Review Article

Orally Disintegrating Tablets: A Review

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ABSTRACT

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Over the past three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. The aim of this article is to review the development of ODTs, challenges in formulation, new ODT technologies and evaluation methodologies, suitability of drug candidates, and future prospects.

Keywords: Orally disintegrating tablet, improved bioavailability, texture analyser.

INTRODUCTION

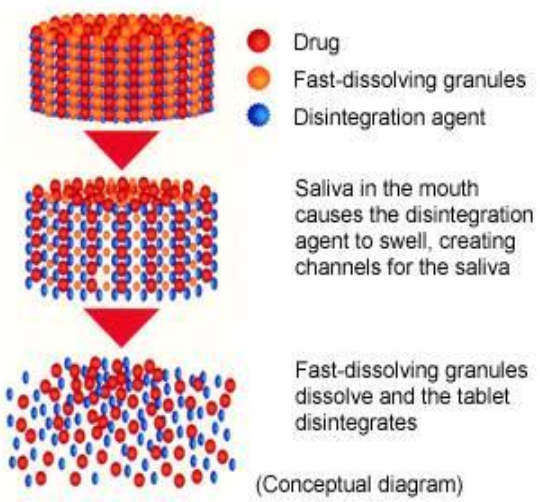
The concept of Fast dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy[5]. 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. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva.

Mechanism of ODT drugs[5]

Generally, ODTs are formulated to disperse rapidly in the mouth, enabling medication to be swallowed without water, thereby increasing convenience and compliance across a broad range of indications and patient types, including the young, elderly, and active patients. "However, ODTs may also be used to deliver drugs to the oral cavity, for local action or, in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake, and reducing undesirable metabolites," The potential for such pregastric absorption rests largely in the physicochemical characteristics of the drug molecule.

Disintegration Mechanisms[16]

Before a tablet dissolves, it has to disintegrate first, unless the tablet is designed for quick surface erosion. The materials used as disintegrates include starches, agar, amylose, cellulose and its derivatives, gum and its derivatives, gelatin, resins, and silicone compounds. A few mechanisms of action of disintegrates have been proposed. The first mechanism is evolution of gas from an effervescent couple, e.g., sodium bicarbonate with citric acid upon absorption of water. The expansion of gas can be enough to cause the tablet to disintegrate. Another mechanism is swelling of disintegrates by absorbing water to break up the tablet structure.



Advantages[14,15]:

a) Clinical benefits
- Improved oral absorption.
- Faster onset of action.
- Minimized first pass effect.
- Improved bioavailability.

b) Medical/ Patient benefits
- better taste
- No water required.
- Improved safety and efficacy
- Improved compliance

c) Technical benefits:
- Accurate dosing compared to liquid products
- Contains sugars and GRAS (Generally Regarded As Safe) excipients
- Improved stability due to better packaging.
- Employ common process and convenient equipments

d) Business benefits
- Unique product differentiation
- Value added product line extension
- Provide exclusive marketing
- Extend patent protection.

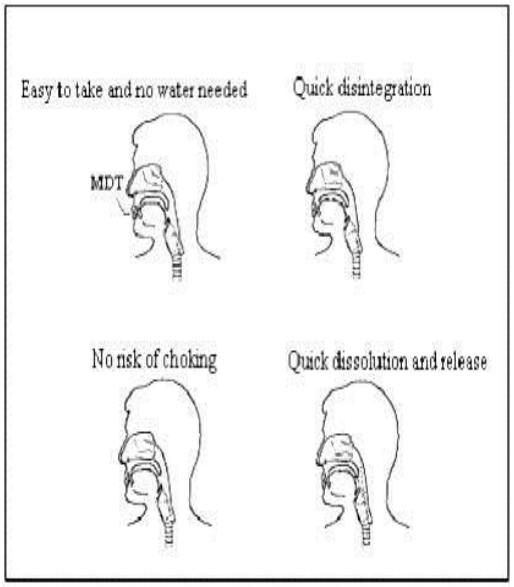


Fig. 1: Diagram Showing Advantages of ODT

Limitations
- limited amount of drug can only be incorporated (For lyophilized dosage forms, the drug dose must be lower than 400mg for insoluble drugs and less than 60 mg for soluble drugs.
- Cannot provide controlled or sustained release, except those that contain slow-dissolving, micro particulate coated drugs, which quickly disperse and are swallowed.
- These are fragile products requiring special unit-dose packaging, which may add to the cost.(Exceptions – WOWTAB, DURASOLV, ADVATAB technologies)

