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A Review on Advancement in Mouth Dissolving Tablets

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ABSTRACT

Recent development in technology have presented viable dosage form alternative for patients who may have difficulties in swallowing tablets or liquid. Mouth dissolving tablet which is one of the good way to easily swallow tablet, which improve bioavailability. The ideal mouth dissolving tablet which is formulated by various technologies employed such as freeze drying, spray drying and sublimation. This technologies used in preparation of vary well known mouth dissolving/disintegrating tablets such as ZYDIES, ORASOLV, DURSOLA, WOWTAB, FLASHTAB and ORAVICK.

Keywords: MDT, superdisintegrants, orodispersible tablet

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INTRODUCTION

Drug Delivery Systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance [1].

The Centre for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."

FDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [2, 3]. Their growing importance was underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet that to be placed in oral cavity where it disperses rapidly before swallowing [4].

There is an important role of drinking water in the swallowing of oral dosage forms but some time people experiences an inconvenience in swallowing. The problems can be resolved by means of Mouth Dissolving Tablets (MDTs), when water is not available as during journey, also in case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. MDTs are also abbreviated as "fastmelting, fast-dissolving, oral disintegrating or orodisperse tablets".

Salient features of fast dissolving drug delivery system

- Should dissolve or disintegrate in the mouth within a few seconds.
- High drug loading should be allowed.
- They should be compatible with taste masking and other excipients.
- The mouth feel should be pleasant.
- After oral administration they should leave minimal or no residue in mouth.
- To withstand the rigors of the manufacturing process and post manufacturing handling, they
- must have sufficient strength.
- They should be less sensitive to environmental conditions such as humidity and temperature.

- The cost of manufacturing of tablets should be low.

Advantages of MDT

- Improve patient compliance.
- Rapid onset of action and may offer an improved bioavailability.
- Patient having difficulty in swallowing tablet can easily administer this type of dosage form.
- Useful for paediatric, geriatric and psychiatric patients.
- Suitable during travelling where water is may not be available.
- Gives accurate dosing as compares to liquids.
- Accurate dosing as compared to liquids.
- Advantageous over liquid medication in terms of administration as well as transportation.
- First pass metabolism is reduced, thus improved bioavailability and thus reduce dose and side effects.
- Free of risk of suffocation due to physical obstruction when swallowed.
- Offering improved safety.
- Suitable for sustained/controlled release actives.

Disadvantages of MDT

- The problem of mouth dissolving tablet is their low physical resistance and high friability. Taste masking is of an acceptable mouth dissolving tablet.
- Current method of taste masking in mouth dissolving/disintegrating tablet include sweeteners and flavours however these are not a sufficient means for taste masking many bitter drugs.
- Frequently, the active drug powder is coated and coating doesn't completely until the drug has been swallowed. Another bioequivalent process of taste masking is a physical process of effervescence [5, 6].

Formulation

Important ingredients that are used in the formulation of MDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Disintegration and solubilisation of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35^{0}C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast- dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as

cocoa butter and hydrogenated vegetable oils can also be used. The most important ingredients of a mouth dissolving tablets are:-

Superdisintegrants

Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates [7]. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.

Sodium starch glycolate, Ac-di-sol (crosscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised starch are some of examples of disintegrants [8-10].

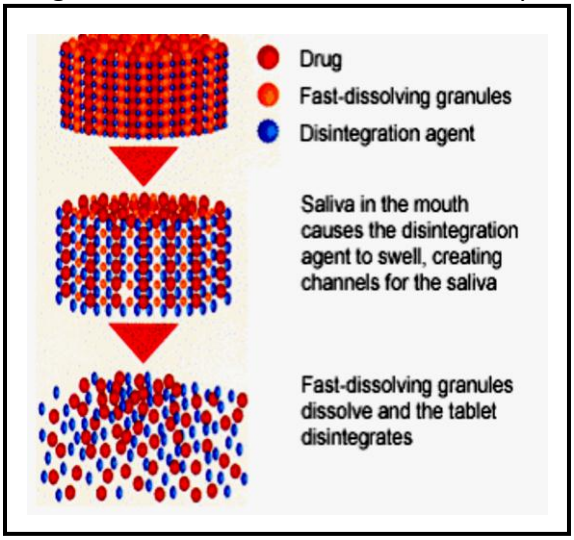

Fig. 1: Mechanism of action of superdisintegrants

Mechanism of Action of Disintegrants

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

a) By capillary action
b) By swelling
c) Because of heat of wetting
d) Due to release of gases
e) By enzymatic action
f) Due to disintegrating particle/particle repulsive forces
g) Due to deformation

Sugar Based Excipients

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. And the basic requirement for designing MDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking [11].

But not all sugar-based materials have fast dissolution rate and good compressibility or compactability. However technologies have been developed to make use of the sugar based excipients in the design of fast dissolving tablets. Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, binders, colors and flavours [12].

Approaches for Preparation of MDT

Freeze Drying

The tablets prepared by freeze-drying or lyophilization are very porous in nature and disintegrate or dissolve rapidly when come in contact with saliva. In this process, water is sublimated from the product after freezing. First of all, the material is frozen to bring it below its eutectic point. Then primary drying is carried out to reduce the moisture to around 4% w/w of dry product. Finally, secondary drying is done to reduce the bound moisture to the required volume. Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapsed temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature, instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva.

However the use of freeze-drying is limited due to high cost of equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs [13].

Sublimation

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 [14-16].

Spray 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 [17].

