ORALLY DISINTEGRATING TABLETS: FORMULATION, PREPARATION, EVALUATION AND RECENT ADVANCES: A REVIEW

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ABSTRACT
Orally disintegrating tablets (ODTs) are tablets with medicinal substances, which can rapidly disintegrate or dissolve in the oral cavity without using water. Their salient immediate release property in many ways make the ODT a popular oral dosage form in special circumstances and situations such as institutionalized patients, travelling patients and patients with swallowing challenges. In this review we will discuss on the latest development in formulation, preparation techniques including their suitability and selection, as well as evaluation of parameters of orally disintegrating tablets. Recent advances in the orally disintegrating tablet dosage form will also be discussed.

KEY WORDS: Orally disintegrating tablets, Disintegration, Formulation, Preparation, Excipients, Evaluation.

1. INTRODUCTION
New technologies are being employed in the advancement of drug delivery systems with the aim of ensuring that effective amount of drug reaches the desired site of action in the body for the required duration of action.¹ In spite of these developments, the oral drug delivery system still remains the most effective way of introducing drugs in the body owing to its ease of administration, accurate dosage, non-invasive, etc.² Tablets and Capsules being the most common oral dosage forms and mostly preferred have also several limitations which many
patients face such as choking, difficult in swallowing especially with pediatrics and geriatrics. This can lead to non-compliance resulting in ineffective therapy.\cite{3-4} Other categories of patient that may encounter difficulties with these conventional oral dosage forms include bedridden patient, institutionalized patients like psychiatric patients, disabled, nauseated, patients on reduced fluid intake diet, and mobile patients who may not easily find water.\cite{5}

To overcome these challenges, a novel dosage forms known as Orally Disintegrating Tablet (ODT) has been developed. This dosage form can disintegrate quickly in the mouth upon contact with saliva, not requiring water.\cite{6} Not requiring water when taking orally disintegrating tablets and lesser disintegration time has benefited a number of patient categories. An orally disintegrating tablet has been defined by the United States Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) as “A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”\cite{7} Also been described by European Pharmacopoeia as “uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within 3 minutes”.\cite{7} Other names that have been given to ODTs have included Fast disintegrating tablets (FDTs), oral dispersible, fast dispersing, fast dissolving, quick disintegrating, fast melt, rapimelt, effervescent drug absorption system.\cite{2, 7}

Orally disintegrating tablets offer benefits of easy swallowing, not requiring water, stability, accurate dosing, suitability to pediatrics and geriatrics, bedridden, mentally retarded,\cite{8} as well as biopharmaceutical advantages such as pre-gastric absorption. During the passage of saliva carrying the drug down to the stomach, some drugs are absorbed in the tract before the stomach leading to greater bioavailability than ordinary dosage forms.\cite{1, 9} Accurate dosing and stability makes it a better dosage form than liquids.\cite{10-11} Pre-gastric absorption makes the drug bypass first pass metabolism resulting in better blood plasma concentration with improved efficacy making it a suitable formulation for drug that undergo extensive pre-systemic metabolism.\cite{9, 12-13} Exception of the pre-gastric absorption would be ODTs whose bitter taste API has been coated with a pH sensitive polymer i.e. Eudragit EPO, which release the drug substance in the stomach, even if the tablet disintegrates in the mouth.\cite{14} Two critical aspects in formulating this dosage form are proper addition of superdisintegrants key
to disintegration time and concealing the bitter taste of drugs significant for patients’ compliance.\textsuperscript{[15]}\textsuperscript{[16]}

2. Formulation approaches for orally disintegrating tablets

Formulation approaches begins with selection of excipients to be incorporated into the formulation then preformulaion studies.

2.1 Selection of excipients

Excipients selected must ensure that the tablets prepared meet the objectives or purpose of this dosage form with shorter disintegrating time and good patient’s compliance to medication. Above all, the prepared tablets should comply with the pharmacopoeia specifications. Recent advances on ODTs formulation has emphasized also on quality by design during excipient selection. This will be discussed under formulation development. Some excipients may be specific to the preparation method employed e.g. acesulfame, a sweetener is used in the recently shown technique for taste masking. This will also be discussed under taste masking. The commonly used excipients are as follows.

