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MOUTH DISSOLVING TABLETS: AN OVERVIEW OF FORMULATION TECHNOLOGY

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ABSTRACT

Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Several techniques have been developed in the recent past, to improve the disintegration quality of these delicate dosage forms without affecting their integrity. Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems. MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, generally within <60 Seconds without the need of water, thus obviating the requirement of water during administration. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true mouth-dissolving tablets. Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients, patients who are uncooperative, and for active patients who are busy and traveling and may not have access to water. This article focuses on the technologies available and the advances made so far in the field of fabrication of mouth dissolving tablets. Apart from the conventional methods of fabrication, this review also provides the detailed concept with their advantages and limitations.

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

INTRODUCTION:[1-2]

Mouth dissolving tablets are also called as Fast-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. 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 significantly greater than those observed from conventional tablets dosage form.

United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) define orally disintegrating tablets in the 'Orange Book' as "**A solid dosage form which contain a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue".**

European Pharmacopoeia described orally disintegrating tablets as "**uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 min"**

REQUIREMENTS OF MDT:[3]

An ideal MDT should[6]

- Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet usi ng conventional processing and packaging equipments.

ADVANTAGES OF MDT[4, 6.]

- Administration to the patients who can't swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.

- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

SALIENT FEATURES OF MOUTH DISSOLVING DRUG DELIVERY SYSTEM: (MDDDS)[5]

- Ease of administration to patients who refuse to swallow a tablet, such as pediatrics and geriatric patients and, psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feels properly of MDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Rapid dissolution of drug and absorption which may produce rapid, onset of action.
- Some drugs are absorbed from the month pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid preparation.

LIMITATIONS OF MDT:

- 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 property.

TECHNIQUES OF MDT FORMULATION: [6-8]

The Mouth-dissolving property of the MDTs is attributed to quick ingress of water into tablet
matrix resulting in rapid disintegration. Hence, the basic approaches to develop MDTs
include:

- Maximizing the porous structure of the tablet matrix.
- Incorporating the appropriate disintegrating agent/agents.
- Using highly water-soluble excipients in the formulation

Various manufacturing techniques for MDDDS include:

a. Lyophilization/Freeze drying
b. Moulding
c. Sublimation
d. Spray Drying
e. Mass Extrusion
f. Nanonization
g. Direct Compression
h. Cotton Candy Process
i. Fast Dissolving Films

a) Freeze-Drying or Lyophilization

In freeze-drying process, the water is sublimed from the product after it is frozen. This technique forms the basis of

Zydis, Quicksolv and Lyoc technologies which are used to manufacture MDTs.
The process involves the following steps:

Stage 1 - Bulk preparation of an aqueous drug solution or suspension and its subsequent precise dosing into pre-formed blisters. It is the blister that actually forms the tablet shape and is, therefore, an integral component of the total product package.

Stage 2 - Passing the filled blisters through a specially designed cryogenic freezing process to control the ultimate size of the ice crystals which ensures that the tablets possess a porous matrix to facilitate the rapid disintegration property. These frozen units are then transferred to large-scale freeze dryers for the sublimation process, where the majority of the remaining moisture is removed from the tablets.

Stage 3 - Sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions.

Excipients-

- MDTs manufactured using lyophilization process, usually contain excipients like **polymers**(e.g., gelatin, alginates and dextrin) to provide strength and rigidity to tablets;
- **polysaccharides** (e.g., mannitol and sorbitol) to impart crystallinity and hardness to the matrix and to improve palatability;
- **collapse protectants** (e.g., glycine) to prevent the product from shrinking in its packaging during manufacturing or storage;
- **flocculating agents** (e.g., xanthan gum and acacia) to provide uniform dispersion of drug particles;
- **preservatives** (e.g. parabens) to prevent microbial growth;
- **permeation enhancers** (e.g. sodium lauryl sulfate) to improve transmucosal permeability
- **pH adjusters** (e.g. **citric acid etc.) to optimize chemical stability;**
- **flavors** and sweeteners to improve patient compliance and
- **Water** to ensure formation of porous units.

