A COMPREHENSIVE REVIEW: ON MOUTH DISSOLVING TABLET

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Abstract:

Over the past few decades, tendency towards innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. pediatrics and geriatrics is orally disintegrating films (MDT). These fast disintegrating films have superiority over fast disintegrating tablets as the latter are associated with the risks of choking and friability. This drug delivery system has numerous advantages over conventional fast disintegrating tablets as they can be used for dysphasic and schizophrenic patients and are taken without water due to their ability to disintegrate within a few seconds releasing medication in mouth. Mouth Dissolving Tablets (MDT) have emerged as a promising class of tablets designed to rapidly disintegrate or dissolve in saliva, providing a convenient and patient-friendly alternative for various populations. This article explores the unique properties, advantages, and potential applications of MDT, emphasizing their role in overcoming challenges posed by conventional oral drug delivery systems. MDT offer rapid dissolution within 15-120 seconds in the buccal cavity, facilitating direct absorption through the buccal mucosa and ensuring quick therapeutic effects. This characteristic proves particularly beneficial for individuals facing swallowing challenges, such as pediatric and geriatric patients, or those with conditions like dysphagia. Recognizing the significance of FDTs, the European Pharmacopoeia (EP) has officially recognized them as “oral dissolving tablets," highlighting their acceptance in both academic and industrial settings. The article delves into the anatomical and physiological characteristics of the oral cavity, shedding light on the buccal epithelium, oral mucosa vascularization, and salivary flow, which play crucial roles in drug absorption.

Keywords: MDT, Lyophilization, Cotton Candy Process, Three-dimensional Printing, 4. Hausner Ratio.

Introduction

Mouth dissolving Tablet, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal.[1] Oral route is commonly used route for the delivery of the drugs till date as it bears various advantages over the other route of drug delivery, but oral drug delivery systems still a date need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. [2] Many pediatric and geriatric patients who having difficulty in swallowing are unwilling to take solid preparations as a result of concern of choking. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as another to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. [3] It was developed on the basis of technology of the transdermal patch. [4] The fast dissolving drug delivery system consists of a very thin strip that is just placed on the patient's tongue or any oral mucosal tissue, instantly wet by secretion the film rapidly hydrates and adheres onto the location. [5] It then quickly disintegrates and dissolves to release the drug for oromucosal and intragastric absorption. Mouth dissolving Tablet offers an elegant route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also, large surface areas of absorption, easy ingestion and swallowing, pain avoidance make the oral mucosa a very attractive and selective site for systemic drug delivery. [6] Recent developments in the technology have presented viable dosage alternatives from oral route for wide variety of group of patients. Mouth dissolving film has become an important route of drug administration for giving the therapeutics effects. [7]

IDEAL CHARACTERISIC

1. Mouth Dissolving Tablet should be stable to guarantee a robust manufacturing and packaging process and ease of handling and administration. [8]
2. The Tablet should be transportable, not tacky and keep a plane form without rolling up.

3. Require no water for oral administration, yet dissolve / disperse/ disintegrate in mouth in a matter of seconds. [9]
4. It should allow high drug loading.
5. They should have ability to provide advantages of liquid medication in the form of solid film preparation.
6. Excellent mucoadhesion property [10]
7. Fast disintegration rate and rapid release
8. Should allow the manufacture of tablet using conventional processing and packaging equipments
9. It should be partially ionized at the PH of oral cavity. [11]

ADVANTAGES OF MOUTH DISSOLVING TABLETS

1. Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients.[12]
2. Patient‘s compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
3. Convenience of administration and accurate dosing as compared to liquid formulations.
4. Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
5. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
6. Beneficial in cases such as motion sickness (kinetosis), sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required.[13]
7. New business opportunities: product differentiation, line extension and lifecycle management, exclusivity of product promotion and patent-life extension.[14]

