2.0 ORALLY DISINTEGRATING TABLETS

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance\(^1\), \(^2\). The most popular dosage forms are conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is dysphagia or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy\(^3\). Recently, orally disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. To overcome such problems, orally disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form. Orally disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. When Faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

These are also called, melt in mouth tablets, rapi-melts, quick dissolving tablets, mouth dissolving tablets, fast disintegrating tablets or dispersible tablets. Their
characteristic benefits like, rapid on-set of action, increased bioavailability, good stability, and better patient compliance make these tablets popular as a dosage form of choice.⁴⁻⁵

**Advantages of Orally Disintegrating Tablets**³⁻⁸

- Convenience of administration and accurate dosing as compared to liquids.

- Ease of administration to patients who cannot swallow a tablet, such as pediatric patients, geriatric patients and, psychiatric patients.

- No need of water to swallow the dosage form, which is a highly convenient feature for patients who are traveling and do not have immediate access to water.

- Good mouth feel property helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.

- Rapid dissolution of drug and absorption which may produce rapid onset of action.

- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.

- Ability to provide advantages of liquid medication in the form of solid preparation.

- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
Technologies used for manufacturing of orally disintegrating tablets

Conventional technologies
1. Freeze drying
2. Tablet molding
3. Spray drying
4. Direct compression
5. Sublimation
6. Mass extrusion

Patented technologies
1. Zydis technology
2. Durasolv technology
3. Orasolv technology
4. Flashdose technology
5. Wowtab technology
6. Flashtab technology

Conventional techniques used for preparation of orally disintegrating tablets\textsuperscript{8-10}

Freeze drying

Freeze drying is a process in which, water is sublimated from the product after freezing. Lyophilization is pharmaceutical technique which allows drying of heat sensitive drugs and biologicals at low temperatures under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.
Tablet molding

In this method, moulded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is moulded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Moulded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

Spray drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus, making tablets of acceptable quality. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent.
Disintegrant addition technique is one popular technique for formulating ODT, because of its easy implementation and cost-effectiveness. The basic principle involved in formulating ODT by disintegrant addition technique is addition of superdisintegrants, like Cross linked carboxymethylcellulose (Crocarmellose), sodium starch glycolate (Primogel, Explotab), polyvinylpyrrolidone (Polyplasdone), indion 414, microcrystalline cellulose and low substituted hydroxypropylcellulose, in optimum concentrations so as to achieve rapid disintegration along with the good mouth feel. Some of the superdisintegrants and their properties which have been used in ODTs are shown in Table 2.0.A

Table 2.0.A Properties of superdisintegrants used in ODTs

<table>
<thead>
<tr>
<th>Superdisintegrant</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croscarmellose sodium</td>
<td>High swelling capacity, effective at low concentration (0.5-2.0%), can be used up to 5%.</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>Completely insoluble in water. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants. Effective concentration (1-3%). Available in micronized grades if needed for improving state of dispersion in the powder blend</td>
</tr>
</tbody>
</table>
Sodium starch glycolate  Absorbs water rapidly, resulting in swelling up to 6%. High concentration causes gelling and loss of disintegration.

Indion 414 Ion  Cross linked polyacrylic with a $-\text{COO}^{-}$ functional group and K + ionic form. High water intake facility.

**Sublimation**

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. Urea, ammonium carbonate, ammonium bicarbonate, naphthalene, urea, camphor etc.) were added to the other tablet excipients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. Mannitol and camphor were used as a tablet matrix material and subliming the material respectively. Camphor was removed by subliming in vacuum at 80°C for 30 minutes to develop pores in the tablets. Additionally, several solvents (e.g. cyclohexane, benzene) can also be used as pore forming agents. Steps involved in sublimation are shown in Fig. 2.0.A.
Mass extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

**Patented technologies for orally disintegrating tablets**\(^{13-17}\)

**Zydis technology**

Zydis, the best known of the orally disintegrating tablets preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also
self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

**Durasolv technology**

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

**Orasolv technology**

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

**Flash dose technology**

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. A flash dose tablet consists of self binding shear form matrix termed as "floss". Shearform matrices are prepared by flash heat processing.
Wowtab technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

