ORO DISPERSIBLE TABLETS

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Abstract

Now-a-days, oro dispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. Over the past three decades, oro dispersible tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. Besides these advantages ODTs are prepared by direct compression method, which is more economical when compared to conventional tablets where the latter were formulated by wet granulation technique which requires a binding agent. But the ODTs don’t require any binding agent because they are prepared by direct compression method. New ODT technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphagia. These recent trends are very much interested about the ODTs because the drug will be disintegrated in less duration of time on the tongue itself, which is very useful to pediatrics and geriatrics avoiding the problem of swallowing. This has encouraged both academia and industry to generate new orally disintegrating formulations and technological approaches in this field. The aim of this article is to review the development of ODTs, challenges in formulation, new ODT technologies, evaluation methodologies, suitability of drug candidates, and future prospects.

Key words: Oro dispersible tablets (ODTs), super disintegrants, fast dissolving tablets, Mouth dissolving drug delivery systems (MDDS), Mouth dissolving tablets.

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INTRODUCTION

ODTs are distinguished from conventional sublingual tablets, buccal tablets, and lozenges, which require more than a minute to dissolve in oral cavity. In the literature, ODTs also are called Orodisperse, mouth-dissolving, quick-dissolve, fast-melt, and freeze-dried wafers. A freeze-dried wafer is a quick-dissolving, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. The saliva is swallowed and the drug is absorbed across the gastrointestinal tract (GIT) [1].

MDTs are known by various names such as “fast-melting, fast-dissolving, oral disintegrating or orodisperse. The European Pharmacopoeia defines the term “orodisperse” as a tablet that can be placed in the mouth where it disperses rapidly before swallowing [2]. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction [3]. MDTs disintegrate and/or dissolve rapidly in saliva; therefore, water is not required during administration. Some tablets are designed to dissolve in saliva within 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 as fast-disintegrating tablets, as they may take about one minute to disintegrate completely.
Advantages of Odt’s

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients [4,5].
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action [6, 7].

Disadvantages of Odt’s

- It requires proper packaging for safety and stabilization of stable drugs.
- It is hygroscopic in nature, so must kept in dry place
- It shows the fragile, effervescence granules property[8]
- If not formulated properly, it may leave unpleasant taste in mouth

Ideal Properties of Odt’s:

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include

1. Allow high drug loading.
2. Provide pleasant feeling in the mouth.
3. Be compatible with taste masking and other excipients.
4. Leave negligible or no residue in the mouth after oral administration.
5. Insensitive to environmental conditions such as humidity and temperature.

Limitations of mouth dissolving tablets:

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly
- Not require water or other liquid 5 to swallow.
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasing taste.
Various Manufacturing Techniques for Mdds:

- Lyophilization
- Moulding
- Direct Compression
- Cotton Candy Process
- Spray Drying
- Sublimation
- Mass Extrusion
- Nanonization
- Fast Dissolving Films

Freeze-drying or lyophilization:

In freeze-drying process, the water is sublimed from the product after it is frozen. This technique forms the basis of Zydis, Quicksolv and Lyocas technologies which are used to manufacture MDTs. Jaccard and Leyder used lyophilization to develop an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability of several drugs such as spironolactone and trolendomycin [9].

Stage 1 - bulk preparation of an aqueous drug solution or suspension and its subsequent precise dosing into pre-formed blisters.

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.

Stage 3 - sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions.

Tablet Moulding:

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

- Compression Moulding Process
- Heat-Moulding Process
- Moulding by Vacuum Evaporation without Lyophilization [10]
Direct compression (dc):

DC is the simplest and most cost effective tablet manufacturing technique for MDTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tabulating excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrates, effervescent agents and sugar based excipients. Another DC based technology; Flash tab contains coated crystals of drug and micro granules along with Disintegrants [11]. In this technology, two types of Disintegrants are used: a disintegrating agent (e.g., modified cellulose), which has a high swelling force and a swelling agent (e.g., starch) which has a low swelling force [12].

Mizumoto et al., [13] have classified sugar-based excipients into two types based on their mouldability and dissolution rate,
Type I saccharides (e.g., lactose and mannitol) exhibit low mouldability but high dissolution rate. Type II saccharides (e.g., maltose and maltitol) exhibit high mouldability but low dissolution rate.

**Cotton candy process:**

The FLASHDOSE® is a MDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament [14, 15]. 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 [16]. The manufacturing process can be divided into four steps as detailed below.

- Floss Blend
- Floss Processing
- Floss Chopping and Conditioning
- Blending and Compression

**Spray-drying:**

Allen et al., [17] have used spray-drying for the production of MDTs. The formulation contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate).