2.1.1 Superdisintegrants

Superdisintegrants facilitate the breaking of the orally disintegrating tablet once it is placed on the tongue. Addition of these materials in the formulation is critical to the disintegration time, and they should be used at their optimal concentration. Superdisintegrants can be used alone or in combination in the formulation and they have concentration ranges within which they work effectively.\textsuperscript{[9, 15, 17]}

The following properties should be considered when selecting the superdisintegrant(s).\textsuperscript{[17]}

- Ability to flow and to be compressed,
- Poor gel formation
- Poor water solubility
- Good hydration
- Inability to form complexes with drugs

Synthetic superdisintegrants which are commonly used have included Sodium starch glycolate, Crosspovidone and carboxymethyl cellulose sodium (Crocarmellose sodium). Natural polymers which are used as superdisintegrants have included; Isapghula Husk Mucilage (Plantago ovata), Lepidium sativum Seed Mucilage, Fanugreek Seed Mucilage,
Gellan Gum, Chitin and Chitosan. Modification of polysaccharides have resulted in superdisintegrants with lower disintegration time. Mahaveer Pr. Khinchi et al (2011) study showed that modified treated agar as a superdisintegrant had lower disintegration time than treated agar and agar in Fenoxidine HCl tablets. Finally, several factors have to be considered when choosing superdisintegrants including; percentage of disintegrants in the formulation, nature of drug, type of mixing and addition, hardening of tablets, presence of surfactant, ability to form less friable tablets, and good mouth feel.

2.1.2 Binders

Binders help to hold particles together in a formulation. Commonly used binders include cellulose or modified cellulose such as microcrystalline cellulose, Sucrose, lactose, starches, cellulose ethers such as hydroxypropyl cellulose (HPC), Hydroxy propyl methylcellulose (HPMC), Sugar alcohols such as xylitol, sorbitol or maltitol, proteins such as gelatin, synthetic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyvinylalcohol (PVA).

During tablet disintegration, the binding forces between particles are overcome and the tablet disperse. Some binders, especially starch and its derivatives are enzyme labile especially to amylase in the saliva thereby reducing the effect of binding making tablet disintegration easier for ODTs.

Binders are categorized according to their usage as solution binders which are employed in wet granulation (e.g. starch, gelatin, cellulose and their derivatives) and dry binders whose addition to the formulation is to the powder mix after completion of wet granulation process or to the powder mixture for direct compression formula. Some examples of dry binders include cellulose, methyl cellulose, Polyvinylpyrrolidone.

During ODT preparation, increasing the concentration of the binder results in less friable tablets. The study by Chikwuma O. Agubata, et al (2012) on the physical and mechanical effects of binder mixtures on sodium salicylate tablets showed that as the binder concentration was increasing, the crushing strength or hardness was generally increasing, and the friability was decreasing.

However, it is important to note that tablet hardness resulting from either increasing the concentration of binders in formulation or compression force can prolong the disintegration time, defeating the whole purpose of this dosage form.
2.1.3 Taste Masking

Orally disintegrating tablets disintegrate in the saliva and during the process the drug may be exposed to taste buds imparting an acrid taste which can lead to poor patient compliance. This makes masking of unpleasant taste of therapeutic agents paramount when developing this dosage form.\textsuperscript{[24]} Several methods have been used in drug dosage formulation to improve taste. Examples include polymeric coatings strategies, complexation with cyclodextrin, ion exchange resins, salt formations, using liposomes, microencapsulation technique and coating or granulation.\textsuperscript{[6]} The use of sugar based excipients as diluents is also one of the approach used. Some examples of these excipients include mannitol, maltose, dextrose, sorbitol, fructose, etc. These improve the mouth feel as they dissolve in saliva.\textsuperscript{[12]}

Aspartame and Saccharine have been widely used as sweetening agents in formulations of orally disintegrating tablets. With reference to sucrose, Aspartame is 200 times sweeter while Saccharin is 450 times sweeter. Sugar based excipients which can be used as diluents, for example mannitol and lactose are 0.60 times and 0.16 times sweeter than sucrose respectively.\textsuperscript{[25]} Addition of sweetening agents and flavoring agents is the easiest way of masking the distasteful sensation, though the approach may not be sufficient for very bitter drugs. In combating the bitter taste, artificial sweetening agents and flavoring agents should generally be used alongside other bitter taste masking approaches.\textsuperscript{[25]}

Table 1: Flavoring agents for taste masking.\textsuperscript{[26]}

<table>
<thead>
<tr>
<th>Basic Taste</th>
<th>Masking (flavoring) agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>Butterscotch, apple, apricot, peach, vanilla, winter green mint.</td>
</tr>
<tr>
<td>Bitter</td>
<td>Wild cherry, walnut, chocolate, mint, anise</td>
</tr>
<tr>
<td>Sweet</td>
<td>Vanilla, fruit and berry</td>
</tr>
<tr>
<td>Sour</td>
<td>Citrus flavor, licorice, root beer, raspberry</td>
</tr>
</tbody>
</table>

Intermediary techniques like coating or matrix entrapment should also be used.\textsuperscript{[27]} For example a lipophilic drug can be taste masked by entrapping it into a lipoidal matrix.\textsuperscript{[27]} An ionic drug can be taste masked with ion exchange resins. Tong Wu et al (2018) successfully prepared orally disintegrating tablets containing mosapride citrate-resin complex which disintegrated within 18 second.\textsuperscript{[28]} Table 2 shows the drug properties which should be considered and the taste masking techniques. Simple techniques involve addition of sweetener, flavoring agent, and other excipients and also complexation. Intermediary techniques involve coating and matrix entrapment whereas complex techniques involve prodrug formation and salt formation.\textsuperscript{[27]}
Table 2: Summary of drug properties and the taste masking techniques.

