Development and Evaluation of the Mouth Dissolving Formulations of some Analgesics and Anti-Inflammatory drugs

INTRODUCTION

Over the past three decades, Mouth Dissolving tablets (MDTs) have gained much attention as a preferred alternative to conventional oral dosage form such as tablets and capsules and other liquid pharmaceutical preparation. MDT is a solid dosage form that disintegrates and dissolves in the mouth without the need of water within a matter of seconds. Dissolution may take place either on or under the tongue or in buccal cavity. The US food and drug administration centre for drug evaluation and research defines in the “orange book” MDTs as a solid dosage form containing medicinal substance which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue. The European pharmacopoeia defines a similar term, Oro-disperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. These tablets in contrast with conventional dosage forms (tablets and capsules) which takes several minutes to dissolve in mouth, MDTs disintegrates and dissolves in the mouth in less than 60 seconds and hence produce a rapid action. There are several synonyms in use of MDTs like orodisperse, orally disintegrating tablets, quick dissolving tablet, fast melt tablets, rapid disintegrating tablets and freeze dried wafers. These tablets releases the medicament in the mouth for absorption through local oromucosal tissue and through pre-gastric (Oral cavity, Pharynx, and oesophagus), gastric (stomach) and post-gastric (small and large intestine) segments of Gastro Intestinal Tract(GIT)\textsuperscript{1-4}. Along with the rapid market growth of ODT products, the technologies, too, have advanced considerably over the years. The newest generation of ODTs can produce more robust, versatile tablets that overcome some of the limitations of earlier ODTs\textsuperscript{5}. Companies such as Eurand can produce pleasant tasting tablets, overcoming the common problem of poor drug taste compromising the benefits of an ODT. In addition, some companies is developing controlled release ODTs, significantly broadening the applications of this dosage form. A key reason that companies choose an ODT over other delivery technologies is that it is a relatively easy and often less risky delivery option to develop. Since the route of administration remains the same, ODTs that are formulated as bioequivalent
line extensions or generic versions of an existing oral dosage form have minimal clinical requirements to gain approval.

**Ideal Properties: An ideal Mouth dissolving tablet should**

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds,
- Allow high drug loading,
- Have acceptable taste masking property,
- Be portable without fragility concerns,
- Have a pleasing mouth feel,
- Leave minimal or no residue in the mouth after oral administration,
- Exhibit low sensitivity to environmental conditions as humidity and temperature,
- Allows the manufacture of tablet using conventional processing and packaging equipment at low cost.

**Significance of Mouth dissolving tablet**

As MDTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and ease of handling by patients.

- No risk of obstruction of dosage form as rapidly dissolves in saliva.
- Administration without water, anywhere and anytime, hence beneficial for traveling patients who do not have access to water.
- Easy to administer for pediatric, geriatric, mentally retarded and psychiatric patients.
- Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Medication as "bitter pill" has changed by excellent mouth feel property produced by the use of flavors and sweeteners in MDTs.
- Bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus is increased.
- Pre gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.
- Suitable for delivering relatively low molecular weight and highly permeable drugs.
Requires minimum number of ingredients and is cost effective dosage form.

Solid oral delivery systems do not require sterile conditions, so less expensive to manufacture\(^7\).

**Characteristics of Mouth dissolving Tablets**

MDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Traditional tablet formulations generally do not require taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overcome the bitter taste of the drug. In fast dissolving/disintegrating tablets include sweeteners and flavors for tastemasking but many bitter drugs are not masked by taste masking agent. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of drug particles\(^8\).

**First-generation ODTs:** While first generation ODT technologies produce tablets that dissolve rapidly in the mouth, provide convenience and ease of swallowing, and have had success in the market, some of them fall short in terms of taste masking and the accommodating high doses and because most first generation technologies can handle only low amounts of APIs, their therapeutic applications are limited and are used only in immediate_release applications. A table 2 list today’s major ODT technologies. First_generation ODTs are commonly characterized by high porosity, low density, and low hardness, making them brittle and difficult to handle. As a result, they often require blister packaging, which is less convenient for patients than bottles and entails high production costs. Freezedried ODTs are especially friable, making them difficult to package conventionally and raising questions about storage stability. Furthermore, it’s difficult to use traditional flavours and sugars to mask poortasting APIs with firstgeneration ODTs, which restricts their application to nonbitter APIs. The common approach is to use flavouring and sweetening agents to overpower the taste rather than neutralize it. Today, there are only a few technologies on the market that provide effective tastemasking capabilities, which requires a physical barrier between the API and the taste buds. One such technique is coacervation (encapsulation). As the ODT market matures, pharmaceutical companies are seeking additional capabilities from these dosage forms. These include higher API loading, more effective taste
masking, controlled release capability, low friability, cost-effective development, and more packaging options\textsuperscript{9-12}.

