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REVIEW ARTICLE ON ORAL DISPERSIBLE TABLETS (ODT'S): NOVEL TECHNOLOGY, DEVELOPMENT, AND EVALUATION

Pooja P. Kulkarni[1]*, Gururaj S. Kulkarni[1] and Padmaa M. Paarakh[2]

[1]Department of Pharmaceutics, [2]Department of Pharmacognosy
The Oxford College of Pharmacy, Bangalore-68.

***Corresponding Author: Pooja P. Kulkarni**

Department of Pharmaceutics, The Oxford College of Pharmacy, Bangalore-68.

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ABSTRACT

The most common and preferred route of administration of drugs is through the oral route. Oral dispersible tablets are gaining more importance among novel oral drug-delivery systems as they have improved patient compliance and have some additional advantages compared to other oral formulations. A new dosage form known as an orally disintegrating tablet (ODT), has been developed which rapidly disintegrates & dissolves in saliva and is then easily swallowed without water which is a major benefit over the conventional dosage form. Thus this type of drug delivery helps a proper peroral administration in paediatric and geriatric populations where trouble arises in swallowing. Various scientists have prepared oral dispersible tablets by following various methods. However, the most common method of preparation is the compression method. Other special methods are moulding, melt granulation, phase-transition, sublimation, freeze-drying, spray-drying, and effervescent method. Since these tablets dissolve directly in the mouth, so, their taste is also an important factor. Various approaches have been to mask the bitter taste of the drug. Several scientists have explored several drugs in this field. The oral dispersible tablets are evaluated for hardness, wetting time, friability, moisture uptake, disintegration test, and dissolution test.

KEYWORDS: ODT's, Disintegration, Dissolution, Bioavailability.

INTRODUCTION

The ideal dosage form in any disease is said to be the one, which immediately attains the desired therapeutic concentration of drug in plasma and maintains it constant for the entire duration of treatment. Drugs are more often taken by oral route. So, the drugs through the oral route are considered the most natural, uncomplicated, convenient, and safe form of administering drugs, with greater flexibility in dosage form design, ease of production, and low cost.[1] Drug delivery through the oral route is the most common and preferred route of drug administration both for solid and liquid dosage forms. However, solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly patient compliance. But many people face difficulty in swallowing. This difficulty in swallowing is called dysphasia. Thus, these conventional dosage forms result in a high incidence of non-compliance and ineffective therapy for swallowing especially in the case of paediatric, geriatric, or any mentally retarded persons.[2] Oral dispersible tablets are also called orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast-disintegrating tablets, and fast-dissolving tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing.[3] Thus, oral dispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, that help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing or inconvenience. Since the absorption is taking place directly from the mouth, so, the bioavailability of the drug increases. Drugs present in oral dispersible tablets are also not suffering from first-pass metabolism. Thus oral dispersible tablets are becoming popular day by day due to their numerous advantages.[4]

Prerequisite for odt: There are some prerequisite or prior conditions for fast disintegrating tablets like,

1. Tablet must disintegrate and disperse in the oral cavity without water intake.
2. It can hold high drug quantities.
3. It should be compatible with taste-masking agents and excipients, and have an optimum sensation effect.
4. Leave minimum to no residue after administration.
5. It should have an optimum capacity to remain intact in formulation processes. It should be stable in the range of temperature and humidity.
6. It should be adaptable and amenable to existing processing and packaging machinery.
7. It should be manufactured at a low cost.[6]

Advantages

- Ease of administration is the major advantage for the patients who have problems with swallowing drugs such as patients in a shocking state, stroke victims, bedridden patients, patients who are suffering from kidney failure, paediatric, and geriatric patients.
- Produces pleasant taste effects that change the medication perception. This factor is useful while preparing doses for paediatric patients.
- There is no risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- Rapid absorption or increase in bioavailability is achieved through pregastric absorption of drugs from the mouth, pharynx, and oesophagus as saliva passes down.
- Accurate dosing when compared to liquids.
- New business opportunities like product differentiation, life cycle management, the exclusivity of product promotion, and patent life extension.[8]