<table>
<thead>
<tr>
<th>Drug property</th>
<th>Drug property attribute</th>
<th>Taste masking technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitterness</td>
<td>Mild</td>
<td>Simple technique</td>
</tr>
<tr>
<td></td>
<td>extreme</td>
<td>Intermediary techniques</td>
</tr>
<tr>
<td>Dose</td>
<td>Low</td>
<td>Simple technique</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Intermediary techniques</td>
</tr>
<tr>
<td>Particle Size</td>
<td>Fine</td>
<td>Simple technique</td>
</tr>
<tr>
<td></td>
<td>coarse</td>
<td>Intermediary techniques</td>
</tr>
<tr>
<td>Particle shape</td>
<td>Spherical</td>
<td>Simple technique</td>
</tr>
<tr>
<td></td>
<td>Irregular</td>
<td>Simple technique, Complex Technique</td>
</tr>
<tr>
<td>Ionic Characteristic</td>
<td>Ionic</td>
<td>Intermediary techniques</td>
</tr>
<tr>
<td></td>
<td>Non-ionic</td>
<td>Simple technique</td>
</tr>
<tr>
<td>Solubility</td>
<td>Hydrophilic</td>
<td>Intermediary techniques</td>
</tr>
<tr>
<td></td>
<td>Lipophilic</td>
<td>Simple technique</td>
</tr>
</tbody>
</table>

Orally disintegrating tablets which are taste masked with either coating or matrix entrapment, the coating material should not dissolve or release the API in the mouth even if the tablet disintegrates but must be able release the API after the tablet leaves the mouth.\[^14^]\ Granulation is one of the convenient and quick process of masking bitter taste of drugs without much challenges.\[^26^]\ The method of sweetener addition during granulation has an influence on the overall taste masking of the orally disintegrating tablets. Yayoi Kawano et al (2009) study showed that mixing the drug and a portion of a sweetener before granulation, and another equal portion of the sweetener added to the granules had favourable masking of the unpleasant taste.\[^16^]\ The recent method in taste masking involves forming a sweet salt of a drug with an artificial sweetener. Usually, mere addition of a sweetener to the formulation may result in physical separation of the sweetener and the drug as the formulation is undergoing manufacturing process. Chances are that the taste buds may be exposed to a bitter drug before interacting with the sweetening agent. However, formation of the salt of drug with sweetener first before addition of other excipients and compression results in the simultaneous release of the drug and sweeter upon contact with saliva resulting in effective taste masking.\[^29-30^]\ Acesulfame, an artificial sweetener has been successfully used in formation of sweet salt with bitter drug. Chenguang Wang et al (2017) prepared Diphenhydramine ODT and Metformin ODT by formation of a sweet salt with acesulfame resulting in significant improvement on the taste of the ODT. Additionally, formation of the sweet salt made it possible for incorporation of a suitable high dose of Metformin, another area of interest as mainly ODTs have a limitation of incorporating large doses.\[^29-30^\]
2.1.4 Diluents

Diluents function as bulking agents especially for drugs with role doses. This is necessary to facilitate exact material handling when preparing the dosage form and subsequent compression.\(^{[31]}\) When smaller amount of the drug is involved, a larger amount of the diluent/filler will be necessary.\(^{[32]}\) Apart from being pharmacologically inert, compatible with drug and other excipients, not hygroscopic, good flowability and compressibility properties, diluents for ODTs should have a pleasant taste.\(^{[22]}\) Mannitol, microcrystalline cellulose, Lactose starch, pregelatinezed starch, sorbitol sucrose, and calcium phosphates are commonly used diluents and are classified based on their chemical nature and solubility.\(^{[31]}\) Mannitol, Lactose and Microcrystalline cellulose have been widely used as diluents in the preparation of orally disintegrating tablets by direct compression because of good compressibility and flowability properties. Microcrystalline cellulose has also been used as a binder, and it has disintegrant properties in tablets prepared by direct compression process because of its swelling properties when in contact with water.\(^{[28]}\)

2.1.5 Lubricants

Lubricants help reducing die wall friction (true lubricants role), preventing sticking of powders to punch faces (anti-adherent role), and to aid flow of granules (glidants role) during ODT preparation.\(^{[22, 33-34]}\) Poor powder (granule) flow may results in tablets with variations in weight and content.