Flashtab technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion spheronisation. All the processing utilized conventional tabletting technology. Some of the marketed products of orally disintegrating tablets are listed in Table 2.0.B and Table 2.0.C.
Table 2.0.B: Marketed fast dissolving tablets in India

<table>
<thead>
<tr>
<th>Name of the product</th>
<th>Active ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imodium Lingual</td>
<td>Imodium</td>
</tr>
<tr>
<td>Pepcidin Rapitab</td>
<td>Quick releasing antiulcer, preparation of pepcid</td>
</tr>
<tr>
<td>Mosid – MT</td>
<td>Mouth melt tablet of Mosapride citrate.</td>
</tr>
<tr>
<td>Calritin Reditabs</td>
<td>Immediate Dissolving formulation of Calritin</td>
</tr>
<tr>
<td>Nimulid – MD</td>
<td>Nimesulide</td>
</tr>
<tr>
<td>Zyrof Meltab</td>
<td>Rofecoxib</td>
</tr>
<tr>
<td>Claritin Reditab</td>
<td>micronized loratadine</td>
</tr>
<tr>
<td>Feldene Melt</td>
<td>piroxicam (10 or 20 mg),</td>
</tr>
<tr>
<td>Maxalt-MLT</td>
<td>rizatriptan (5 or 10 mg), peppermint flavour</td>
</tr>
<tr>
<td>Pepcid RPD</td>
<td>famotidine (20 or 40 mg),</td>
</tr>
<tr>
<td>Zyprexa Zydis</td>
<td>olanzapine (5, 10, 15 or 20 mg),</td>
</tr>
<tr>
<td>Zofran ODT</td>
<td>ondansetron (4 or 8 mg), strawberry flavor</td>
</tr>
<tr>
<td>Remeron Soltab</td>
<td>mirtazepine (15, 30, or 45 mg), orange flavor</td>
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</tbody>
</table>
Table 2.0.C: List of US FDA approved odts available in the market

<table>
<thead>
<tr>
<th>Products</th>
<th>Name of the Company</th>
<th>Active Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claritin</td>
<td>R. P. Scherer / Schering Plough, Kenilworth, USA.</td>
<td>Micronized loratidine (10mg)</td>
</tr>
<tr>
<td>Reditab</td>
<td>Kenilworth, USA.</td>
<td></td>
</tr>
<tr>
<td>Feldene Melt</td>
<td>Pfizer Inc, NY, USA.</td>
<td>Piroxicam (10 or 20 mg)</td>
</tr>
<tr>
<td>Maxalt-MLT</td>
<td>R.P.Scherer / Merck &amp; Co., NY, USA.</td>
<td>Rizatriptan (5 or 10 mg)</td>
</tr>
<tr>
<td>Pepcid RPD</td>
<td>Merck &amp; CO., NY, USA.</td>
<td>Famotidine (20 or 40 mg).</td>
</tr>
<tr>
<td>Zyprexa Zydis</td>
<td>R.P.Scherer/Eli Lilly, Indianapolis, USA.</td>
<td>Olanzapine (5, 10, 15 or 20 mg)</td>
</tr>
<tr>
<td>Zofran ODT</td>
<td>R.P.Scherer/Glaxo Wellcome, Middlesex, UK.</td>
<td>Ondansetron (4 or 8 mg)</td>
</tr>
<tr>
<td>Remeron Soltab</td>
<td>CIMA / Organon, Glaxo Wellcome, Middlesex, UK.</td>
<td>Mirtazepine (15,30 or 45 mg)</td>
</tr>
<tr>
<td>Tempra First</td>
<td>CIMA / Mead Johnson, Bristol Myers</td>
<td>Acetaminophen (80 or 160 mg)</td>
</tr>
<tr>
<td>Tabs</td>
<td>Squibb, NY, USA.</td>
<td></td>
</tr>
<tr>
<td>Nulev</td>
<td>CIMA/Schwarz Pharma.</td>
<td>Hyoscine sulphate (0.125mg)</td>
</tr>
<tr>
<td>Zoming ZMT</td>
<td>CIMA / AstraZeneca, Wilmington, USA.</td>
<td>Zolmitriptan (2.5mg)</td>
</tr>
</tbody>
</table>
REFERENCES


