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Review Article

Mouth Dissolving Tablet: A Review

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Abstract

Oral route is the most common and safest route of drug delivery but possessing certain limitations like poor bioavailability, delayed action and difficulty in swallowing to old persons and children. Since last decades novel drug delivery system is the widely used technique in oral drug delivery one of such technique is the mouth dissolving tablet which disintegrates and dissolves rapidly in mouth after coming in contact with saliva without the need of swallowing and minimizing the side effects of oral conventional tablet. The aim of present review was to focus on various approaches in formulation techniques along with the recent advances so far for mouth dissolving tablet, evaluation parameters, patented technologies and various preparations available in the market. The future trends in innovations of drug delivery will continue to bring together technological disciplines and formulation aspects to create novel technologies

Keywords: Mouth dissolving tablet, Formulation technology, Evaluation parameters, MDT

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1. Introduction

Oral drug delivery is the most preferred route for drug administration due to advantages like ease of administration, Safe, economical, accurate dosage, self- medication, pain avoidance, and patient compliance, apart from these advantages the oral delivery has certain disadvantages like delayed effect, difficulty in swallowing to old persons and children and low bioavailability (due to hepatic first pass effect) these disadvantages can be minimized by formulating the drug into mouth dissolving tablet which disintegrates and dissolves in oral cavity after coming in contact with saliva.(1) The oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of langerhans cells makes oral mucosa tolerant to potential allergens.(2)

1.1. Oral Mucosa(3)

The oral cavity comprises the lips, cheeks, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as oral mucosa and includes buccal, sublingual, gingival, palatal and labial mucosa. Oral mucosa also comprises many sensory receptors including the taste receptors of the tongue.

The blood supply of the buccal mucosa originates primarily from:

- The buccal artery - a branch of the maxillary artery
- The anterior superior alveolar artery of the infraorbital artery - a branch of the third part of the maxillary artery
- The middle and posterior superior alveolar arteries - branches of the maxillary artery
- Accessory vessels from the transverse facial artery - a branch of the superficial temporal artery**.**

1.2. Saliva

Saliva is the fluid present in the mouth. It consists of approximately 99% water, containing number of electrolytes and proteins. The total content of salivary fluid is 1-3 ml. at rest, without exogenous or pharmacological stimulation, there is small continuous salivary flow (SF), denominated basal unstimulated secretion, present in the form of a film that covers, moisturizes and lubricates the oral tissues. A healthy person's mean daily saliva production ranges from 1-5 L. In adults normal total stimulated SF ranges from 1-3 ml/min. the normal salivary pH is from 6-7. (4)

2. Mouth Dissolving Tablet

These are novel types of tablets that disintegrate / disperse /dissolve in saliva within few seconds without water. Mouth dissolving tablets are also called as orodispersible tablets(ODTs), fast disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets.(5) US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the „Orange Book", an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"**.** According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem**.** These dosage forms disintegrate/dissolve in oral cavity within a minute without need of water or chewing. (6)

2.1. Advantages (7)

1. No need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. Accurate dosing as compared to liquids.
4. Dissolution and absorption of drug is fast, offering rapid onset of action.
5. No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance
6. Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.
7. No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.
8. Good mouth feels, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.
9. No specific packaging required. It can be packaged in push through blisters.
10. Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

2.2. Disadvantages

1. The tablets usually have insufficient mechanical strength. So, 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
4. amoxicillin with adult dose tablet containing about 500 mg of the drug.(8)
5. Patients who concurrently take anticholinergic medications & patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.(9)

2.3. Ideal properties of MDTs

They should (10)

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Allow high drug loading.
- Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.

- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

2.4. Selection of Drugs: (11)

The ideal characteristics of a drug for in vivo dissolution from an ODT include:

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

2.5. Formulation Techniques

1. Lyophilization
2. Moulding
3. Direct Compression
4. Cotton Candy Process
5. Spray Drying
6. Sublimation
7. Mass Extrusion
8. Nanonization
9. Fast Dissolving Films

2.5.1. Freeze-Drying or Lyophilization (10)

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. Thirteen products are currently available in the market, which had been manufactured using this technology. In U.S., the MDT products available are: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt- MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. In the worldwide market, Zydis formulations are also available for oxazepam, lorazepam, loperamide, and enalapril. ZT utilizes a unique freeze-drying process to manufacture finished dosage units which significantly differ from conventional oral systems. 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. Lyoc is a porous and solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus Its unusual properties are the result of its unique method of preparation, which involves freezing a thickened (paste like) emulsion containing the active as bulk or as coated microparticles. This product is capable of accommodating high dose and disintegrates rapidly but possesses poor mechanical strength.

Quicksolv is a porous solid form obtained by freezing an aqueous dispersion/solution of the drug containing matrix and then drying it by removing the water using excess of alcohol (solvent extraction). The final form disintegrates very rapidly but is limited to low drug content and can be used only for those drugs that are insoluble in the extraction solvent. The ideal drug characteristics required for this technology are relative low aqueous solubility, fine particle size < 50 μm and good aqueous stability in the suspension.

The maximum drug loading capacity for water insoluble and soluble drugs are 400 mg and 60 mg, respectively. The primary problems associated with water soluble drugs are the formation of eutectic mixtures resulting in freezing-point depression and the formation of a glassy solid on freezing which might collapse on drying due to loss of supporting structure during sublimation process.

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 mouthfeel 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.

2.5.2. Tablet Moulding (10)

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

2.5.2.1. Compression Moulding Process

This manufacturing process involves moistening the powder blend with a hydroalcoholic 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.

2.5.2.2. Heat-Moulding Process

Heat-moulding process involves setting the molten mass containing a dispersed drug. 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.