It is important to determine the concentration of the lubricant, and the manner into which it is incorporated into the ODT formulation. Mainly, the addition of lubricants should be in a dry form when other ingredients in the formulation are uniform. Addition and mixing should be within 2 to 5 minutes as opposed to the 10 to 30 minutes which is usually the case for complete mixing of powder for granulation. Very low concentration of lubricants and insufficient powder mixing may result in sticking, binding in the die cavity, punch filming, and picking.\(^{[34-35]}\) Higher concentration of lubricants in the formulation, or prolonging mixing time may result in tablets with reduced strength and incompressible powder blend because of particle coating which in turn reduce particle-particle binding forces. Increased tablet disintegrating time, as well as a reduction in the dissolution rate may result if there is higher lubricant concentration in the formulation.\(^{[34-35]}\)

Abhishek Y. Kanugo et al (2013) study evaluating and comparing highly soluble sodium stearyl fumerate with other lubricants (magnesium stearate and talc) in vitro showed that
disintegration time and tablet hardness were increasing and reducing respectively with increasing the concentrations of the lubricant in the formulation.[36]

Table 3: commonly used lubricants in ODTs.[34-35, 37-38]

<table>
<thead>
<tr>
<th>Lubricant</th>
<th>Water Solubility</th>
<th>Concentration range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium Stearate (lubricant, glidant and adherent)</td>
<td>Hydrophobic</td>
<td>0.25 - 2</td>
</tr>
<tr>
<td>Stearic Acid (lubricant)</td>
<td>Hydrophobic</td>
<td>0.25-2</td>
</tr>
<tr>
<td>Talc (anti-adherent)</td>
<td>Hydrophobic</td>
<td>1-5</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate (lubricant)</td>
<td>Hydrophilic</td>
<td>1-5</td>
</tr>
<tr>
<td>Fumed Silicon Dioxide (anti-adherent, glidant)</td>
<td>Hydrophobic</td>
<td>anti-adherent role, 1-2 glidant role, 0.1- 0.5</td>
</tr>
</tbody>
</table>

Other excipients used in ODT formulation depend on certain properties of tablets to be achieved and also on the preparation technique involved, i.e. citric acid and sodium bicarbonate may be used as dissolution enhancers in some preparation, and camphor can be used as a subliming agent if preparation technique employed is sublimation.

2.2 Formulation development

Selection of excipients to be included in the formulation should follow quality by design principles. Recent advances in ODT formulation and preparation have embraced application of certain systems and particle engineering techniques to improve the formulation properties.[39-40]

This is increasingly becoming of great consideration in manufacturing ODT to minimize try and errors during formulation development and wastage of materials and above all to improve the quality of the product. The emphasis is on understanding and adjusting formulation parameters/variables during the process. One System which has been applied in ODT formulation to ensure quality by design is the SeDeM expert system, which was first defined in 2005. It is used in preformulation and formulation development to characterize powders for oral solid dosage form. This system has been used to characterize powders for ODT preparation by direct compression. Twelve parameters are evaluated using this system and include dimension parameters which are bulky density and tapped density, compressibility parameters including inter-particle porosity, carr index and cohesion index, flowability parameters such as Hausner ratio, angle of repose and powder flow, lubricity/stability parameters including loss on drying and hygroscopicity, and finally lubricity/dosage parameters such as particle size and homogeneity index. Quality by design
has resulted in the development of processed excipients or functional excipients with the aim of attaining suitable powder characteristics for compression. Table 4 summarizes some of the available functional excipients and their composition.

Table 4: Functional excipients and their composition.\[40-41\]

<table>
<thead>
<tr>
<th>Functional Excipients</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludiflash</td>
<td>D-mannitol, crospovidone, polyvinyl acetate and small amounts of povidone</td>
</tr>
<tr>
<td>Pharmburst</td>
<td>consisting of Mannitol, Starch, Crosspovidone, Crosscarmellose Sodium, Colloidal Silica and Silica</td>
</tr>
<tr>
<td>Parteck</td>
<td>spray-granulated D-mannitol and croscarmellose sodium</td>
</tr>
<tr>
<td>F-MELT</td>
<td>Mannitol, Xylitol, Calcium Sulphate, Crosspovidone, and Mangesium Aluminosilicate</td>
</tr>
<tr>
<td>Ludipress</td>
<td>Lactose, Kollidon 30 and Kollidon CL</td>
</tr>
</tbody>
</table>

Sıla Gülbağ et al (2017) prepared memantine ODT formulation employing SeDeM expert system during selection of excipients, and Parteck, the functional excipient was used in the final formulation with other ingredients (Avicel PH-102, magnesium stearate, and Aerosil) as it showed highest compressibility value compared to Ludiflash and Ludipress.

