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A REVIEW ON MOUTH DISSOLVING TABLET

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ABSTRACT

The demand for MDT (Mouth Disintegrating Tablet) has been increasing from the last decade particularly in geriatric, pediatric and patient with some sort of disabilities in swallowing. MDTs are those tablets which when placed in mouth get dissolved rapidly in saliva without the need of liquid and can be swallowed. European pharmacopoeia adopted the term Orodispersible tablet for MDTs. Mouth disintegrating tablets are also known as Fast melting tablets, Orodispersible tablets, fast dissolving/dispersing tablets or melt in mouth tablets. This article reviews the potential benefits offered by MDTs as an oral drug delivery system for various kinds of patients suffering from different diseases and disabilities. Desired characteristics and challenges for developing fast disintegrating drug delivery systems, quality control tests, various techniques used in the preparation of fast disintegrating drug delivery systems like lyophilization technologies, tablet molding method, sublimation techniques, spray drying techniques, mass extrusion technology, direct compression method and uses of super-disintegrates. It also reviews the patented technologies for fast dissolving tablets, advantages and disadvantages of different technologies for preparing fast disintegrating dosage form, future prospective for MDTs. The growing importance for MDTs is due to the potential advantages offered by this technology. MDT is a New Drug Delivery system with least disintegration time and ease of self administration

INTRODUCTION

Many patients, especially elderly find it difficult in swallowing tablets, capsules, fluids and thus do not comply with prescription, which results in high incidence of non-compliance oriented research has resulted in bringing out many safer and new drug delivery system. Rapidly disintegrating/dissolving tablet is one of such example, for the reason of rapid disintegration or even with saliva. Considering quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the mouth dissolving tablet (MDT) is the most widely preferred commercial products. The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like Tablets, Capsules, and Liquid preparations are administered by oral route. During the last decade, mouth dissolving tablet (MDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention. The MDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All MDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good MDTs varies from several seconds to about a minute. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric population who has difficulty in swallowing conventional tablets and capsules. Additionally

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pediatrics patients may suffer from ingestion problems as results of underdeveloped muscular and nervous control.

Moreover, patients traveling with little or no excess to water, limit utility of orally administer convectional tablet capsule. MDT result in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastrics absorption when formulated as MDTs may show increased oral bioavailability. It provides good stability accurate dosing, and easy manufacturing [1 – 4]

Ideal Properties [2]

An ideal MDT should**:**

1) Require no water for oral administration.
2) Have a pleasing mouth feel.
3) Have an acceptable taste masking property.
4) Be harder and less friable.
5) Leave minimal or no residue in mouth after administration.
6) Exhibit low sensitivity to environmental conditions (temperature and humidity).
7) Allow tablet manufacturing by conventional processing and packaging equipments.

Advantages [3]

1) Administration to the patients who cannot swallow, such as the elderly, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2) Rapid drug therapy intervention.
3) Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
4) Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
5) The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
6) New business opportunity will be getting generated due to the product differentiation.

Salient Features [4]

1) Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients.
2) Convenience of administration and accurate dosing as compared to liquids.
3) Rapid dissolution of drug and absorption which may produce rapid, onset of action.
4) Some drugs are absorbed from the pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
5) Ability to provide advantages of liquid medication in the form of solid preparation.
6) Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

Limitations of Mouth Dissolving Tablets [4]**:**

1) The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2) The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
3) Drugs with relatively larger doses are difficult to formulate into MDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
4) Patients who concurrently take anticholinergic medications may not be the best candidates for MDT. Similarly patients with dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Desired characteristics and challenges for developing fast disintegrating drug delivery systems:

1) Time required for disintegration
2) MDTs should disintegrate/dissolve/disperse or melt in mouth without the need of water in very short duration of time, possibly within 60 seconds.
3) Taste of the active ingredient
4) As most drugs are unpalatable, fast disintegrating drug delivery systems usually contain the medicament in taste-masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.
5) **Tablet strength, Friability and porosity:** In order to allow fast disintegrating tablets to disintegrate in the mouth, they are made of either very porous or soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are

difficult to handle, often requiring specialized peel-off blister packaging.

6) Hygroscopic nature: Several fast disintegrating drug delivery dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

7) Mouth feel: Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product [5].