**Sublimation:**

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylenetetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose [18].
Mass-extrusion:

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste [19].

Nanonization:

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 [20]. The nano crystals 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.

Fast dissolving films:

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, hydroxylpropyl 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 [21].

**Fig.6: Fast dissolving film**

**Fig.7: Mouth dissolving tablets**

**Mechanism of Action of Disintegrants**

The super disintegrants in the ODTs will act by different mechanisms. They are

1. By capillary action
2. By swelling
3. Because of heat of wetting
4. Due to release of gases
5. By enzymatic action
6. Due to disintegrating particle/particle repulsive forces
7. Due to deformation

By Capillary Action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles [22]. Water uptake by tablet depends upon hydrophilicity of the drug/excipients and on tableting conditions.

By Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again.

Because of Heat of Wetting (Air Expansion)

When disintegrants with exothermic properties get wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however,
is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

**Due to Release of Gases**

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these Disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets [23].

**By Enzymatic Reaction**

Here, enzymes present in the body act as disintegrant. These enzymes destroy the binding action of binder and helps in disintegration.

**Due to Disintegrating Particle/Particle Repulsive Forces**

Another mechanism of disintegration attempts to explain the swelling of tablet made with „non-swellable” Disintegrants. Guyot- Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

**Due to Deformation**

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous
media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression [24].

**Super Disintegrants Used in Mdts**

As day’s passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate Disintegranites i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. This Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

**Types of Super Disintegrantes Used**

- Cross povidone
- Microcrystalline cellulose
- Sodium starch glycollate
- Sodium carboxy methyl cellulose or cross carmelose sodium
- Pregelatinized starch
- Calcium carboxy methyl cellulose
- Modified corn starch. Sodium starch glycollate has good flowability than cross carmellose sodium.

**Factors considered for selection of super disintegrantes:**

- It should produce mouth dissolving when tablet meets saliva in the mouth
- It should be compactable enough to produce less-friable tablets.
- It should has good flow since it improve the flow ability of the total blend.

**Evaluation of Odt’s**

Various evaluating parameters [24, 25] of ODT’s are-

- Weight variation.
- Hardness.
- Friability Test.
- Dissolution Test
- Wetting time.
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.

<table>
<thead>
<tr>
<th>Average Weight of Tablet</th>
<th>% Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg or less</td>
<td>10</td>
</tr>
<tr>
<td>More than 80 mg but less than 250 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>250 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm².

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.

Friability (F)

Friability of the tablet determined using Roche 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. Preweighted 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.

\[
F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100
\]
Wetting Time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. 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.

\[ \frac{DL}{dt} = r \cos \theta (4 \pi) \]

Where \( L \) is the length of penetration, \( r \) is the capillary radius, \( \theta \) is the surface tension, \( h \) is the liquid viscosity, \( t \) is the time, and \( q \) is the contact angle.

Dissolution Test

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counterparts.

**Tabel-2 list of super Disintegrants**

<table>
<thead>
<tr>
<th>Superdisintegrants</th>
<th>Example</th>
<th>Mechanism Of action</th>
<th>Special comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosscarmellose®</td>
<td>Crosslinked Cellulose</td>
<td>-Swells 4-8 folds In &lt; 10 seconds.</td>
<td>-Swells in two dimensions.</td>
</tr>
<tr>
<td>Ac-Di-Sol® Nymce</td>
<td></td>
<td></td>
<td>-Direct compression or granulation</td>
</tr>
<tr>
<td>ZSX®</td>
<td></td>
<td></td>
<td>-Starch free</td>
</tr>
<tr>
<td>Primellose®Solutab®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivasol®L-HPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>Crosslinked PVP</td>
<td>-Swells very little andreturns to original size aftercompression but act by capillary action</td>
<td>-Water insoluble and spongy in nature so get porous tablet</td>
</tr>
<tr>
<td>Crosspovidon M®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kollidon®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyplasdone®</td>
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<td></td>
</tr>
</tbody>
</table>
### Sodium starch glycolate  
Explotab®  
Primogel®

<table>
<thead>
<tr>
<th>Crosslinked starch</th>
<th>-Swells 7-12 folds in &lt; 30 seconds</th>
<th>-Swells in three dimensions and high level serve as sustain release matrix</th>
</tr>
</thead>
</table>

### Alginic acid NF  
Satialgine®

<table>
<thead>
<tr>
<th>Crosslinked alginic acid</th>
<th>-Rapid swelling in aqueous medium or wicking action</th>
<th>-Promote disintegration in both dry or wet granulation</th>
</tr>
</thead>
</table>

**Future Prospects**

These dosage forms 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. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs which may release these drugs in the oral cavity are very promising for the delivery of high molecular weight protein and peptide.

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