2.3 Preformation studies in orally disintegrating tablets

This should be number one step in developing a dosage form of the drug. It is at this stage where possible physical and chemical interactions of the API with other inactive ingredients are explored. These studies facilitate in the selection of the excipients to be used in the formulation which will be compatible with the API.\[42-43\] Despite these excipients being pharmacologically inactive, their interaction with the API may have an effect on the properties and stability of the dosage form.\[43-44\] It is therefore, necessary to carry out drug-excipient compatibility studies to ascertain that no interactions are taking place.

A lot of methods have been used to study drug-excipient compatibilities and these have included Thermal method of analysis (i.e. Differential Scanning Calorimetry), Spectroscopic techniques (i.e. Fourier Transform Infra-Red Spectroscopy), Microscopic Techniques (i.e. Scanning Electron Microscopy), Chromatographic Techniques such as High Performance Liquid Chromatography (HPLC).\[44\] Differential scanning calorimetry has been used as it measures the power/heat required to heat substances. With the principle that the API and excipients have different melting points, their DSC thermograms should be obtained individually first followed by that of the drug excipient blend in a one to one ratio. Interaction is considered to have occurred if there is elimination of the exo/endothermic peak, reduction
in the area of the peak, appearance of new peaks or change in the shape of peaks on the drug-excipient thermogram. A slight change in the onset of the peak, height or width may not be considered as interaction because it may occur due to differences in geometry of the mixture.\textsuperscript{[44-45]}

Fourier Transform Infra-Red Spectroscopy (FTIR) and other spectroscopic methods consider the structure of the functional group of the API and excipients. The spectrum of the API and excipients are obtained individually first followed by that of the mixture. A change in the spectrum suggests interaction and thus incomparability. Scanning electron microscopy considers the surface morphology of the substance with regard to the crystal habit. A change in the morphology after mixing the drug and excipients suggests interaction.\textsuperscript{[44]} High Performance Liquid Chromatography (HPLC) use in preformulation studies is mainly to measure the amount of the drug remaining in the drug-excipient blend after storage under high temperature (Isothermal stress testing - to accelerate interaction) for few weeks comparing to the API alone stored under similar condition. Results showing similar percentage loss of the API in the drug-excipient mixture and the API alone suggests no interaction and vice versa.\textsuperscript{[44-45]}

3. Evaluation of powder properties before compression

Powder flow affects both the quality and quantity of the tablets produced. One of the factors leading to consistence in weight, hardness and content uniformity in tablets is good powder flow characteristics.\textsuperscript{[46]} Notwithstanding many parameters various systems have proposed for evaluation, the main parameters which should be evaluated in characterization of the powder flowability and compressibility are as follows.\textsuperscript{[2, 47-48]}

3.1 Bulky density

This powder parameter expresses the ratio of the weight of powder sample not tapped/unperturbed to its volume including the volume of the space not covered by particles. The units are in grams per millilitre (g/ml) even though its international units are kilogram per cubic metre. As most times this parameter is measured using a measuring cylinder, the units of grams per cubic centimeter may also be used. It can be obtained by weighing the powder sample and putting it into a measuring cylinder then recording the untapped volume, or by first introducing the powder into the measuring cylinder recording its untapped volume and then weighing the powder. Bulky density is calculated using the following formula;
3.2 Tapped density

It is the ratio of the tapped volume of the powder sample to the weight of the powder sample. It is determined by mechanically tapping the graduated cylinder into which the drug excipient blend of known weight is contained then measuring the new volume called tapped volume. Once tapped volume has been determined, the tapped density of the powder/drug-excipient blend is calculated using the following formula:

\[
Tapped\ Density = \frac{Weight\ of\ powder}{Tapped\ volume\ of\ powder}
\]

3.3 Carr index

This parameter measures how compressible the powder mixture is and is determined using the following formula.

\[
Compressibility\ Index = \frac{Tapped\ density - Bulky\ density}{Tapped\ density} \times 100
\]

3.4 Hausner’s ratio

This is another parameter for powder characterization which measures the flowability of the powder or granules.

\[
Hausner\ Ratio = \frac{Tapped\ density}{Bulky\ density}
\]

3.5 Angle of Repose

This parameter also measures the flow of the powder mixture relating to friction. The method of determining this parameter is by the use of a fixed funnel. Several approaches have been used but one of the simplest involves the use of a plain paper which is placed on the working table then funnel is fixed using any fixing object such as a clamp stand such that the tip is on top of the powder/graule apex when the weighed amount of powder or granules are allowed to pass through the funnel. After fixing the funnel, the drug-excipient blend is taken and let it pass through the funnel freely to the surface of the plain paper then the height of the powder cone is measured. The base boundary of the powder or granule cone is also marked/circled using a pen or pencil to obtain the diameter. Having the height and the diameter, the angle of repose is obtained using the equation below.
\[ \tan \theta = \frac{h}{r} \]

Where \( h \) is the height of the cone and \( r \) is the radius of base of the cone as shown in the figure below.

