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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET: A REVIEW

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ABSTRACT

Mouth dissolving tablets are gaining more prominence as a novel drug delivery system & emerges as one of the popular and widely accepted dosage forms, especially for pediatric patients because of incomplete development of muscular and nervous system & in case of geriatric patients suffering from parkinson's disorder or hand tremors, from both pharmaceutical industries as well as patients because they are convenient to be manufacture & administered free of side effects, offering immediate release and enhance bioavailability, so as to achieve better patients compliance MDT is good choice for pediatric and geriatric patients because it troubleshoots the problem of dysphagia.

Keywords: Mouth dissolving tablet, Superdisintegrant, Dysphagia, Bioavailability, etc.

INTRODUCTION

A solid dosage form is drug delivery system that include tablets, capsules, sachets and pills as well as bulk or unit -dose powders and granules. Oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulate to produce systemic effects in the united states are produce as oral dosage forms. Tablets and capsules are currently accounted for the highest proportions of the all drug presentations. this is because several reasons like

- Ease of administration
- accurate dosage
- self medication
- pain avoidance
- patient compliance

The most common solid dosage forms in contemporary use are tablets, which may be defined as unit forms of solid medicaments prepared by compaction. Now there are many types of tablet formulations that provide for the release of drug to be delayed or control the rate of the drugs availability but one important drawback of solid dosage form dysphagia or difficulty in

swallowing for many patients almost 50% population is affected by such problem.

This problem of dysphagia/swallowing conventional dosage forms is seen mainly in case of pediatric patients because of incomplete development of muscular & nervous system & in case of geriatric patients suffering from parkinson's disorder or hand tremors also it can be seen in case of mentally ill & bedridden patients, who are uncooperative or nauseated, patients having persistent cough or gag reflex in case of stroke, AIDS cerebral palsy. to overcome all these problems scientist has developed an innovative new drug delivery system known as mouth dissolving drug delivery of FDT MDT are those when placed on tongue, disintegrates instantaneously, realizing the drug, which dissolves in saliva. as drug go into solution the absorption is quick & onset of clinical effect.

some drugs are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach. in such cases, bioavailability of drug is

significantly greater than those observed from conventional tablet dosage form. The dispersible tablets allows dissolution in water prior to administration but MDT instead of disintegrating in water is expected to dissolve in oral cavity without drinking water [1-3].

MDT also known as

- orally disintegrating tablet
- orodispersible tablet
- fast dissolving tablet
- quick disintegrating tablet
- Porous tablet
- rapimelt tablet
- Rapid dissolving tablet

The centre for drug evaluation and research defines orally disintegrating tablets as a dosage form "a solid dosage form which disintegrates rapidly within a matter of seconds when placed under the tongue [4,5] the disintegrating time for orally disintegrating tablet varies from seconds to minutes, depends upon the size of tablet and formulation.

Desired Criteria for MDDS

Mouth dissolving tablet should be

- Not require water to swallow
- Have a pleasing mouth feel.
- Be portable without fragility concern.
- Be compatible with taste masking.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibits low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost [6,7].

Advantages of MDT

- No need of water to swallow the tablet.
- Can be easily administered to pediatric, elderly and mentally disabled patients.
- Accurate dosing.
- Rapid onset of action.

Bioavailability of drug is increased

Allow high drug loading

- Transportation
- Allow high drug loading

Limitations of Mouth Dissolving Tablets

- Insufficient mechanical strength.
- Careful handling is required.
- Unpleasant taste
- Grittiness in mouth if not formulated properly.
- Drugs with relatively larger doses are difficult to formulate into MDT.
- Decreased saliva production may not be good candidates for these tablet formulation.

Drug candidates suitable for Mouth dissolving tablets

Selection of drug candidate for mouth dissolving tablet is very crucial step while developing such dosage forms because of the following:

- Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
- Drugs which are very bitter taste because taste masking cannot be achieved.
- Patients with dryness of the mouth due to decreased saliva production may not be good candidates for MDT formulations.
- Drugs with a short half-life and frequent dosing.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g. selegiline, apomorphine etc

Technologies used for manufacturing of MDTs

- Freeze drying or lyophilization
- Sublimation
- Spray drying
- Cotton candy process
- Moulding
- Mass extrusion
- Direct compression

Patented technologies for MDT tablet:

- Zydis technology
- Durosolv technology
- orasolv technology
- Flash dose technology
- Wowtab technology
- Flashtab technology

FREEZE DRYING/LYOPHILLISATION

It is one of the first-generation technique for preparing MDT, in which sublimation of water takes place from the product after freezing. The formulations show enhanced dissolution characteristics due to the appearance of glossy amorphous structure to bulking agent and to sometimes drug. The ideal drug characteristics for this process are relative water solubility with fine particle size and good aqueous stability in suspension. Primary problems associated with water soluble drugs are formation of eutectic mixtures because of freezing point depression and formation of glassy solid on freezing which might collapse on sublimation. The addition of mannitol or crystal forming material induces crystallinity and imparts rigidity to amorphous material. The advantage of using freeze drying process is that pharmaceutical substances can be processed at non elevated temperature

thereby eliminating adverse thermal effect. High cost of equipment and processing limits the use in this process [8].