Moulding

Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on whether and to what extent it dissolves in the wetted mass [18]. The drug can exist as discrete particles or micro particles in the matrix. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undissolved and dispersed in the matrix [19]. Different moulding techniques can be used to prepare mouth-dissolving tablets.

a. Compression moulding: The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.
b. Heat moulding: A molten matrix in which drug is dissolved or dispersed can be directly moulded into Mouth dissolving tablets [20].
c. No vacuum lyophilization:- This process involves evaporation of solvent from a drug solution or suspension at a standard pressure [21]. Moulded tablets possess porous structure, which facilitates rapid disintegration and easy dissolution. Moulded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But moulded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs [22].

Mass Extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste [23, 24].

Direct Compression

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 is involved.
e. Cost-effectiveness [25, 26].

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 [27].

(a) 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.

(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.

Patented Technologies for Preparation of MDT

Several technologies are available for preparing Mouth dissolving tablets. But some commercially useful technology.

Zydis technology

'Zydis' is the first mouth dissolving dosage form in the market. It is a unique freeze-dried tablet in which the active drug is incorporated in a water-soluble matrix, which is then transformed into blister pockets and freeze dried to remove water by sublimation.

These form a glossy and amorphous structure. Mannitol or sorbitol is added to impart crystallinity, elegance and hardness. Various gums may be added to prevent sedimentation of dispersed drug particles. Water is used as a medium to ensure the formation of a porous dosage form. Collapse protectants like glycine may be used to prevent shrinkage of dosage form during freeze drying and long term storage [28].

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Orasolv technology

It is CIMA lab's first mouth dissolving formulation. This technology involves taste masking of active drug.

Effervescent disintegrating agent is also used. Conventional blenders and tablet equipments are used for preparation of tablets. Less force of compaction is used for manufacturing so as to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system.

Table 1: List of superdisintegrants

Superdisintegrants	Example	Mech of Action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-HPC	Crosslinked cellulose	-Swell 4-8 folds in < 10 Sec. -Swell & wicking both	-Swells in two dimensions. -Direct compression of granules.
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	Swells very little andreturns to original size aftercompression but act by capillary action	-Water insoluble and spongy inn nature so get porous tablet
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aq. medium	-Promote disintegration in both dry or wet granulation
Calcium silicate		-Wicking action	- Highly porous - Light weight -optimum conc. Between 20-40%
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix

Durasolv technology

This too has been developed by CIMA labs. This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tabletting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid.

Wowtab technology

Yamanauchi pharmaceutical company patented this 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 mouldabiity saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15sec. or less. Wowtab product can be packed in both into conventional bottle and blister packs [29].

Table 2: Commercially available fast dissolving tablets

Trade Name	Active Drug	Manufacturer
Cefadur DT	Cefadroxil	Cipla (protec)
Cefinar DT	Cefixime	Zydus Alidac
Zofran ODT; Vomokind MD	Ondansetron	Glaxo Wellcome; Mankind
Torrox MT; Dolib MD;	Rofecoxib	Torrent pharmaceuticals; Panacea;
Acivir DT	Acyclovir	Cipla
Dom DT; Domestal DT	Domperidone	Dr. Morepen; Torrent Pharma
Mosid MT	Mosapride	Torrent Pharma

Flashdose 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

Prographarm labs. have a patent over this 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.

Shearform Technology

In this technology, a shearform 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 [17].

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.

Nanocrystal technology

For MDT, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the d For fast dissolving tablets [30].

Newer Formulation techniques for mouth dissolving tablets

Some of the new advanced technologies which are commonly being used in last few decades are summarized as:

Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ 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:

(**a) 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 [31].

(b) 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 [32-34].

(c) Floss chopping and conditioning: In this step fibers are converted into smaller particles in a high shear mixer granulator. The partial crystallization is done by spraying ethanol (1%) onto the floss and subsequently evaporated it to impart improved flow and cohesive properties to the floss [35].

(d) Blending and compression: Finally, the chopped and conditioned floss fibers are blended with the drug and other excipients and compressed into tablets. Exposure of the dosage forms to elevated temperature and humidity conditions (40°C and 85% RH for 15min) improves the mechanical strength of tablets due to expected crystallization of floss material that result in binding and bridging, to improve the structural strength of the dosage form [36].

Nanonization Technology: A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique [37]. 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).

Fast Dissolving Films Technology: It is a newer developing front in MDDDS 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 after evaporation of solvent. In case of bitter drugs, resin adsorbate or coated micro particles of the drug can be incorporated into the film [38]. This film when placed in mouth, melts or dissolves rapidly and release the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 sec with instant drug delivery and flavored taste [39].

CONCLUSION

Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. They require smaller amount of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. In addition, MDTs may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Because drugs delivered in MDTs may be absorbed in the pregastric sites of highly permeable

buccal and mucosal tissues of the oral cavity, they may be suitable for delivering relatively low-molecular weight and highly permeable drugs. MDT need to be formulated for paediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in travelling, has difficulty in swallowing and may not have access to water. MDT offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid.

Future Prospect

Future possibilities for improvements in MDTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from MDTs have yet to be fully realized. Still there is an unmet need for improved manufacturing processes for fast dissolving tablets that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets. To fulfil these medical needs, formulators have devoted considerable efforts to develop a novel type of dosage form (tablet) for oral administration. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen, while also targeting underserved and under-treated patient populations. However, substantial amount of research remains to be conducted for the development of natural polymer based system which is highly site specific. Furthermore, development of such system correlating well with all desired characteristics for effective delivery would nevertheless be an appropriate futuristic endeavor. Therefore in coming era, there is going to be continued interest for the development of natural polymers based orally disintegrating tablets. The future trends in innovations of drug delivery systems will continue to bring together different technological disciplines and formulation aspects to create novel technologies.

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