Various techniques used in the preparation of mouth disintegrating drug delivery systems

1) Freeze–drying (Lyophilization technologies)
2) Tablet molding method
3) Sublimation techniques
4) Spray drying techniques
5) Mass extrusion technology
6) Direct compression method
7) Use of disintegrates

1) Freeze drying or Lyophilization technology

A process by which, water get sublimated from product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allows removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability [6, 7]. R. P. Scherer patented Zydis technology by employing freeze drying process for the preparation of mouth dissolving tablet. On the basis of patent issued to Gregory *et al.* [8] Seager discussed formation, process technology & bioavailability of fast dissolving tablets prepared by using Zydis technology [8].

2) Molding method

Moulded tablets are prepared by using water-soluble ingredients so that the tablet dissolve or disintegrate rapidly and completely. Powder is moistened with the help of hydro alcoholic solvent and then moulded into tablets under pressure less than the conventional dosage form. The solvents are removed by air-drying. The tablet Possesses porous structure, which facilitates easy dissolution. Adding sucrose, acacia or PVP k30 may increase the mechanical strength of tablet [6, 7].

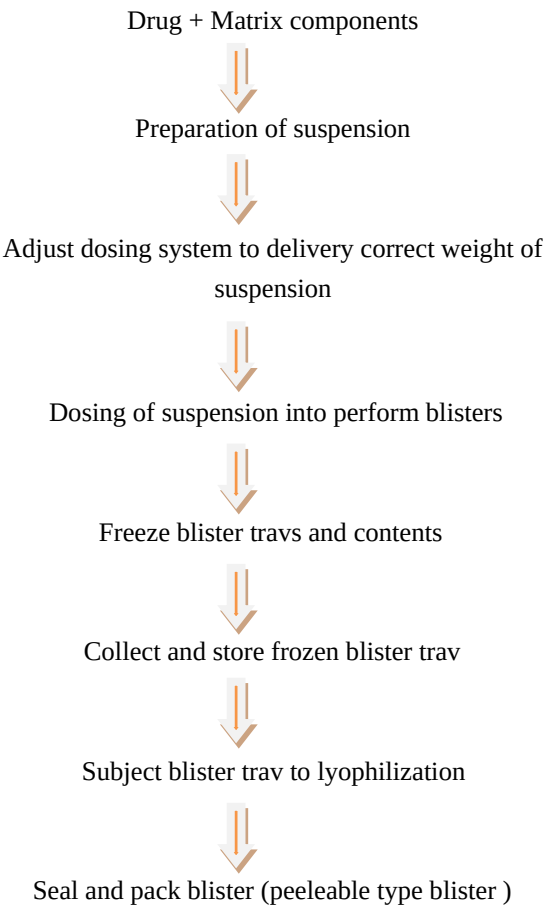

Figure 1: Steps involved in freeze drying technology

3) Sublimation method

The basic principle involved in preparing fast dissolving tablets by sublimation technique is addition of a volatile salt to the tableting components, mixing the components to obtain a substantially homogeneous mixture & volatizing a volatile salt. The removal of volatile salts creates pores in the tablet, which help in achieving rapid disintegration when the tablet comes in contact with saliva. Camphor, Naphthalene, Urea, ammonium bicarbonate, etc, can be used to prepare porous tablets of good mechanical strength [6-7]. Koizumi *et al.* used mannitol as diluent and camphor as a volatile material to prepare porous compressed tablets [9]. The tablets were subjected to vacuum at 80°C for 30 min to eliminate the camphor and thus form the

pores in the tablet. Makino *et. al* utilized water as a pore forming material in order to prepare porous tablets with excellent mechanical strength & dissolution character [6-7, 9].