![Diagrammatic presentation for the measurement of angle of repose.](image)

Depend on the value of the angle of repose, Hausner’s ratio, and Carr’s index, the powder flow properties and compressibility can be characterized.

<table>
<thead>
<tr>
<th>Flow properties</th>
<th>Angle of Repose</th>
<th>Hausner’s Ratio</th>
<th>Carr index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25 – 30</td>
<td>1.00 – 1.11</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Good</td>
<td>31 – 35</td>
<td>1.12 – 1.18</td>
<td>11 – 15</td>
</tr>
<tr>
<td>Fair</td>
<td>36 – 40</td>
<td>1.19 – 1.25</td>
<td>16 – 20</td>
</tr>
<tr>
<td>Passable</td>
<td>41 – 45</td>
<td>1.26 – 1.34</td>
<td>21 – 25</td>
</tr>
<tr>
<td>Poor</td>
<td>46 – 55</td>
<td>1.35 – 1.45</td>
<td>26 – 31</td>
</tr>
<tr>
<td>Very poor</td>
<td>56 – 65</td>
<td>1.44 – 1.59</td>
<td>32 – 37</td>
</tr>
<tr>
<td>Very very poor</td>
<td>&gt;66</td>
<td>&gt;1.60</td>
<td>&gt;38</td>
</tr>
</tbody>
</table>

### 4. Orally disintegrating tablets preparation techniques

There are three major methods employed in the preparation of orally disintegrating tablets. These are compression, freeze drying, and molding methods. Tablets prepared by freeze drying have short disintegration time due to the porous structure formed after evaporation of water, though usually have low strength and requires special packaging.\(^{[49]}\) Compression being the most common method, many particle engineering techniques are employed to improve the powder flow and compressibility properties and also to achieve certain desired properties of tablets. For example, spray drying of the drug excipient blend is employed to obtain a highly porous structure which is then compressed into tablets in which water/saliva
ingress is very rapid hence fast disintegration. Spray drying is suitable for heat sensitive drug because of shorter contact time of heat and drug excipient blend.\textsuperscript{[50-51]} Granulation methods i.e. wet granulation, melt granulation can be employed to obtain good flow and compressible powder blend.\textsuperscript{[52]}

Direct compression of the drug excipient powder blend is simplest way of preparing orally disintegrating tablets because ordinary machinery, facilities, devices, readily available excipient materials and few processing steps are employed in this method. However, the powder blend should have good flow and compressibility properties before compression to ensure content and weight uniformity in the tablets. Directly compressible materials like mannitol, microcrystalline cellulose, and spray dried lactose are commonly used as bulking agents.\textsuperscript{[52-53]} To attain a porous structure when using this method, excipients like subliming agent such as camphor, ammonium bicarbonate etc are included in the formulation. The prepared tablets are then taken into a hot air oven for sublimation for some hours (usually 2-6 hours). The removal of these volatilizable components results in the generation of tablets with a porous matrix which facilitate fast disintegration.\textsuperscript{[54-55]}

Mass extrusion of the drug into microspheres or small granules before compression has been employed mainly with the aim of masking the unpleasant taste.\textsuperscript{[56]} Cotton candy process is also another technique employed before compression of the powder blend largely with the aim of improving the taste of the medicament as most excipients used are saccharides and disaccharides.\textsuperscript{[57]} This process is so named because it makes use of a spinning mechanism to produce a floss-like crystalline structure which looks like a cotton candy. The flossy is formed using excipients alone (saccharides or disaccharides) or in combination with the drug. The first step of the process involves formation of the sugar matrix (candy floss) achieved through double action of melting and centrifugal action of the sugars (mannitol, sucrose, xylitol). Re-crystallization can be done to improve the flow properties the floss. The candy floss formed is then milled and blended with the active ingredient (s) and other excipients and compressed into tablets. Other techniques employed in the preparation of ODTs are patented and have include the following as contained in Table 6.
Figure 2: Schematic diagram for cotton candy process technique for preparation of orally disintegrating tablets.

