



REVIEW ARTICLE

PHARMACEUTICS

ORODISPERSIBLE TABLETS: AN OVERVIEW OF FORMULATION AND TECHNOLOGY*Corresponding Author***K.B.DESHPANDE**

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ABSTRACT

Now-a-days, orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. Over the past three decades, orodispersible 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. New ODT technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for paediatric, geriatric, and psychiatric patients with dysphagia. 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.

KEYWORDS

Orodispersible tablets(ODTs), Improved bioavailability, Superdisintegrants, orodispersible technologies. Orodispersible drug delivery systems (ODDDS).

INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to many other routes¹. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms.

Those who are traveling or have little access to water are similarly affected^{2, 3, 4}. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orodispersible Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms^{5, 6, 7}.

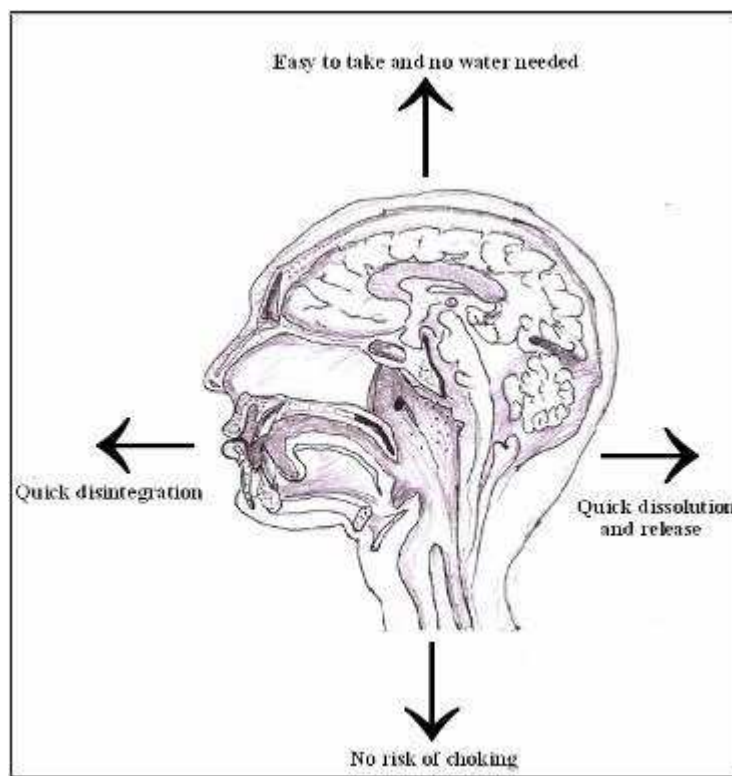


Figure 1
Mechanism of action of orodispersible tablet



When such tablets are placed in oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration⁸. Recent market studies indicate that more than half of the patient population prefer ODTs to other dosage forms⁹. Most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs over regular tablets or liquids (>80%)¹⁰. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue"¹¹. The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing¹².

Ideal properties of ODTs¹³:

- Require no water for oral administration, yet dissolve/disperse/disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable
- Leave minimal or no residue in mouth after administration. Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipments.

Advantages of Orodispersible tablets¹⁴:

Fast dissolving technology offers:

- No water needed
- No chewing needed
- Better taste
- Improved stability
- Suitable for controlled/sustained release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Cost- effective

- rapid drug therapy intervention
- High drug loading is possible.
- Have acceptable taste and pleasant mouth feeling.
- Leave minimum residue.

Limitations to orodispersible tablets¹⁵:

- i) Drugs with relatively larger doses are difficult to formulate into ODTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
- ii) Patients who concurrently take anticholinergic medications may not be the best candidates for ODTs.

Need to formulate orodispersible tablets¹⁶:

The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. ODT is one such dosage form which is useful for Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.

- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.
- Especially for Patients with persistent nausea for a long period of time are unable to swallow.
- Mentally challenged patients, bedridden patients and psychiatric patients.

Challenges in formulation orodispersible tablets¹⁷:

I. Mechanical strength and disintegration time:

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Many ODTs are fragile and there are many chances that such fragile tablet will break during packing, transport or handling by the patients. Tablets based on technologies like



Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential.

II. Taste masking:

Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

III. Mouth feel:

ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODTs should be as small as possible. ODTs should leave minimal or no residue in mouth after oral administration. Moreover addition of flavours and cooling agents like menthol improve the mouth feel.

IV. Sensitivity to environmental conditions:

ODTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in ODTs are meant to dissolve in minimum quantity of water.