Molding

There are two types of molding process.

- 1) solvent method
- 2) heat method.

Solvent method involves moistening the powder blend with a hydro-alcoholic solvent followed by compression low pressures in molded plates to form a wetted mass (compression molding). Air-drying is done to remove the solvent. The tablets manufactured so formed are less compact than compressed tablets and possess a porous structure that hastens dissolution. Heat molding process a suspension is prepared that contains a drug, agar and sugar. This suspension is poured in the blister packaging wells, and then agar is solidified at the room temperature to form a jelly and dried at 30°C under vacuum. The main concern about these molded tablets is their mechanical strength, which can be achieved by using binding agents. The spray congealing of a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form was used to prepare the taste masked drug particles. As compared to the lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial scale manufacturing [9].

Sublimation

The process involves addition of some inert volatile substances like urea, naphthalene camphor etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolve.

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method [10].

Spray drying

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 [11-13].

Mass - Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. This softened mass is extruded through the extruder or syringe and a cylindrical shaped extrude is obtained which are finally cut into even segments using heated blade to form tablets. Granules of bitter drugs can be coated using this method to mask their taste [14].

Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. MDT can be prepared by using excipients like super-disintegrants and sugar based excipients.

Super-disintegrants

The rate of disintegration gets affected by the addition of superdisintegrants and hence the dissolution. Other ingredients like water-soluble excipients and effervescent agents also increase the disintegration.

Sugar based excipients

The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactitol, maltitol, 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. Mizumoto 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 mould ability but high dissolution rate. Type 2 saccharides (maltose and maltitol) exhibit high mouldability but low dissolution rate [15-19].

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).

Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shear form technology in association with Ceform TITM technology to eliminate the bitter taste of the medicament. A matrix known as 'floss', with a

combination of excipients, either alone or with drugs is prepared by using shear form technology. Like cotton-candy fibers floss is fibrous material made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and poly-dextrose can be transformed into fibers at 30–40% lower temperature than sucrose. Due to this modification thermo labile drugs can be safely incorporated into the formulation. This process results in a highly porous product and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below:

Floss blend

The floss mix is prepared by blending the 80% sucrose in combination with mannitol/dextrose and 1% surfactant. The surfactant maintains the structural integrity of the floss fibers by acting as crystallization enhancer. This process helps in retaining the dispersed drug in the matrix, thereby minimizes the migration out of the mixture) 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 [20].

PATENTED TECHNOLOGIES

Zydis technology

Zydis is a unique freeze dried oral solid dosage form that can be administered without water and it dissolves instantly on tongue in less than 3 sec. The drug is physically trapped in a water-soluble matrix, and then freeze dried to produce a product that rapidly dissolves. The matrix consists of water soluble saccharides and polymer (gelatin, dextran, alginates) to provide rapid dissolution and to allow sufficient physical strength to withstand handling. Water is used during the process to produce porous units for rapid disintegration. Various gums are used to eliminate sedimentation problem of dispersed drug. Glycine is used to prevent the shrinkage of zydis unit during the process and long term storage. As the zydis dosage form is weak physical strength, unit is contained in peelable blister pack, which allows removal of product without damaging it. An ideal drug candidate for zydis would be chemically stable and water insoluble and should have small particle size (Less than 50 microns). Water soluble drugs might form eutectic mixtures and not freeze adequately, hence the dose is

limited to 60mg. larger drug particles might present sedimentation problem during processing [21].

Orasolv technology

It is CIMA lab’s first fast dissolving formulation. Tablets are prepared by direct compression at low compression force in order to minimize oral disintegration and dissolution time. Orasolv technology is an example of slightly effervescent tablet that rapidly dissolve in mouth. The active medicaments are taste masked and dispersed in saliva due to the action of effervescent agents. It provides the pleasant sensation in mouth of the patient. The major disadvantage of Orasolv technology is its low mechanical strength. The tablets produced are soft and friable and need to be packaged in specially designed pack.

Durasolv technology

It is also a patented technology by CIMA lab, producing second generation MDT’s. The tablets prepared by this technology contain drug, fillers, lubricant and tablets prepared by conventional equipment’s. Durasolv formulations have higher mechanical strength than its predecessors due to application of higher compaction pressure. Durasolv product is so durable that it can be packed in either traditional blister pack or vials. It is one of the appropriate technologies for product requiring low amounts of active ingredients [22].