TECHNIQUES FOR PREPARING MOUTH DISSOLVING TABLETS

These are the following method to prepare the MDT

1. Freeze drying/Lyophilization

2. Molding

3. Direct Compression

4. Cotton Candy Process

5. Spray drying

6. Sublimation

7. Mass Extrusion

8. Melt granulation

9. Nanonization

10. Fast Dissolving Films

11. Phase Transition Process

12.Three-dimensional Printing (3DP)

1. Lyophilization or Freeze-Drying:

A process in which water is sublimated from the product after freezing is called freeze drying. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze- drying technique has demonstrated improved absorption and increase in bioavailability.[15]

2. Tablet Molding

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and

sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 300C under vacuum.[16]

3. Direct Compression:

Direct compression represents the simplest and most cost effective tablet manufacturing technique. MDT can be prepared by using this technique because of the availability of improved excipients especially super-disintegrate and sugar based excipients.[17]

(a) Super-disintegrants:

The rate of disintegration gets affected by the addition of superdisintegrants and hence the dissolution.

(b) Sugar based excipients:

The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel. Mizumito et al 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 but low dissolution rate.[18]

4. Cotton Candy Process:

Another technology for manufacturing fast dissolving tablets is the cotton candy process, also known as candy floss process, which involves centrifugation to produce a floss-like crystalline structure. In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shear foam process. The matrix is cured and milled to make flowable, compactible, and highly soluble filler. Because of the formation of the formation of porous threedimensional structures with the active ingredients encased in the pores, the resulting surface area is high. Therefore, dispersion and dissolution occur quickly when the product is placed in the mouth. This technology is patented as FlashDose® by Fuisz Technology (Chantilly, Virgina, U.S.A.).[19]

5. Sprays-Drying:

Allen et al., have used spray-drying for the production of MDTs. The formulations contained

hydrolyzed and non hydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. By adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate) disintegration and dissolution were further enhanced. The porous powder was obtained by spray drying the above suspension which was compressed into tablets. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium.[20]

6. Sublimation:

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva [21]

. Granules

containing nimusulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure [22]

. Conventional

methods like dry granulation, wet granulation and direct compression with highly soluble excipients, super disintegrants and/or effervescent systems can also be used.[23]

7. Mass Extrusion:

This technology involves softening the active blend using the solvent mixture of water olublepolyethylene 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.[24]

8. Melt Granulation:

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water soluble drugs, such as griseofulvin This approach to prepare MDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilizes rapidly leaving no residues.[25]

9. Nanonization:

A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (up to 200 mg of drug per unit).[26]

10. Fast Dissolving Tablet:

It is a newer developing front that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, CMC, HPMC, HEC, HPC, PVP, PVA etc.), drug and other taste masking ingredients are dissolved in non-aqueous solvent to prepare non-aqueous solution, which on evaporation of solvent forms a film. Resin adsorbate or coated micro particles of the drug can be incorporated into the film if the drug is bitter. This film when placed in mouth melts or dissolves rapidly and releases the drug in solution or suspension form. This system forms the thin films of size less than 2x2 inches which dissolves within 5 sec with instant drug delivery and flavored taste.[27]

11. Phase Transition Process:

Kuno et. al., investigated processes for the disintegration of MDTs by phase transition of sugar alcohols using erythritol (m. pt. 122°C), xylitol (m.pt. 93-95°C), trehalose (97°C), and mannitol

(166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting

points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.[28]

12. Three-dimensional Printing (3DP):

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system

Table 1: Some of the important patented technologies for preparation of MDTs

S.No	Technique	Novelty	Advantages
1	Zydis	First to market, Freeze Dried [36]	Quick dissolution, Self-preserving and Increased bioavailability
2	Orasolv	Unique taste-masking, lightly compressed [37]	Taste-masking is twofold, quick dissolution
3	Durasolv	Compressed dosage form, Proprietary taste Masking	Higher mechanical strength than Orasolv, Good rigidity
4	Wowtab	Combination of low mouldability and high Mouldability saccharides. SMOOTHMELT action gives superior mouth fee [38]	Adequate dissolution rate and hardness
5	Oraquick	Uses patented taste masking technology	Faster and efficient production