Table 6: Patent techniques for preparing ODTs.[58]

<table>
<thead>
<tr>
<th>Patented technique</th>
<th>Patent owner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zydis Technology</td>
<td>R.P. Scherer, Inc</td>
</tr>
<tr>
<td>Durasolv Technology</td>
<td>CIMA labs</td>
</tr>
<tr>
<td>Orasolv Technology</td>
<td>CIMA labs</td>
</tr>
<tr>
<td>Flash Dose Technology</td>
<td>fuisz</td>
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<td>Wow tab Technology</td>
<td>Yamanouchi Pharmaceutical Company</td>
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<td>Flash tab Technology</td>
<td>Prographarm laboratories</td>
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5. Evaluation of orally disintegrating tablets[4,59-61]

Orally disintegrating tablets should be evaluated to ensure that variations within tablets are in acceptable limits (specifications). The United States Pharmacopoeia stipulates the test which should be carried and include the following:

- Tablet thickness
- Tablet hardness
- Tablet friability
- Weight variations
- Content uniformity
- Tablet disintegration time
- In vitro dissolution testing.
Additionally, some parameters may be required to be evaluated depending on the attributes of the ODTs prepared. For example, the advent of muco-adhesive ODTs may require evaluation of the adhesive properties and particle retention ratio of the tablets. Fixed dose combination will require a comparative dissolution testing and apparent permeability testing for the drug in combination and single formulation. [62-63]

Another important study that can be done after preparation of ODTs is stability study. This can be done for a specified period of time, i.e. one month, two months, or three months at accelerated specified test conditions i.e. 40°C temperature and 75% relative humidity then tablet parameters such as appearance hardness, friability, disintegration and dissolution and content uniformity are evaluated.

6. Recent advances and development in orally disintegrating tablets

Notable advances in this novel dosage form are increasing both in formulation and therapeutic aspects. In the former, new techniques of masking bitter taste of unpleasant drug and quality by design techniques have been shown and developed. Quality by design and new technique of masking unpleasant taste of drug have been discussed already. The advent of fixed dose combination, modified release formulation as well as the novel disintegration tester for orally disintegrating tablets is another milestone achieved in this dosage form.

6.1 Fixed Dose combination (FDC) [41, 62, 64]

This is another breakthrough in orally disintegrating tablets. Mostly, conventional FDC tablets are large and pose challenges in swallowing. This challenge is overcome by formulating such in an ODT as the tablet will disintegrate in the mouth making swallowing easy.

The FDC formulation should be compared with single formulations of the FDC component to ensure bioequivalence. Parameters such as in dissolution testing, apparent permeability and pharmacokinetic modelling should be investigated. Sharma et al (2018) prepared orally disintegrating tablets in fixed-dose combination of Ambroxol Hydrochloride and Salbutamol Sulphate by direct compression method while Thomas J Dennison et al (2017) developed FDC ODTs containing amlodipine and atorvastatin.
6.2 Orally disintegrating tablets modified release formulations[63, 65–68]

Development of modified release formulations of ODTs marks another revolution in this dosage form.

6.2.1 Extended release formulations

ODT extended release formulations have now become available on the market. Amphetamine (Adzenys XR-ODT) and methylphenidate (Cotempla XR-ODT) extended release (ER) ODT formulation of Neos Therapeutics received FDA approval in 2016 and 2017 respectively. The formulation principle for ODT modified release formulation is the same as that used for conventional dosage form. For example, ER methylphenidate ODT attains extended release by coating of the microparticles (70-75) while the immediate release is achieved by the uncoating a certain (25 -30%) proportion of the particles. Hemlata G. Patil et al (2016) Formulated and developed orodispersible sustained release tablet of domperidone employing microspheres technique. In vitro release showed an initial burst of 23% of the drug in one hour followed by sustained release in nine hours. The immediate release was attributed to the drug on the surface of the microspheres.

6.2.2 Enteric coated orally disintegrating tablets

These ODT formulations have also been developed and are suitable for drugs which are irritant to the stomach or get inactivated by gastric fluid. Hadyah Faleh Alotaibi et al (2019) developed enteric orodispersible tablets of diclofenac sodium. They first designed diclofenac sodium pellets followed by coating with Eudragit L 100 as an enteric coat, then Eudragit E 100 for taste masking. These pellets only showed 1.4 % drug releases in simulated gastric fluid and complete dissolution in simulated intestinal fluid. The pellets were used to prepare the orodispersible tablets which showed dissolution of less than 10% in simulated gastric fluid and complete dissolution in simulated intestinal fluid. The disintegration time ranged from 20 to 46 second in simulated saliva fluid.