Disadvantages

- Sometimes ODTs are highly fragile.
- In each dose low amount of drug can be incorporated.
- Since ODTs don't have enough hardness they must be handled with great care.
- Most of the time soluble diluents used for formulating ODTs might render hygroscopic dosage which may lead to stability issues.
- The tablets may leave an unpleasant taste and/or grittiness in the mouth if not formulated properly.
- Specialized packing might be required for hygroscopic and light-sensitive drugs.
- Light-sensitive drugs, ODTs may not be suitable as no option for film coating.[9]

Techniques in preparation of oral dispersible tablet:

1. **Freeze drying/ Lyophilization:** Lyophilization means drying at a low temperature under the condition that involves the removal of water by sublimation. The Drug is dissolved in a water-soluble matrix which is then freeze-dried to give a highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat-sensitive drugs i.e. thermo-labile substances. The freeze-drying process normally consists of three steps: Material is frozen to bring it below the eutectic point. Primary drying to reduce the moisture by around 4% w/w of dry product. Secondary drying to reduce the bound moisture up to the required final volume.[10]

2. **Spray drying:** Spray drying technique is based on a particulate support matrix, that is prepared by spray drying an aqueous composition containing support matrix and other components that form highly porous and also fine powders. These are then mixed with active ingredients and compressed into tablets. The formulations are then incorporated by hydrolyzed and non-hydrolyzed gelatins as supporting agents, mannitol used as a bulking agent, sodium starch glycolate(SSG) or croscarmellose sodium as disintegrating agents, and an acidic material and/or alkali material to enhance disintegration and dissolution. Tablet compressed from the spray-dried powder disintegrated within 20 seconds when immersed in an aqueous medium.[11]

3. **Moulding:** Tablets prepared by this method are solid dispersions. Moulded tablets offer improved taste due to water-soluble sugars present in the dispersion matrix. The moulding process is of two types i.e. solvent method and heat method. The solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure. The heat moulding process involves the preparation of a suspension that contains a drug, agar and, sugar (e.g. mannitol or lactose) and pouring the suspension into the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30^0C under vacuum.[12]

4. **Sublimation:** In this method, a subliming material like (Ammonium bicarbonate, Ammonium carbonate, Urea, Benzoic acid, Naphthalene, and camphor) is removed by sublimation from compressed tablets, and porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to the sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to the sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.[10]

5. **Mass extrusion:** In this mass extrusion technique the mixed ingredients are softened by water-soluble ingredients i.e. polyethylene glycol, using methanol as a solvent, passing through an extruder to form thin cylinders. Which further get sliced with a heated blade to form small tablets. Characteristics of this method are these products can be used to mask bitter tasting drugs making small granules thus enhancing oral bioavailability.[12]

6. **Cotton candy process:** This method involves simultaneous action of rapid melting and spinning to

prepare a matrix of polysaccharides. This candy floss matrix is then recrystallized milled and mixed with active drugs along with excipients and compressed to form a fast-dissolving tablet. Characteristics of this method are high quantity of doses can be accommodated in this dosage form with high mechanical strength.[12]

7. **Nanonization:** a recently built technology called nanomelt technology that reduces the particles to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against the agglomeration process by surface adsorption on selected stabilizers, which are then incorporated into mouth dissolving tablets. This is for poorly water-soluble drugs. The other advantages of this technique are the fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost-effective manufacturing process, and conventional packaging due to exceptional durability.[12]

8. **Compaction methods:** Conventional methods for the preparation of tablets such as dry granulation, wet granulation, and direct compression also exist for the preparation of orodispersible tablets. Some important super disintegrants, which are used during the preparation of orodispersible tablets, are crospovidone, croscarmellose sodium, sodium alginate, and acrylic acid derivatives. Baclofen orodispersible tablets were prepared by direct compression method using crosspovidone and sodium starch glycolate as super disintegrants. Even orodispersible tablets of Carbamazepine were prepared by this method having microcrystalline cellulose and crosspovidone (2%-10%). In all the cases it has been found that preparation by compression method along with the addition of super disintegrants in correct concentration obey all the properties of orodispersible tablets.[12]

Patented technologies

Flashtab technology: Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this method consist of drug/ active ingredients in the form of microcrystals. Drug micro granules may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion spheronisation. All these processes use conventional tableting techniques.[13]