2.5.2.3. Moulding by Vacuum Evaporation without Lyophilization

This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process. Unlike lyophilization, vacuum drying helps to densify the matrix and thereby improves the mechanical strength of the product. Pebley et al. evaporated the frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol or maltodextrin) and solvent in a tablet-shaped mould to design a MDT with a disintegration time of about 20– 60 secs. Tablets produced by moulding are solid dispersions. The drug, depending on its solubility in the carrier, exists either as discrete particles or microparticles dispersed in the matrix and is dissolved totally/partially to form a solid solution/dispersion in the carrier matrix.

Advantages

As the dispersion matrix is made from water-soluble sugars, moulded tablets disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the moulding process are used. In comparison to lyophilization process, tablets produced by moulding technique are easier to adapt to the industrial scale.

Disadvantage

As the moulded tablets have poor mechanical strength, they may undergo erosion and breaking during handling. Though hardening can increase the strength of the tablets but it would be at the cost of their disintegration time.

2.5.3. Direct Compression (7)

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

a. High doses can be accommodated and final weight of the tablet can exceed that of other methods.

b. Easiest way to manufacture the tablets.

c. Conventional equipment and commonly available excipients are use

d. A limited no. of processing steps are involved.

e. Cost-effectiveness.

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

2.5.4. Cotton Candy Process (10)

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

I. Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to

complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

II. Floss Processing

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

III. Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator.

The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.

IV. Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.

2.5.5. **Spray Drying** (10)

This technology produces highly porous and fine powders as the processing solvent is evaporated during the process. In this method to prepare MDTs hydrolyzed and nonhydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent and sodium starch glycolate or crosscarmellose sodium as superdisintegrant. Disintegration and dissolution were further increased by adding acidic substances like citric acid or alkali substance like sodium bicarbonate. This formulation technique gives porous powder and disintegration time < 20 sec.

2.5.6. Sublimation (12)

Syed developed the mouth dissolving tablet of naratriptan hydrochloride. Mouth dissolving tablet was prepared by sublimation technique camphor was used as a sublimating agent. Sodium starch glycolate and crospovidone were used as superdisintegrants in different proportions. Mannitol and microcrystalline cellulose were used as diluents. All the ingredients were passed through sieve no.60 separately. The drug and ingredients except mag. stearate were mixed uniformly and set aside. Finally mag. Stearate was added and the blended mixture was directly compressed using 6.5 mm punch in Karnavati tablet punching machine to form a tablet of 100 mg. The compressed tablets were subjected for drying at a temperature of 60°C to facilitate the volatilization of sublimable component i.e. camphor. The tablet disintegrates in vitro within 12-20 sec.

2.5.7. Mass extrusion: (7)

It 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.

2.5.8. Nanonization (10)

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. 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 200 mg of drug per unit).

2.5.9. Fast Dissolving Films (10)

It is a new frontier in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste.

2.6. Evaluation of Mouth Dissolving Tablet (12,13)

2.6.1. General Appearance:

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

2.6.2. Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled. A compressed

tablet`s shape and dimensions are determined by the tooling during compression process.

2.6.3. 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. The thickness of the tablets can be recorded using micrometer.

2.6.4. Weight variation:
Weigh 20 tablets individually calculate the average weight and compare the individual tablet weight to average. The tablets meet the test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. Limits are as per given in table: 01.

2.6.5. Hardness
Monsanto hardness tester was used to check the hardness of the tablet. The tablet can be placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw gauge. By turning the screw, the load can be increased and at collapse the applied pressure from the spring can be measured in kg/cm2.

2.6.6. Friability
Twenty tablets were weighed and placed in a Roche friabilator (Electrolab, India). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured as per the following formula,

$$\% \text{ loss} = \frac{\textit{Initial wt. of tablets - Final wt. of tablets}}{\textit{Initial wt. of tablets x 100}}$$

2.6.7. In-vitro Disintegration test
The Test was carried out on 6 tablets using tablet disintegration tester Electrolab, Mumbai.
Distilled water at 37°C ± 2°C was used as a disintegration media and the time in second taken for the complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

2.6.8. Wetting Time
The wetting time of the tablet can be measured using a simple procedure. A piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and time for complete wetting of tablet was noted.

2.6.9. Water absorption Ratio
A piece of tissue paper folded twice was placed in a small Petridish containing 6ml of water.
A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was
Weighed. Water absorption ratio, R was determined using following equation.

$$R = Wa - Wb / Wa \times 100$$

Where,
Wa = weight of tablet after water absorption
Wb= weight of tablet before water absorption

2.6.10. *In-vitro* Dissolution Study
The release rate of mouth dissolving tablets can be determined using USP dissolution testing apparatus II (paddle method). The dissolution test can be performed using 900 ml of dissolution media maintained at 37°C ± 0.5°C or as specified in individual monograph.

Patented technologies of mouth dissolving tablet as per given in table: 02.
Table: 03 illustrate the list of commercially available mouth dissolving tablet.

3. Conclusion
Recent article demonstrate how the various technologies can be utilized for formulation of mouth dissolving tablets for pediatric, geriatric, bedridden, psychotic patients, travelling patients and dysphagic patients, also the evaluation parameters for mouth dissolving tablets are helpful in the formulation development of the specific drug.

4. Future Prospective
With the advances in techniques there should be improved manufacturing processes for mouth dissolving tablet that are mechanically strong allowing ease of handling and packaging and with production costs similar to conventional tablet. There should be development of natural polymer based system which is highly site specific.
The future trends in innovations of drug delivery will continue to bring together technological disciplines and formulation aspects to create novel technologies.

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