

THE PHARMA INNOVATION - JOURNAL

A Review Article on Orodispersible tablet Formulation.

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Recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. ODTs are those when put on tongue disintegrates rapidly releasing the drug which dissolves in the saliva. The faster the drug disintegrates the faster the onset of action. In such cases bioavailability of the drug observed is greater than the conventional tablet dosage form. This is because the drug absorbed from mouth, pharynx the saliva passes down to the stomach. In this article focuses on the orodispersible tablet, superdisintegrants, mechanism of action, patented technology and the evaluation of ODTs.

Keyword: Orodispersible Tablet, Superdisintegrants, Conventional Technology and Evaluation

1. Introduction

The concept of orodispersible tablet emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus without the need for water during administration, an attempts that makes them highly attractive for pediatric and geriatric patients^[1]. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients. This disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS etc. One study showed that 30% out of 1600 patients experienced difficulty in swallowing tablets due to their large size and by their surface, shape and taste. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain a healthy life. Children may also have difficulty in ingesting

because of their underdeveloped muscular and nervous systems. The problem of swallowing tablets is also evident in travelling patients. Above mentioned problems can be resolved by means of orodispersible Tablets (ODTs)^[2]. ODTs are known by various names such as "fast-melting, fast-dissolving, mouth disintegrating Tablet or (MDTs)". Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics. ODTs disintegrate and/or dissolve rapidly in saliva; therefore, water is not required during administration. Some tablets are designed to dissolve in saliva within few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast-disintegrating tablets, as they may take about one minute to disintegrate completely.

ODTs offers several advantages over other dosage forms like effervescent tablets, dry syrups and chewing gums or tablets, which are

commonly used to enhance patient's compliance^[3]. Administering effervescent tablets/granules and dry syrups involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage form if the taste masking is not done in proper way^[4].

1.1 Requirements of fast disintegrating tablets

1. Have a pleasing mouth feel.
2. Require no water for oral administration.
3. Have an acceptable taste masking property.
4. Be harder and less friable.
5. Exhibit low sensitivity to environmental conditions (temperature and humidity).

1.2 Salient features of fast disintegrating tablets

1. Does not require water for oral administration.
2. Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
3. Allow high drug loading.
4. Insensitive to environmental conditions such as humidity and temperature.
5. Adaptable to existing processing and packaging machineries.
6. Cost effective
7. Have a pleasant mouth feel

A. Advantages

1. Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. Rapid drug therapy intervention.
3. Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.

4. Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
5. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
6. The risk of choking during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

B. Limitations of fast disintegrating tablets

1. The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

1.3 Desired Characteristics and Development Challenges of Odt

Because administration of FDTs is different from administration of conventional tablets, the ODTs should maintain several unique properties, as listed below.

A. Oral Fast Disintegration

ODTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 mL) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. The “fast disintegration” usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible^[6].

B. Taste of Active Ingredients

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds.

After swallowing, there should be minimal or no residue in the mouth^[7]. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste-masking materials used in the dosage forms should be kept low:

“AS LOW AS POSSIBLE”? to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations^[8]. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the FDT formulations^[10].

C. Drug Properties

For the ideal ODT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of ODTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration. The ODT technology should be versatile enough to accommodate unique properties of each drug^[11].

D. Tablet Strength and Porosity

Because ODTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network^[12]. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption

while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided^[12].

E. Moisture Sensitivity

ODTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect ODTs from various environmental conditions^[12-13].

1.4 Main ingredients used in preparation of ODT

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Disintegration and solubilization of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents. Excipients balance the properties of the actives in FDTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Binders keep the composition of these fast-melting tablets together during the compression stage. The right selection of a binder or combination of binders is essential

to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35°C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi-solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast-dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used^[14].

The most important ingredients of a mouth dissolving tablets are:

1.5 Super disintegrants:

Use of disintegrants is the basic approach in development of ODTs. Disintegrants play a major role in the disintegration and dissolution of ODT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates¹⁴. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing

the disintegration and dissolution^{15,17}. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant.

1.6 Mechanism of Action of Superdisintegrants

Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases¹⁸. Sodium starch glycolate, Ac-di-sol (crosscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised starch are some of examples of disintegrants.

1.7 Mechanism of action of disintegrants

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

- a) By capillary action
- b) By swelling
- c) Because of heat of wetting
- d) Due to release of gases
- e) By enzymatic action
- f) f. Due to disintegrating particle/particle repulsive forces
- g) Due to deformation.

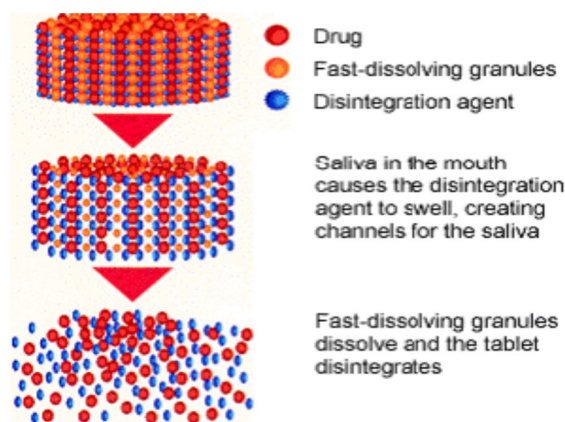


Fig. 1.1: Mechanism of Action of Superdisintegrants Conventional methods used for the preparation of Oral disintegrating tablets.

1.8 Addition of superdisintegrants

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are crosscarmellose, crospovidone and sodium starch glycolate, which are a cross linked cellulose, cross linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets. Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch glycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants.