Quick-dis technology: The novel intra-oral drug delivery system, trademarked as Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. When the film is placed on the top or the floor of the tongue, it is withheld at the site of application and quickly releases the active agent for local or systemic absorption. The typical disintegration time is only 5-10 seconds for the Quick-Dis™ film with a thickness of 2 mm.[13]

Oraquick technology: The Oraquick fast-dissolving or disintegrating tablet formulation utilizes patented taste-masking technology. This taste masking process does not utilize solvents of any kind, so produces faster and more efficient products. This technique is suitable for heat-sensitive drugs because the process involved processes low heat. K.V Pharmaceuticals also claims that the matrix which surrounds and protects the drug powder in the microencapsulated particle is more pliable. This technique is used in bitter-tasting drugs because it gives a drug good taste and also quick dissolution is achieved.[14]

Wowtab technology: Wowtab Technology is patented by "Yamanouchi Pharmaceutical Co. "WOW" means "Without Water". In this process, a combination of low mouldable saccharides and high mouldable saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldable saccharide and granulated with a high mouldable saccharide and compressed into a tablet.[14]

Zydis technology: 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 a heated blade to form the tablets. The dried cylinder can also be used to mask the bitter taste of the drug by coating the granules.[13]

Evaluation of oral dispersible tablets

Pre-compression parameters:[15]

Organoleptic properties: Organoleptic properties of API like color, odour and stability were observed and recorded. Solubility was observed in methanol and sodium hydroxide.

Angle of repose: The Angle of repose can be determined using the fixed funnel method. The powder blend when poured through a funnel that is raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose can be calculated using the formula.

$\Theta = \tan^{-1}(h/r)$

Where; Θ= angle of repose,

H=height of the pile and

r = radius of the pile.

Sl. No.	Angle of repose	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>35	Very poor

Bulk density: Bulk density is the ratio of a given mass of powder and its bulk volume. Bulk density can be determined by measuring the volume of a known mass of

powder sample that has been passed through the screen into a graduated cylinder or through a volume measuring apparatus into the cup.
Bulk density = M / V_0
Where M= mass of the powder;
V_0=bulk volume of the powder.

Tapped density: to measure the tapped density a known quantity of powder was transferred into a graduated cylinder and volume V_0 was noted. The cylinder was fixed to a density determination apparatus, tapped 500 times then readings were observed. The density was achieved by mechanically tapping the measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume readings were taken until little further volume changes were observed.
Tap density = M / Vr
Where M = mass of the powder,
Vr = final tapping volume of the powder.

Hausner's ratio: Hausner's ratio was determined as the ratio between the tapped density to that bulk density. It can be calculated by the formula:
Hausner's Ratio =TD/BD.
Where TD= tapped density and BD= bulk density.

Compressibility: The compressibility index was determined by Carr's compressibility index.
Carr's Index % = TD-BD/ TD x 100
Where 'TD' is the tapped density and 'BD' is the bulk density.

Post-compression parameters

Content uniformity

The test for uniformity of content is based on the assay of the individual content of drug substance(s) in several individual dosage units to determine whether the individual content is within the limit. The test for content uniformity is required for tablets containing <25 mg or <25% of one tablet. The content of the active ingredient is determined in each of 10 dosage units taken at random using the method described in the assay. The preparation complies with the test if individual content is 85-115% of average content.[16]

Hardness

The hardness of the tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion, or breakage under the condition of storage transformation and handling before usage depends on its hardness. The hardness of the tablet of each formulation was determined using the Monsanto Hardness tester. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets.[17]

Thickness

The thickness and diameter of the tablets were determined using a micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.[18]

Friability test

Friability is the loss of weight of a tablet in the container due to the removal of fine particles from the surface. A friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling, and transport. Roche friabilator is employed for finding the friability of the tablets. Friabilator consists of a plastic chamber that revolves at 25 rpm and drops the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and was subjected to 100 revolutions. Tablets were de-dusted utilizing a soft muslin cloth and reweighed, the loss in the weight of the tablet is the measure of friability and is expressed in percentage as.[19]

$$\% F = \frac{\text{Weight of tablet before the test - Weight of tablet after test}}{\text{Weight of tablet before the test}} \times 100$$

Uniformity of weight

The weight variation test is done by weighing 20 tablets individually and calculating the average weight of the tablet and then comparing the individual tablet weight to the average weight.[16]

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. The water absorption ratio (R), was determined using the following equation,[20]

$$R=10\times WaWb$$

Where,
Wb= weight of tablet before water absorption and
Wa= weight of tablet after water absorption.

