
- High drug loading should be allowed.
- They should be compatible with taste masking and other excipients.
- The mouth feel should be pleasant.
- After oral administration they should leave minimal or no residue in mouth.
- To withstand the rigors of the manufacturing process and post manufacturing handling, they must have sufficient strength.
- They should be less sensitive to environmental conditions such as humidity and temperature.
- The cost of manufacturing of tablets should be low [6].

The Need for Development of MDTs

The need for Mouth Dissolving drug delivery systems persists due to patient's poor

acceptance and or compliance. Mouth Dissolving dosage forms are particularly suitable for patients, who have inconvenient to swallow traditional tablets and capsules.

These include the following:

Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms

- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water [7].

Advantages of Mouth Dissolving Tablets

- Patient's compliance for disabled bedridden patients and for travelling

and busy people who do not have ready access to water.

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- Good mouth feel property of Mouth Dissolving Drug Delivery System helps to change the basic view of medication drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension.

Limitations of Mouth Dissolving Tablets

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly [8].

Drug selection criteria

The ideal characteristics of a drug for Mouth Dissolving tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for MDT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for MDT [9].

The role of excipients is important in the formulation of Mouth Dissolving tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the

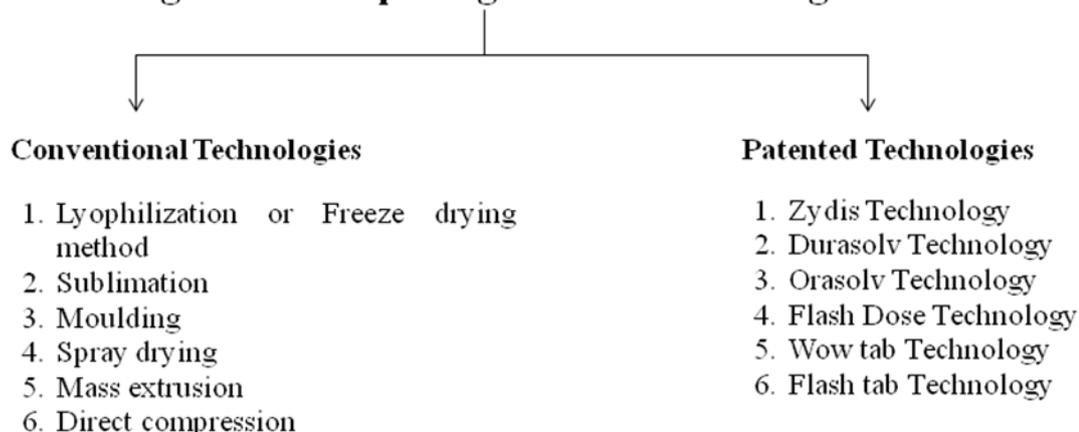
desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Binders keep the composition of these Mouth Dissolving tablets together during the compression stage.

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 [10].

TECHNOLOGIES FOR PREPARING MOUTH DISSOLVING TABLETS

The basic approaches to developing Mouth dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation. Various technologies used in the manufacture of Mouth dissolving tablets include

Technologies For Preparing Mouth Dissolving Tablets



I. Conventional Technologies

1. Lyophilization or Freeze drying method

A process in which water is sublimated from the product after freezing is called as lyophilization. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, and which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolves rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomyacin. Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug on the basis of which US Patent 6,010,719 was granted. Tablets prepared by lyophilization, are fragile and possess low mechanical

strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions [11].

2. Sublimation

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylenetetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix [12].

3. Molding

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent

(usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as *compression molding*.) Then the solvent can be removed by air-drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Recently, the molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as *heat molding*) or by evaporating the solvent from a drug solution or suspension at ambient pressure (*novacuum lyophilization*) [13].

4. Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen *et al.* have reported applying this process to the production of fast dissolving tablets. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatine as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g.,

citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 second in an aqueous medium [14].

5. 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 [15].

6. Direct compression

Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescent agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution.

Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Effective Superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water absorption capacity. Studies revealed that the water insoluble Superdisintegrants like sodium starch glycolate and Croscarmellose sodium show better disintegration property than the slightly water soluble agents like Crospovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants [16].

II. Patented Technologies for Mouth Dissolving Tablets

1. Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or

dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength [17].

2. Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

3. Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine 100 is used to produce the

tablets. The tablets produced are soft and friable [18].

4. Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

5. Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means “Without Water”. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol), granulated with a high mouldability saccharide (eg. Maltose, oligosaccharides) and then compressed into tablet [19].

6. Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists 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 extrusion spheronisation. All the processing utilized conventional tableting technology [20].

EVALUATION OF MOUTH DISSOLVING TABLETS

1. Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using micrometer [21].

2. Weight variation

Standard procedures are followed as described in the official books [22].

3. Friability

Friability Attempts for decreasing the disintegration time increase the friability of MDTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with

each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100$$

4. Hardness (Crushing strength)

Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of MDTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation [23].

5. Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the MDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. Five circular tissue papers of 10cm diameter are placed in a petri dish. Ten milliliters of water soluble dye solution is added to petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For

measuring water absorption ration the weight of the tablet before keeping in the petri dish is noted (Wb). The wetted tablet from the petri dish is taken and reweighed (Wa). The water absorption ratio,

R can be the determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

6. Disintegration time

According to the European pharmacopoeia the fast disintegrating or Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. However it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth.

To overcome these problems, several new methods have been proposed. One of these methods uses a Charge Couple Device (CCD) camera or texture analyzer to evaluate the disintegration time of tablets. In another method, a modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid

that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature at 37°C and a magnetic stirrer. DT is noted at 25 rpm. One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted [24].

7. In vivo disintegration time

In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth.

8. Dissolution test

The dissolution method for oral disintegrating tablets is the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used. The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets.

9. Stability study (Temperature dependent)

The mouth dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) $40 \pm 1^\circ\text{C}$

(ii) $50 \pm 1^\circ\text{C}$

(iii) $37 \pm 1^\circ\text{C}$ and RH $75\% \pm 5\%$

The tablets were withdrawn after 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C [25].

CONCLUSION

Mouth dissolving tablet offer's numerous advantages over conventional dosage forms because of improved efficacy, better patient compliance, and acceptance. Mouth dissolving tablet have characteristic advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in today's scenario of hectic life. Considering the many benefits of Mouth dissolving tablets, a number of formulations are prepared in MDT forms by most of the pharmaceutical companies. By Using the Mouth dissolving tablet the bioavailability of drug and rapid onset can be achieved.

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