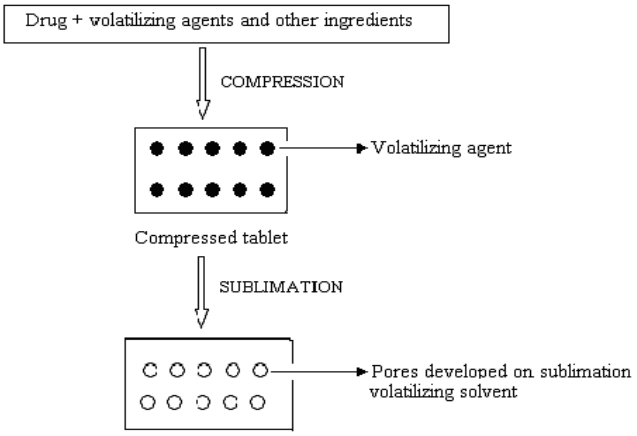

Figure No. 2: Steps involved in sublimation technology

3) Spray drying method

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 [10]. Spray Drying can be used to prepare rapidly dissolving tablet. This technique is based upon a particulate support matrix that is prepared by spray drying and aqueous composition containing support matrix and other components to form a highly porous & fine powder. This is then mixed with active ingredient & compressed into tablet. Fast dissolving tablet prepared by spray drying technique disintegrated within 20 seconds [6-7, 10].

Patented technologies for mouth dissolving tablets [11]

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 materials 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. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in 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 in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment [11].

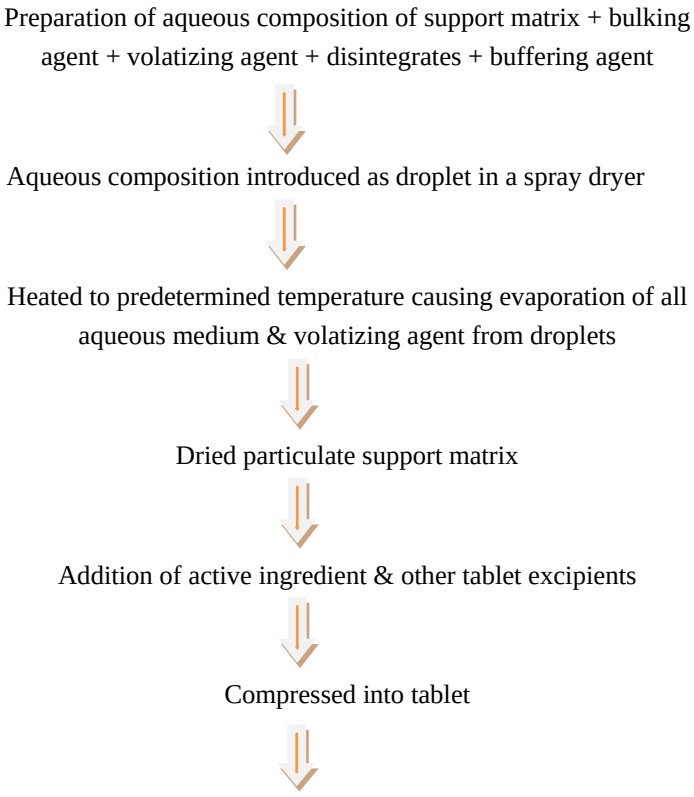

Figure No. 3 Steps Involved spray drying method

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 tabletting equipment and have goodrigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients [11]

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 is used to produce the tablets. The tablets produced are soft and friable [11].

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 selfbinding shear form matrix termed as "floss".Shear form matrices are prepared byWOW 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 (e.g. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides) [11]

5) 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 tablet technology [11]

Super Disintegrants Used in MDTs

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Super disintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. This super disintegrants act by swelling and 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 [12]. Various types of Super disintegrants used are as follows –

1) Crosspovidone
2) Microcrystalline cellulose
3) Sodium starch glycollate
4) Sodium carboxy methyl cellulose /Cross carmelose sodium
5) Crosscarmellose sodium
6) Calcium carboxy methyl cellulose
7) Modified corn starch
8) Kyron

Factors to be considered for selection of super disintegrants [12]

1. It should produce mouth dissolving when tablet meets saliva in the mouth
2. It should be compactable enough to produce lessfriable tablets. It can able to produce good mouth feel to the patient. Thus, small particle size is preferred to achieve patient compliance.
3. It should have good flow since it improve the flowability of the total blend.

Evaluation of mouth dissolving tablets [13, 14]

MDTs formulations have to be evaluated for the following evaluation test.

1) General Appearance: The general appearance of tablets includes size, shape, color, taste, odour, surface texture.

2) Size, Shape, Thickness and diameter: The size and shape of the tablet can be dimensionally described, monitored and controlled. Thickness of tablets is an important characteristic for appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets should be taken and their thickness is required to measure by vernier caliper.