Advantages-

The major advantage of using this technique is that the tablets produced by this technology have very low disintegration time and have great mouth feel due to fast melting effect.

Disadvantages-

Although being a fairly routine process, lyophilization has some disadvantages like it is a relatively expensive and time consuming process. Furthermore, the product obtained is poorly stable and fragile, rendering conventional packaging unsuitable.

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b) Moulding[14-16]

Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly. Following are the different tablet moulding techniques-

Compression Moulding Process

This manufacturing process involves moistening the powder blend with a hydro-alcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution [15].

Heat-Moulding Process

Heat-moulding process involves setting the molten mass containing a dispersed drug [29].This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C under vacuum.

c) Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammo nium bicarbonate, hexa methelene tetramine, camphor etc.) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. Additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents,

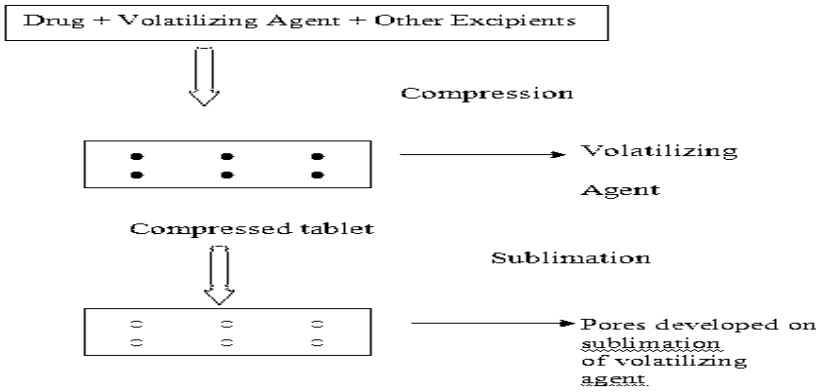


Fig.1 – Steps Involved in sublimation

d) Spray-Drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

e) Mass-Extrusion[10]

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

f) Nanonization[13]

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling

technique [62]. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs. 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 doses (up to 200mg of drug per unit)

g) Direct Compression[6-8]

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent.

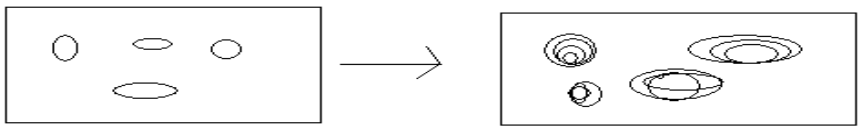
(a) Superdisintegrants[7]
(b) Sugar Based Excipients:

a) Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of
Superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration. Demand for faster disintegrating formulation is increased now a days that is superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But they have one drawback that it is hygroscopic in nature thus cannot be used with moisture sensitive drugs.

Mechanism of action:

Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes the tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.



Granules with Superdisintegrants.

Swelling of granules due to superdisintegrants.. in aqueous media.

A) Crosscarmellose 1)Ac-Di-Sol 2)Nymce ZSK 3)Primellose 4)Solutab 5)Vivasol	-swells 4-8 folds in <10 sec. - Swelling,wicking both	-swells in two dimensions -Direct compression or granulation -starch free
B) Crosspovidone 1)Crosspovidon M 2)Kollidon 3)Polyplasdone	----	- Water insoluble and spongy in nature so get porous tablet
C) Sodium starch glycolate 1)Explotab 2)Primogel	- swells 7-12 folds in < 30 seconds	- swells in three dimensions and high level serve as sustain release matrix
D) Alginic acid NF 1)Satialgine	-Rapid swelling in aqueous medium or wicking action.	-promote disintegration in both dry or wet granulation
E) Soy polysaccharides 1)Emcosoy	----	-does not contain any starch or sugar. Used in nutritional products.
F) Calcium silicate	- Wicking action	- highly porous - light weight -Optimum concentration between 20 – 40 %
G) Ion Exchange Resin 1)Indion 414	Remarkable swelling tendency -No lump formation	-free from organic matter -optimum concentration between 0.5-2%

MECHANISM OF TABLET DISINTEGRANTS[4]

The tablet breaks to primary particles by one or more of the mechanisms listed below

- By capillary action
- By swelling
- Because of heat of wetting
- Due to disintegrating particle/particle repulsive forces.
- Due to deformation
- Due to release of gases
- By enzymatic action

1) 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.