Wowtab technology:

wow means ‘without water’. The active ingredients may constitute upto 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldability saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs.

Flash dose Technology

This technology is patented by Fuisz. This system uses the combination of both Shearform and Ceform technologies in order to mask the bitter taste of the drug. A sugar based matrix, called ‘Floss’ is used, which is made up of a combination of excipients (crystalline sugars) alone or in combination with drugs. Nurofen meltlet, a new form of Ibuprofen, as a mouth-dissolving tablet is the first commercial product prepared by this technology and launched by Biovail Corporation.

Flashtab technology

In this technology, microgranules of the taste masked active drug are used. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion spheronisation. All these processes utilize conventional tableting technology. These taste masked micro crystals of active drug, disintegrating agent, a swelling agent and other excipients like soluble diluents etc are compressed to form a multiarticulate tablet that disintegrates rapidly. Shear form Technology: In this technology, a shear form matrix, 'Floss' is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass. The flowing mass comes out through the spinning head that flings the floss. The produced floss is amorphous in nature. So by various techniques, it is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before recrystallising it. Ceform technology: This technology involves preparation of microspheres of the active drug. Drug material alone or in combination with other pharmaceutical substances, and excipients is placed into a precision engineered rapidly spinning machine. The centrifugal force comes into action, which throws the dry drug blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form a sphere, without affecting the drug stability. The microspheres thus formed are compressed into tablets. As the drug and excipients both can be processed simultaneously, it creates a unique microenvironment in which the materials can be incorporated into the microspheres that can alter the characteristics of the drug, such as enhancing solubility and stability.

Preformulation studies of mouth dissolving tablet

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form. The following preformulation studies were performed on the sample of drug:

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight of powder into a measuring cylinder and initial weight was noted. Initial volume called as bulk volume. It is expressed in g/ml and is given by

$$D_b = M / V_b$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

Tapped density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume as measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volume is less than 2%.

$$D_t = M / V_t$$

Where, M is the mass of powder

V_t is the tapped volume of the powder.

Angle of repose (q)

The friction forces in a loosed powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan(q) = h / r$$

$$q = \tan^{-1}(h / r)$$

Where, q is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Evaluation of mouth dissolving tablets

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P is shown in Table 3.

Hardness

Hardness is tablet crushing strength. The force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in Kg/cm²

Friability(F)

Friability of the tablet determined using Roche friabilator or Electro lab friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a

tablet at 1 height of 6 inches in each revolution. Prewighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$\% \text{Friability} = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

Mechanical strength

Tablets should possess adequate strength to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters to evaluate a tablet for its mechanical strength.

Crushing Strength

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported.

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = \frac{r^2 \cos \theta}{4\eta l}$$

Where l is the length of penetration, r is the capillary radius, η is the surface tension, h is the liquid viscosity, t is the time, and θ is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between

wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

In vitro dispersion time

Tablet was placed in 10 ml phosphate buffer solution, 6.86.8±0.5°C. time required for complete dispersion of a tablet was measured

In vitro disintegration time

The process of breakdown of a tablet into smaller particle is called disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±20°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±20°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer. The mean SD values were calculated. Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer. The mean SD values were calculated.

Table 1. Angle of Repose as an Indication of Powder Flow Properties

Serial no.	Angle of repose	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very poor

Table 3. Weight Variation Specification as per IP

Average weight of tablet	% deviation
80mg or less	+/-10
More than 80mg but less than 250mg	+/-7.5
250mg or more	+/-5

Table 1. Marketed Preparation Of MDT-

TRADE NAME	ACTIVE DRUG	MANUFACTURER
Nimulid-MD	Nimesulide	Panacea Biotech, New Delhi,

		India.
Feldene Fast Melt	Piroxicam	Pfizer Inc., NY, U.S.A
Pepcid RPD	Famotidine	Merck and Co., NJ, U.S.A
Torrox MT Olanex Instab Olanzapine Ranbaxy Labs Ltd., New Del	Rofecoxib	Torrent Pharmaceuticals, Ahmedabad, India
Olanex Instab Ranbaxy Labs Ltd., New Del	Olanzapine	Ranbaxy Labs Ltd., New Delhi.
Zofran ODT Glaxo Wellcome, Middlesex, UK	Ondansetron	Glaxo Wellcome, Middlesex, UK
Febrectol Paracetamol Prographarm, Chateauneuf, France	Paracetamol	Prographarm, Chateauneuf, France

CONCLUSION

Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules.

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Nil

CONFLICT OF INTEREST

No interest

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