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ORODISPERSIBLE TABLETS: A SYSTEMATIC REVIEW

Sachin Gholve[1]*, Amar Kaware[1], Sanjay Thonte[2], Dattahari Kaudewar[2] and Omprakash Bhusnure[1]

[1]Department of Quality Assurance, Channabasweshwar Pharmacy College (Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India-413512.

[2]Channabasweshwar Pharmacy (Polytechnic) College, Kava Road, Basweshwar Chowk, Latur, Maharashtra, India-413512.

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***Corresponding Author**
Sachin Gholve
Department of Quality Assurance, Channabasweshwar Pharmacy College (Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India-413512.

ABSTRACT

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. 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 pediatric, geriatric, and psychiatric patients with dysphagia. Orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. 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, Bioavailability, Superdisintegrants, Orodispersible technologies. Orodispersible Drug Delivery Systems (ODDDS).

INTRODUCTION

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. When such tablets are placed in oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration[1]. Recent market studies indicate that more than half of the patient population prefer ODTs to other dosage forms[2]. Most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs over regular tablets or liquids (>80%).[3]

EVALUATION OF ORODISPERSIBLE 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 variation[4]

Standard procedures are followed as described in the official books.

3. Friability[5]

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: % Friability = 1- (loss in weight / Initial weight) X 100.

4. Hardness (Crushing strength)[6]

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 time[7]

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 Yunixia 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[8-11]

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.

Advantages of ODT[12]

1. It can be administered to the patient who cannot swallow conventional dosage form.
2. Good mouth feel property helps to mask the bitterness of medicines.
3. Rapid drug therapy intervention.
4. It provides rapid absorption of drugs and increased bioavailability.
5. It allows high drug loading.
6. No chewing needed.

Disadvantages of ODT's[13]

1. It requires proper packaging for safety and stabilization of stable drugs.

2. It is hygroscopic in nature, so must kept in dry place.
3. It shows the fragile, effervescence granules property.
4. If not formulated properly, it may leave unpleasant taste in mouth

APPROACHES

1. Freeze Drying Technology (Zydis Technology)

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless. Lyophilization is relatively expensive and time consuming manufacturing process. Other drawback includes fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition.

2. Tablet Moulding

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is moulded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

3. Spray Drying

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous

composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets. Allen et al used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 seconds.

4. Direct Compression Method

In this method, 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 pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The disintegrant addition technology is cost effective and easy to implement at industrial level. The tablets disintegrate in the mouth in less than 60 seconds. Gas Evolving disintegrants have been used to formulate fast dissolving tablets. Michaelson described the use of intimate mixture of algenic acid and a water-soluble metal carbonic acid to prepare tablets. When tablet was placed in water, an acid base reaction takes place forming a metal alginic acid salt and carbonic acid. The salt caused the tablet to swell and the carbonic acid produced carbon dioxide within the swelling tablet whereby rapid disintegration of tablet was effected.

5. Sublimation Technique

The basis of this technique is to add inert solid ingredients that volatilize readily, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure. Mannitol and camphor were used as a tablet matrix material and subliming the material respectively. Camphor was iminated by subliming in vacuum at 80°C for 30 minutes to develop pores in the tablets. Makino et al described a method of producing a fast dissolving tablet using water as a pore forming material.

6. Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent 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 for bitter drugs and thereby achieve taste masking.

7. Taste Masking

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking ingredients can be achieved by various techniques; Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers. Cefuroxime axetile 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.

EXCIPIENTS USED FOR PREPARATION OF ODTS:

1] Superdisintegrant

It increases the rate of disintegration and dissolution. For the success of orally disintegrating tablet, the tablet having quick dissolving property which is achieved by super disintegrants.

Examples - Crosspovidone, MCC, Sodium starch glycolate, CMC, etc.

2] Sweeteners and sugar based excipients

Sugar based excipients act as bulking agents. They exhibit high aqueous solubility and sweetness and impart taste masking property.

Examples -Aspartame, Sugar derivative, Dextrose, Fructose, Mannitol, Sorbitol, Maltose.

3] Flavors-It increases patient compliance and acceptability

Examples -Vanilla, Citrus oil, Fruit essence, Eucalyptus oil, Clove oil, Peppermint oil.

4] Surface Active agents

It reduces interfacial tension and thus enhances solubilization of ODTs. Examples- Sodiumlaurlysulfate, Sodium – doecylsulfate etc.

5] Binder- It maintains integrity of dosage form

Examples- PVP, Polyvinylalchol, Hydroxy propyl methylcellulose.

6] Colour

It enhances appearance and organoleptic properties of dosage form.