Disintegration time

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996. Distilled water at 37°C ± 2°C was used as a disintegration medium and the time in the second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.[21,22]

Modified disintegration test

Many reports suggest that conventional disintegration test apparatus may not give correct values for disintegration tests for ODTs. The amount of saliva available in the oral cavity is very inhibited (<6 ml) whereas the conventional disintegration test apparatus utilizes a substantial amount of dihydrogen monoxide with very rapidly up and down forms of kineticism. In the simplest method to surmount this quandary, 6 ml of

phosphate buffer of pH 6.8 was taken in a 25 ml quantifying cylinder. The temperature was maintained at 37± 2°C. An ODT was put into it and the time required for consummate disintegration of the tablet was noted.[23]

Wetting time

Wetting time indicates the inner structure of the tablets and the hydrophilicity of the excipients. Thus, the wetting time of a dosage form is related to the contact angle. The lower the wetting time the quicker is the disintegration of the tablets. The wetting time can be measured by using five circular tissue papers of 10 cm in diameter, which are placed in a Petri dish of 10 cm in diameter. Ten milliliters of water-soluble dye like eosin solution are added to the Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet is noted as the wetting time. For measuring the water-absorption ratio, the weight of the tablet before keeping it in the Petri dish is noted (Wb). The wetted tablet from the Petri dish is taken and reweighted (Wa). The water absorption ratio, *R* can be determined according to the following equation:[18]

$R = 100 (Wa - Wb)/Wb.$

Moisture-uptake studies

It is an important study in the case of orodispersible tablets. This study is carried out to assess the stability of the tablets. Ten tablets were kept in the desiccators over calcium chloride at 37°C for 24 h. The tablets were then weighted and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccators for 3 days. One tablet as a control (without super disintegrant) was kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded.[24]

Disintegration test

The *in-vitro* disintegration time was determined by the disintegration test apparatus. The time for the disintegration of orodispersible tablets is generally <1 min and the actual disintegration time that patients can experience ranges from 5 to 30 s. A tablet is placed in each of the six tubes of the apparatus, and one disc is added to each tube. The standard procedure of performing disintegration tests for these dosage forms has several limitations. It is expected that the disintegration test for orodispersible tablets should mimic disintegration in the mouth within salivary contents by using modified United States Pharmacopoeia Apparatus II by taking 900 ml of medium maintaining 37°C with r/min 100. Orodispersible tablets were placed in a basket sinker in the middle of the vessel at a distance of 6-8.5 cm and carried out the disintegration test with the rotary shaft method. The apparatus consisted of stainless steel wire gauze on which orodispersible tablets were placed and slightly immersed in the medium. Here, the rotary shaft is used to provide rotation and mechanical stress.[25]

Dissolution test: Dissolution studies were carried out by using USP Dissolution Apparatus at 50 rpm. The drug release profile was studied in 500 mL of pH buffer by maintaining at 37±0.5°C. Aliquots (5 mL) of dissolution medium were withdrawn at specific time intervals, filtered and the amount of drug released was determined spectrophotometrically. Three trials for each batch were performed and the average percentage of drug release with standard deviation was calculated and recorded.[25]

CONCLUSION

The introduction of orodispersible tablets has solved some of the problems encountered in the administration of drugs to pediatric and elderly patients. ODTs are solid unit dosage forms containing super disintegrants that impart quick disintegration in the presence of saliva and without producing any difficulty in swallowing the tablet. As soon as the tablet gets disintegrated in the mouth, the drug is released, then it is dissolved or dispersed in saliva and is absorbed sublingually. This results in greater bioavailability. ODTs offers advantage such as self-administration, quick or immediate onset of action, no water required for swallowing, avoiding first-pass metabolism of the drug, and increased bioavailability. Thus, ODTs can be used as an appreciable alternative shortly.

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