Selection of ODT drug candidates[5]

The ideal characteristics of a drug for *in vivo* dissolution from an ODT include
- No bitter taste
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

Unsuitable drug characteristic for ODT
- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release.

Characteristics of Fast Dissolving Delivery Systems[14]

1. Ease of administration

Fast Dissolving Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

2. Taste of the medicament

As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

3. Hygroscopicity

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging[11].

4. Friability

In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either

very porous and soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets.

***5. Mouth feel*[9]**

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

Approaches for Fast Dissolving Tablets

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

TECHONOLOGIES FOR PREPARING ODT'S[1,14,15]

Various technologies used in the manufacture of Fast dissolving tablets include

- Freeze –drying or lyophilization
- Tablet Molding
- Direct compression
- Spray drying
- Sublimation
- Taste masking
- Mass extrusion

a. Freeze drying or Lyophilization

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation[16]. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolves rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomycin[17].

b. Molding

Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases is absorbed through the mucosal lining of the mouth. Molded forms are also prepared using a heat-molding process that involves setting the molten mass that contains a dispersed drug[20]. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at -30C under vacuum.

c. Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen et al. have reported applying this process to the production of fast dissolving tablets[22]. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatin as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 s in an aqueous medium.

d. Sublimation

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe, Knitsch et al., and Roser and Blair, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine,

naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a table[23].

e. 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. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar-based excipients.

Excipients used in direct compression ODT formulations[2,3]

a) Super disintegrants: Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

b) Flavours: Peppermint flavour, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptos oil thyme oil, oil of bitter almonds. Flavoring agnets include, vanilla, citus oils, fruit essences

c) Sweetners: Aspartame, Sugars derivatives.

d) Fillers: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide.

e) Lubircants: Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide

Addition of disintegrants: Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction so-called superdisintegrants and a better understanding of their properties have increased the popularity of this technology[24]. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases[33].

Sugar-based excipients: another approach to fast dissolving tablets by direct compression is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol), which display high aqueous solubility and sweetness, and hence, impart taste masking and a pleasing mouthfeel.

Method of addition of disintegrants

Disintegrants, an important excipient of the tablet formulation, are always added to the tablet to induce break up of the tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which include are known as disintegrants.

Superdisintegrants are generally used at low level in solid dosage forms, typically 1-10% by weight relative to the total weight of dosage unit. Examples of superdisintegarnts are crosscarmelose sodium, crosspovidone, Sodium starch glycolate which represent example of a cross linked cellulose, cross linked polymer and a cross linked starch respectively.

The ideal characteristics of a disintegrates are

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good molding and flow properties
- No tendency to form complexes with the drugs.

There are three methods of incorporating disintegrating agents into the tablet;

- Internal addition (Intragranular)
- External addition (Extra granular)
- Partly Internal and external

Mechanism of tablet disintegrants[16]:

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

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

7. By enzymatic action.

f. Taste masking

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Drugs with unacceptable bitter taste can be microencapsulated into p^H sensitive acrylic polymers[26]. Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted hydroxypropyl cellulose) when coated with a water insoluble polymer (e.g. ethyl cellulose) masked the bitter taste of sparfloxacin. The addition of low substituted hydroxypropyl cellulose as disintegrant to the drug in cores resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets.

g .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.

CONCLUSION

Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms. The target population has expanded to those who want convenient dosing anywhere, anytime, without water. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for ODTs in the days to come.

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