Examples -Sunset yellow, Red iron oxide, Amaranth3.

7] Lubricants

It helps reduces friction and wear by introducing a lubricating film.

Examples -Stearic acid, Magnesium stearte, Zinc stearte, Talc, Polyethylene glycol.

8] Fillers

It enhances bulk of dosage form.

Examples -Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate.

EVALUATION PARAMETERS[14-22]

Precompression Parameters.

Angle of Repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using formula (Rockville et al., 2007). = −1 ( ) Where, θ is angle of repose, h is height of pile and r is the radius of the base pile.

Bulk Density

Apparent bulk density (LBD) was determined by pouring blend into a graduated cylinder. The bulk volume (Vo) and weight of powder (M) was determined. The bulk density was calculated using the formula (Rockville et al., 2007; Lieberman et al., 1990). = h h ( )/ h ()

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight of powder blend (M) as measured. The tapped density (TBD) was calculated using the formula (Rockville et al., 2007; Mukesh et al., 2009). = h h ( )/ h ( ).

Carr's Compressibility Index

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (C) which is calculated by using the following formula. C = [(-)] ×100.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula (Rockville et al., 2007). Hausner's ratio = ( )/ ( ) Where TBD is tapped density and LBD is bulk density. Lower Hauser ratio (< 1.25) indicate better flow properties than higher ones (>1.25).

Post compression parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution.

Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the Table 3 and none deviate by more than twice the percentage The mean and standard deviation were determined.

Thickness

The thickness and diameter of the tablets was 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.

Hardness

Test The hardness of the tablet was determined using Monsanto Hardness Tester (Rockville et al., 2007) and other tester is Fizer, Erweka, Strong Kob etc. Limit-: Not less than 2.0 kg/cm2.

Friability Test

Six tablets from each batch were examined for friability using Roche Friabilator and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, deducted and reweighted and % friability was calculated. = h − h / h ×100 Limit- Not more than 1.0% w/w.

Water Absorption Ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation. = wa−wb/ wawb ×100 Where Wb and Wa are the weight before and after water absorption, respectively.

Wetting Time

A piece of tissue paper (12cmX10.75cm) folded twice was placed in a small Petri dish (ID = 9 cm) containing 6ml pH 6.8 phosphate buffer, A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

Content Uniformity Test

Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 200mg of Lansoprazole was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, The absorbance was measured at wavelength 291nm using double beam UV-Visible spectrophotometer (IP, 2007). Content uniformity was calculated using formula % Purity = 10 C Absorbance of unknown (Au) Absorbance of Standard (As) Where, C - Concentration.

In Vitro Disintegration Time

Initially the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time (EP, 1988).

In Vitro Dissolution Testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electro lab, Mumbai, India.). The dissolution test was per-formed using900ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 37°C±0.5°C. Ten ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 291nm.

Table 1: Marketed product of orodispersible tablets.

Name of the Product	Active Ingredients
Imodium Lingual	Imodium
Pepcidin Rapitab	Quick releasing antiulcer preparation of pepcid
Mosid – MT	Mouth melt tablet of Mosapride citrate
Calritin Reditabs	Immediate Dissolving formulation of Calritin
Nimulid – MD	Nimesulide
Zyrof Meltab	Rofecoxib
Claritin Reditab	Micronized loratadine
Feldene Melt	Piroxicam (10 or 20 mg),

MECHANISM OF ACTION OF SUPERDISINTEGRANT[23-25]

1. Because of heat of wetting (air expansion).
2. Swelling.
3. Porosity and capillary action (Wicking).
4. Due to disintegrating particle/particle repulsive forces.
5. Due to deformation.
6. Due to release of gases.

(1) By Capillary Action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

(2) By Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

(3) Because of Heat of Wetting (Air Expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

(4) Due to Release of Gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants

are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

(5) By Enzymatic Reaction

Enzymes presents in the body also act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

(6) Due to Disintegrating Particle/Particle Repulsive Forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

CHALLANGES IN THE PRODUCT DESIGN, FORMULATION AND MANUFACTURE OF ODTs

• Palatability

As most of the drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence taste masking of drugs become critical to patient compliance.[26]

• Mechanical strength

In order to allow ODTs to disintegrate in the oral cavity, 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 brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi- Shaklee, and Durasolv® by CIMA labs.[27]

• Amount of drug

Application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. In case of Lyophilized dosage forms, drug dose must be less than 400mg – insoluble drugs less than 60mg -- soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films.

• Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm. While the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.[28]

CONCLUSION

Orally disintegrating tablets have better patient acceptance, 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 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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