2) By Swelling: It's the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack or adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worth while to note that if the packing fraction is very high, fluid is enable to penetrate in the tablet and the disintegration again slows down.

3) 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.

4) Due To Disintegrating Particle/Particle Repulsive Forces: Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

5) Due To Deformation: Disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. This increase in size of the deformed particles produces a break up of the tablet.

6) Due To Release Of Gases: Carbon dioxide is 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.

7) By Enzymatic Action: Enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration

ENZYMES	BINDER
Amylase	Starch
Protease	Gelatin

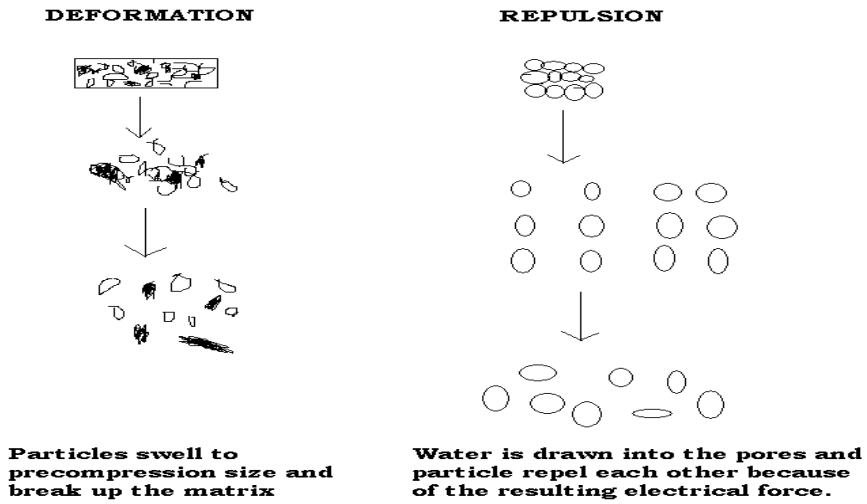


Fig.2 Disintegration by deformation

(b) Sugar Based Excipients:[11]

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose,mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides: (lactose and mannitol) exhibit low mouldability but high dissolution rate.
Type 2 saccharides: (maltose and maltilol) exhibit high mouldability and low dissolution rate.

EVALUATION OF MDT[7-8]

Tablets from all the formulation were subjected to following quality control test.

General Appearance: The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.

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. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Average weight of Tablets (mg)	Maximum percentage different allowed
130 or less	10
130-324	7.5
More than 324	5

Tablet hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The 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.

Friability

It is measured of mechanical strength of tablets. Roche fribaiator was used to determine the friability by following procedure. A preweighed tablet was placed in the fribaiator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

%Friability = loss in weight / Initial weight x 100

In Vivo Disintegration test

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass

remaining in the apparatus was measured in seconds.

Wetting time

The method reported by yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation was also determined.

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

CONCLUSION:

There is a clear opportunity for new enhanced oral products arising within this market 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. It is developing a novel, cost effective one step MDDT manufacturing process using conventional tabletting technology. This proprietary technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. 'super generics' for veterinary or human application.

A new tablet dosage format, the mouth dissolving tablet has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally within <60 seconds (range of 5-50seconds). Due to the constraints of the current MDDT technologies as highlighted above, there is an unmet need for improved manufacturing processes for mouth dissolving tablets that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets. To fulfill these medical needs, formulators have devoted considerable effort to developing a novel type of tablet dosage form for oral administration, one that disintegrates and dissolves rapidly in saliva without the need for drinking water. The development of a mouth-dissolving tablet also provides an opportunity for a line extension in the marketplace. Pharmaceutical marketing is another reason for the increase in available mouth-dissolving/disintegrating products. 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. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, mouth-dissolving/disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer.

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.

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