6.2.3 Muco-adhesive orally disintegrating tablets

This is another added attribute to the orally disintegrating tablets with the view of extending the local action. During the preparation, muco-adhesive polysaccharides are added to the formulation to ensure that the disintegrated particle remain at the site of action for a long time for a sustained action. The active ingredient is first coated with a muco-adhesive polymer/polysaccharide using an adsorbent aqueous solvent. Thereafter other excipients are added before compression or molding into tablets. One typical example of this development
is the muco-adhesive orally disintegrating tablets containing tamarind gum – coated tea powder for oral care by Rika Kiniwa et al (2019) which disintegrated in 30 seconds or less with the highest adhesive and particle retention properties compared to other tablets prepared using other polysaccharides.

6.3 Novel disintegration tester for orally disintegrating tablets \([{}^{29, 63, 69}]\)

As disintegration is a crucial attributes of the ODTs, many pharmaceutical scientists have suggested that the basket rack disintegration test apparatus may not be suitable for testing orally disintegrating tablets as the conditions do not mimic those of the mouth with regard to volume of the disintegration medium, relative humidity, as well as the action of placing the tablet between the tongue and the upper palate. Additionally, the “USP Guidance for industry: Orally Disintegrating Tablets” has recommended the need of an alternative test that mimic the in vivo conditions disintegration of ODTs. It is in this regard that researchers have now come up with alternative testers mimicking the conditions of the mouth.

A texture analyzer with a probe has been used to measure disintegration time as a function of distance moved over time. The tablet is placed in the container and the probe approaches the centre of the tablet at the prescribed speed and pressure. As the probe approaches the tablet, freshly prepared simulated salivary fluid is introduced to cover the surface of the tablet. The probe moves down the tablet as it begins to disintegrate at the same prescribed force. The disintegration profile graph is obtained containing two plateaus. The first plateau represents the contact between the dry tablet and the probe while the second plateau region represents the contact between the probe and the base of the container when disintegration is complete. Disintegration time is considered as the difference in time between the two plateau regions.

A typical example is the Aston disintegration tester proposed by Jasdip S. Koner et al (2019) which is specific for the ODTs. It comprised of the condition which represent those of the oral cavity that is temperature, relative humidity, flow rate of the disintegration medium and the pressure applied on the tablet. In this apparatus, the test hosing was placed on top of the hot plate to maintain the temperature of 37°C. Potassium chloride was also contained in test housing to form saturated salt, maintaining a relative humidity of 93 %. The disintegration bed was flattened, containing silicon pipes with holes of 4 mm diameter to allow simulated saliva fluid at a flow rate of 10 ml/s over the pipes. A probe of a texture analyser moving at a speed of 2 mm/sec was connected to the disintegration compartment, which when in contact
with the disintegration bed, a constant 50 g weight was applied for a certain period of time. Disintegration time was obtained from the plot of distance versus time.

Rika Kiniwa et al (2019) also used a novel disintegration tester (ODmate Imotoseisakusyo, Kyoto, Japan) to test muco-adhesive orally disintegrating tablets. It has a bottom surface with 4 mm mesh where the tablet is placed on the centre and a tester loading tool on top of the tablet. The disintegration medium in this case simulated salivary fluid is placed in the beaker and stirred at 1000 rpm. Then the tablet (between the loading tool and the bottom surface) is lowered into this beaker at the set position. Disintegration time is determined as the time interval between the time of lowering the tester arm at the set position and the time the loading tool touches the bottom of the mesh. The photo microsensor records the start and end points.

6.4. Limitations of orally disintegrating tablets\(^\text{[70-71]}\)

Despite the several advantages that orally disintegrating tablets offer compared to conventional oral dosage form, they also have some limitations. These limitations have include;

- Low mechanical strength which may pose a challenge in handling. Special packaging may be required for fragile tablets to avoid breaking during transportation, storage and patients handling.
- If taste masking is not effectively done, bitterness may remain in the mouth eve after swallowing the saliva. This may affect patient’s compliance.
- Drugs with high doses tend to be difficult to be formulated in orally disintegrating tablets
- Since the excipients used in the formulation of this dosage form are meant to disintegrate/dissolve in minimum water, ODTs may attract water from the surrounding and hence they should be kept in a dry place.
- Special Population - Patients on anticholinergic drugs or with dry mouth condition due to decreased saliva production (Sjogren’s syndrome) may not be best candidates for this type of tablets.

**CONCLUSION**

Orally disintegrating tablets have great potential in enhancing medication therapy. As the oral route of administration still remains the most preferred route of administering medicaments to patients, there is a need to develop an oral dosage form which patients will find very easy and
convenient to take, and very palatable. Orally disintegrating tablets have most of these desired features and with the advanced knowledge in the Pharmaceutical Sciences, and recent development seen in this dosage form, it is hoped that orally disintegrating tablets that will overcome the current limitations will be formulated.

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