Table 2: List of patented technologies and their products

S.No	Technology	Process Involved	Patent Owner	Drugs Used (Brand Name)	Drug Release
1	Zydis	Lyophillization	R.P. Scherer Inc. [38]	Loratidine Cisapride	Dissolves in 2-10 sec.
2	Quicksolv	Lyophillization	Jansen Pharmaceuticals [39]	Cisapride monohydrate	Dissolves in 2-10 sec.
3	Flashtab	Lyophillization	Ethypharm	Ibuprofen	Dissolves within 1 min.

Evaluation Parameters

1. Angle of Repose (θ)

The frictional forces in case of loose powder are measured by the angle of repose. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by funnel method. Angle of Repose was calculated using the formula.[40]

$$\tan \theta = 2h/d$$

Where : θ = Angle of repose, H = height of the pile (cms),

r = radius of heap (plane surface occupied by the powder)

Sr no.	Angle of Repose(°)	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-40	Passable
4	>40	Very Poor

2. Bulk Density (Db)

It is the ratio of total mass of powder (M) to the bulk volume (Vb). Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight “as it is”. Bulk density (expressed in gm/ml) was calculated according to formula mentioned below [40]

Db = M/ Vb

Where, M = Mass of the Powder Vb= Bulk volume of the powder

3. Tapped Density (Dt)

It is the ratio of total mass of powder to the taped volume of powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 seconds interval.[41] The tapping was continued until no further change in volume was noted. Tapped density (expressed in gm/ml) was calculated according to formula mentioned below: Dt = M/Vt Where, M = Mass of the Powder Vt = Tapped volume of the powder

4. Carr’s Index (Carr’s Consolidation Index)

It indicates the powder flow properties. It is expressed in percentage and is given by formula: % compressibility (I) = [Tapped density – Bulk density/ Tapped density] x 100 43. shows the relationship between % compressibility and Flowability. [42]

4. Hausner Ratio

It is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner ratio= Tapped density/ Bulk density Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25)

5. Porosity

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by [43]

€= Vb - Vp/ Vp =1- Vp/ Vb

Porosity is frequently expressed in percentage and is given as: % € = (1 - Vp/ Vb) X 100

6. Dissolution test

The development of dissolution method for MDT is comparable to approach taken for conventional tablets and is practically identical when MDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1NHcl, pH 4.5 and pH 6.8 buffers should be used for evaluation of MDT.[44] Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of MDT tablets, where a paddle speed of 50 rpm is commonly used. The USP 1 (basket) apparatus may have certain applications for MDT but used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile.[45]

7. Friability

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for MDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time.[46] This test is again not applicable for lyophilized and flash dose tablets, but is always recommended for tablets prepared by direct compression and molding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

8. Disintegration time

The methods for evaluation of in-vivo disintegration time had been explained in literature28-30. However, the results from this type of test typically reveal unsatisfactory reproducibility and are not reliable as the difference in disintegration time is few seconds in most cases. In addition, the in-vivo disintegration test has its own limitation of issues related to ethics and the safety of the volunteers.[47] At present, the disintegration time of MDTs is measured using the disintegration test for conventional tablets that is described in the Pharmacopoeias. EP has set the limit of 3 mins for disintegration time of MDTs using conventional disintegration apparatus. However, no special apparatus is mentioned in the pharmacopoeias for disintegration test of MDTs and the conventional method available seems to be inappropriate for MDTs. This is because of the extreme operating conditions in the disintegration apparatus which fails to provide a significant discrimination among the rapidly disintegrating tablets.[48] Furthermore, the conventional test employs a relatively huge volume of test solution (900 ml) compared to the volume of saliva in human buccal cavity, which is less than 6 ml.[49]

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