V. Cost:

The technology used for ODTs should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

Selection of ODT Drug Candidates:

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. It is assumed that the absorption of a drug molecule from the ODT occurs in the post gastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An ODT may have varying degrees of pre-gastric absorption and thus, the pharmacokinetic profiles will vary²¹. Therefore, the ODT will not be bioequivalent to

the conventional oral dosage form. For example, ODT formulations of selegiline, apomorphine and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form^{18, 19}. It is possible that these differences may, in part, be attributed to the drug molecule, formulation or a combination of both. If significantly higher plasma levels have been observed, pre-gastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT²⁰.

Technologies used to manufacture orodispersible tablets:

CONVENTIONAL TECHNOLOGIES

- i. Freeze Drying.
- ii. Tablet Molding.
- iii. Direct Compression
- iv. Spray Drying.
- v. Sublimation.

PATENTED TECHNOLOGIES

- i. Zydis Technology.
- ii. Orasolv Technology.
- iii. Durasolv Technology.
- iv. Wowtab Technology.
- v. Flashdose Technology.
- vi. Flashtab Technology

1. Freeze drying

ZYDIS® (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of fast disintegrating dosage forms. There are approximately 12 marketed ZYDIS® products, including lorazepam, piroxicam, loperamide, loratidine, enalapril²¹. 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 biological at low temperature under conditions that allow removal of water by sublimation.

2. Moulding



In this method, molded 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 molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

3. **Spray drying:**

The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscarmellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.

4. **Sublimation:**

Sublimation has been used to produce ODTs 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. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix.

5. **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.

6. **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. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into ODTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit)²².

7. **Cotton candy process:**

The flashdose® is an ODDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shear form 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. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation.

8. **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 method.

Table no.1
showing some patented technologies

Sr. No.	Patented Technologies	Inventers
1.	Zydis technology	Zydis
2.	Takeda technology	Takeda (Osaka, Japan)
3.	Novartis technology	Novartis Consumer Health (Basel, Switzerland)
4.	Nippon Shinyaku technology	Nippon Shinyaku (Kyoto, Japan)
5.	Flashtab technology	Ethypharm (Paris, France)
6.	Wowtab technology	Yamanouchi (Tokyo, Japan)
7.	Daiichi technology	Daiichi (Tokyo, Japan)
8.	Orasolv technology	Cima Labs (Eden Prairie, MN)
9.	Ziplets technology	Eurand (Pessano con Bornago, Italy)
10.	Lyoc technology	Pharmalyoc
11.	Nanocrystal technology	Elan, King of Prussia

Evaluation of fast dissolving tablets:

1. Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using micrometer.

2. Weight variation²³:

Standard procedures are followed as described in the official books.

3. Friability²⁴:

Friability Attempts for decreasing the disintegration time increase the friability of ODTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic

chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100$$

4. Hardness (Crushing strength)²⁵:

Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation.

5. Wetting time²⁶:



The initial process in the disintegration of a ODT involves water uptake and wetting of the tablet. So determination of wetting time is also important. It also helps in studying the effect of various excipients in the disintegration of the tablet. The method reported by Yunxia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet as put on the paper, and the time for complete wetting was measured.

6. *Disintegration time*²⁷:

According to the European pharmacopoeia the fast disintegrating or Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen. However it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. To overcome these problems, several new methods have been proposed. One of these methods uses a Charge Couple Device (CCD) camera or texture analyzer to evaluate the disintegration time of tablets. In another method, a modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature at 37°C and a magnetic stirrer. DT is noted at 25 rpm. One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted.

7. *In vivo disintegration time*²⁸:

In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth.

8. *Dissolution test*²⁹:

The dissolution method for oral disintegrating tablets is the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used. The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets.

9. *Stability study (Temperature dependent)*:

The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) $40 \pm 1^\circ\text{C}$

(ii) $50 \pm 1^\circ\text{C}$

(iii) $37 \pm 1^\circ\text{C}$ and RH 75% \pm 5%

The tablets were withdrawn after 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 ° C.

Industrial Applications:

Industrial applications include the following:

- To develop an orally disintegrating dosage forms and to work with existing disintegrants
- To further improvise upon the existing technology of ODTs
- To optimize the blend of disintegrants or excipients to achieve ODTs
- To select and develop proper packaging material and system for enhanced stability of the product and also develop a cost-effective product



- To arrive at various taste-masking agents and prepare palatable dosage forms thereby increasing patient compliance
- To develop disintegrants from different polymers which are used as coating materials by certain modifications and use them for formulating ODTs

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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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. By paying close attention to advances in technologies, pharmaceutical companies can take advantage of ODTs for product line extensions or for first-to-market products. 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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