1.9 Direct compression

It is one of the easiest way to manufacture tablets. conventional equipments, commonly available excipients and a limited number of processing steps are involved in direct compression. Sawant k et al. prepared orodispersible tablets of ondansetron HCl by direct compression using superdisintegrants and they reported that *in vitro* dispersion time of these tablets has been found to be 5 minutes where as conventional tablets have shown 30-35 minutes.

1.10 Freeze drying or Lyophilization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are

passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying.

1.11 Sublimation

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. Ex: Ravi kumar et al. prepared aceclofenac fast dissolving tablets by sublimation method using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants.

1.12 Mass extrusion

In this method active blend is softened using the solvent mixture of water-soluble polyethylene glycol and methanol and then subsequent expulsion of softened mass through the extruder or syringe is made to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

1.13 Spray drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or crosscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium

1.14 Patented technologies for Fast disintegrating tablets

A. Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or

dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis units during freeze-drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

B. Durasolv Technology

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

C. Orasolv Technology

CIMA labs have developed Orasolv Technology. 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.

D. 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. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

E. SWow tab Technology

Wow tab 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 (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide eg. Maltose, oligosaccharides

F. Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists 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 spherulisation. All the processing utilized conventional tableting technology

G. Evaluation of Blends

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics-of blends produced.

1.5 The various characteristics of blends tested are as given below:

A. Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powder is allowed to flow

through the funnel fixed to a stand at definite height (h). The angle of repose is then calculated by measuring the height and radius of the heap of powder formed.

$$\tan \theta = h/r$$

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

Where,
 θ = angle of repose,
 h = height,
 r = radius.

B. Bulk Density (Db)

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and may be therefore be more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder. Apparent bulk density (gm/ml) is determined by pouring bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. Bulk density can be calculated by the following formula,

$$\text{Bulk Density, } D_b = M / V_b$$

Where,
 M = mass of the powder
 V_b = bulk volume of the powder

C. Tapped density (Dt)

Tapped density is the bulk density of a powder which has been compacted by tapping or vibration. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached a minimum. The tapped density is computed by taking the weight of drug in cylinder and final volume.

$$\text{Tapped Density, } D_t = M / V_t$$

Where,
 M = mass of the powder
 V_t = bulk volume of the powder

D. Compressibility Index (Carr's Consolidation Index).

Another indirect method of measuring powder flow form bulk densities was developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. It is calculated according to the following equation,

$$\text{Carr's index (\%)} = (D_t - D_b / D_t) \times 100$$

Where, D_t = tapped density of the powder
 D_b = bulk density of the powder

E. Hausner Ratio

Hausner Ratio is an indirect index of ease of powder flow. If the hausner ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the following formula

$$\text{Hausner Ratio} = D_b / D_t$$

Where,
 D_t = tapped density of the powder
 D_b = bulk density of the powder

F. Void Volume

The volume of the spaces is known as the void volume "V" and is given by the formula,

$$V = V_b - V_p$$

Where,
 V_b = Bulk volume (volume before tapping)
 V = True volume (volume after tapping)

G. Porosity

The porosity ϵ of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by

$$\epsilon = (V_b - V_p) / V_b = 1 - V_p / V_b$$

Porosity is frequently expressed in percentage and is given as

$$\% \epsilon = (1 - V_p / V_b) \times 100$$

The porosity of powder indicates the types of packaging a powder undergoes when subject to

vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

H. Evaluation

Tablets from all the formulation were subjected to following quality control test.

I. General Appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

J. Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

K. 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. Ten tablets were taken and their thickness was recorded using micrometer.

L. Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The limit for weight variation is given in Table 2.

Table 2: I.P. Limit for Weight Variation

Average Weight of Tablets (mg) percentage different allowed	Maximum
80mg or less	10
60mg but < 250mg	7.5
250mg or more	5

M. Tablet hardness

Hardness of 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 condition of storage transformation and handling before usage depends on its hardness.

Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

N. Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A preweighed tablet was 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 were rotated in the friabilator for atleast 4 minutes. At the end of test tablets were adusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{Friability} = \frac{\text{loss in weight}}{\text{Initialweight}} \times 100$$

O. Wetting time

The method reported by yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm * 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 was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

In-vitro dispersion time

In-vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

In-vitro Disintegration test

The test was carried out on 6 tablets using the apparatus specified in I.P. 1996 distilled water

at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

In vitro Drug Release Studies

In-vitro drug release studies were carried out by using USP XXIII Dissolution Apparatus II (Paddle type) [Electrolab (TDT-06T) Tablet Dissolution Tester] at 50 rpm. The drug release profile was studied in 900 ml of hydrochloric acid buffer at pH 1.2 by maintaining at $37 \pm 0.5^{\circ}\text{C}$. Aliquots of dissolution medium were withdrawn at specific time intervals, filtered and the amount of drug released was determined spectrophotometrically. Six trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.

1.6 Stability testing of drug (temperature dependent stability studies)

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 a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C .

1.6.1 Packaging

Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. Unlike these other quick-dispersing and/or dissolving oral delivery systems, the system can be packaged using various options, such as single pouch, blister card

with multiple units, multiple-unit dispenser, and continuous roll dispenser, depending on the application and marketing objectives.

1.6.2 Future Possibilities:

Rapid disintegrating tablets constitute an innovative dosage form, which overcomes the problem of swallowing and provides a quick onset of action. The paediatric and geriatric populations are the primary. The availability of the various technologies and manifold advantages of rapid disintegrating tablets will surely increase its popularity in the near future.

Future Possibilities for improvements in ODTs and drug delivery aree bright , but the technology is still relatively new.

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