3) Uniformity of weight: In Indian pharmacopoeia procedure for uniformity of weight was followed, ten or twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. Then the average weight of one tablet is required to be finding out from collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

4) Hardness of tablets: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. Resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto hardness tester.

5) Friability of tablets: Friabilator consist of plastic chamber revolves at 25 rpm, dropping those tablets at distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 min. At the end of these test tablets are required to be dedusted and reweighed, the loss in the

weight of tablet is the measured of friability and is expressed in percentage as

$$\%friability = \frac{initial\ weight - final\ weight}{Initial\ weight} \times 100$$

6) **Disintegration time:** As described in pharmacopoeia, tablets are placed in the disintegration tube and time is noted. According to the European pharmacopoeia the fast disintegration or orodispersible tablets should disintegrate within 3 min without leaving any residue on the screen.

7) ***In-vitro* dispersion time test:** To determine dispersion time take a 10ml of measuring cylinder and pour a 6ml of distill water in it, then drop a tablet in the same. Finally the time required for complete dispersion was determined as a dispersion time.

8) **Wetting time:** Take five circular tissue papers of 10 cm diameter and placed them in a petridish with a 10 cm diameter. Ten millimeters of watercontaining Eosin, a water-soluble dye, is required to add in petridish. Then place a tablet carefully on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

9) **Water absorption ratio:** Fold a piece of tissue paper twice and place it in a small Petri dish containing 6 ml of water. Place a tablet on the paper & record the time required for complete wetting. Then note down the weight of a wetted tablet. Finally water absorption ratio (R), is find out using the following equation,

$$R = 10\left(\frac{W_a}{W_b}\right)$$

Where- W_b is weight of tablet before water absorption & W_a is weight of tablet after water absorption

10) ***In vitro* dissolution test:** *In vitro* dissolution study has to be performed by using USP type II Apparatus (paddle type) [Electrolab (ETC -11L) Tablet dissolution tester] at 50 rpm. Phosphate buffer pH 6.8, 900 ml is mainly used as dissolution medium which is required to maintain at 37±0.5°C. Aliquot of (10ml) dissolution medium is required to withdraw out at specific time interval (2min) and then it is required to subject for process of filtration. The amount of drug dissolved was determined by UV Spectrophotometer (Shimadzu, japan) by measuring the absorbance of the sample. Three trials of each batch were performed and average % drug release with standard deviation was calculated and recorded.

11) **Accelerated Stability study:** The Orally disintegrating 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 ± 1°C
    (ii) 50 ± 1°C
    (iii) 37 ± 1°C and Relative Humidity= 75% ± 5%

Withdraw the tablets after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C [15]

Future Prospective for MDTs

Now there are various products available commercially in market which is produced by fast dissolving tablet technologies. Still there is wide area for research on this technology. Some of the challenges like formulating a drug of bitter taste and moisture absorbing nature create problems for formulation scientist. When the dose of drug is large it causes problem of increased disintegration time. The two points to be considered in case of MDTs are shortening. Future prospective with continued innovations in pharmaceutical excipients, one can expect the emergence of more novel technologies for MDTs in the days to come. These innovations may involve modifying formulation composition and processing to achieve new performance end-points or the merger of new technological advances with traditional pharmaceutical processing techniques for the production of novel mouth dissolving dosage forms.

It is reasonable to expect that future trends in innovations of drug delivery systems will continue to bring together different technological disciplines to create novel technologies.he disintegration time at the same time keeping other parameters like friability, taste, and mouth feel and tablet strength within the accepted range. Using taste masking agents and super-disintegrating agents without significant increase in the weight & volume of final dosage forms. Also, there is a scope to

develop better packaging system to make FDTs more stable during handling.

CONCLUSION

The MDTs have potential advantages over conventional dosage forms, with their improved patient compliance, convenience, bioavailability and rapid onset of action had drawn the attention of many manufactures over a decade. MDTs formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. There is a clear opportunity for new enhanced oral products arising within this market segment. Approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness.. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally within <60 seconds (range of 5- 50seconds). The development of a fast-dissolving tablet also provides an opportunity for a line extension in the marketplace; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage form. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form.

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