**New Generation of ODTs:** New generation of ODTs available today, is one that can be combined with a proprietary process to improve taste masking, allow a modified release profile, and enhance bioavailability. As a result, formulators can tastemask even extremely poortasting drugs, use high doses of API, and expand the range of therapeutic applications. These ODTs comprises of rapidly dispersing microgranules, a direct compression blend, and an external tablet lubrication method. The result is an ODT with excellent physical robustness, mouthfeel, and disintegration properties. The tablets dissolve in 15 to 30 seconds (depending on dosage strength) and produce a smooth, pleasant tasting mixture of API granules and carrier that is easy to swallow. The tablets are made on standard presses, accept printing on both sides, typically have a friability of less than 0.5 percent, and can be packaged in bottles or blister packs. Combining microencapsulation with ODT technology effectively can masks bitter APIs and can be applied to soluble and poorly soluble substances, as well as to high dose products. One technology is based on coacervation, a coating technique that encapsulates individual drug particles completely and provides superior taste masking. The coacervation process places a uniform coating of polymeric membranes of varying thicknesses and porosities directly onto dry crystals or granules, creating particles that are typically 150 to 300 microns. The membranes create an inert barrier between the API and the taste buds and a stabilization barrier between the API and the tablet excipients. This coacervation technique has taste_masked a wide range of extremely poor_tasting drugs, including zolpidem (for insomnia), sumatriptan (for migraines), ranitidine (for gastro-esophageal reflux disorder), and cetirizine (for allergic rhinitis). It has also been applied to theophylline, ibuprofen, acetaminophen, and pseudoephedrine, and products on the market that have incorporated the technique include Children’s Chewable Advil, Rulid (roxithromycin), and the Benadryl line of products. One of the biggest challenges for an ODT that uses taste_masking polymers is achieving bioequivalence with the conventional form (reference product). The polymers can impede API release in the gastrointestinal (GI) tract, delaying the onset of action. Using a microencapsulation technique restricts dissolution of the API in the mouth, but allows rapid dissolution in the GI tract, thus overcoming the bioequivalence obstacle\textsuperscript{13}. 


**Approaches for Preparation of MDTs:** Various technologies used in the manufacture of Mouth dissolving Tablets include:

- Freeze-drying,
- Sublimation,
- Molding,
- Spray drying,
- Mass extrusion

**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. First of all, the material is frozen to bring it below its eutectic point. Then drying is carried out 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. However the use of freeze-drying is limited due to high cost of equipment and processing, low mechanical strength, poor stability at higher temperature and humidity.\(^\text{14-16}\).

**Sublimation:** This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, menthol, ammonium bicarbonate, etc. to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores (Figure 1) in tablet structure, due to which tablet dissolves when comes in contact with saliva. Mouth dissolving Tablets with highly porous structure and good mechanical strength can be developed by this method.\(^\text{17-18}\).

**Molding:** Tablets prepared by this method are solid dispersions. The drug can exist as discrete particles or micro particles in the matrix. Molded tablets are less compact than compressed tablets, with a porous structure that facilitates rapid disintegration and easy dissolution. Molded tablets offer improved taste due to water-soluble sugars present in dispersion matrix. But molded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength.\(^\text{19,20}\).
**Spray drying:** A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet. It provides immediate dissolution (<20 sec). However this approach involves high cost and time of production, and also very poor mechanical strength of tablets\textsuperscript{21,22}.

**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\textsuperscript{23,24}.

In future MDT may be most acceptable and prescribed dosage form due to its quick action (within minute). Their characteristic advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in today’s scenario of hectic life. Considering the many benefits of MDTs, a number of formulations are prepared in MDT forms by most of the pharmaceutical companies. Because of increased patient demand, popularity of these dosage forms will surely expand in future.