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A REVIEW – ORAL DISPERSIBLE TABLETS

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ABSTRACT

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Over the three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. Products of ODT technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding. 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 and evaluation methodologies, suitability of drug candidates, and future prospects.

Keywords: Orally disintegrating tablet, Improved bioavailability, Superdisintegrant.

INTRODUCTION

The Oral route is the most convenient and accepted for drug administration. Oral route still preferred way of administration of therapeutic agents used to produce systemic effects, and provides high patient compliance.[1] The Demand for formulation of oral disintegrating tablets (ODTs) has increase significantly as it has good impact on the patient compliance. These dosage form are appreciated by populations who have difficulty in the swallowing , called Dysphagia (difficulty in swallowing).[2] It is also called as orally disintegrating tablets, fast disintegrating tablets , fast dissolving tablets, mouth dissolving tablets, porous tablets and rapimelts. United states pharmacopoeia also approved these dosage forms as ODTs. European pharmacopoeia has also used the term orodispersible tablet for those tablets which are disperses within 3 minutes in mouth before swallowing.[3] Oral dispersible tablets are some like conventional tablets used in formulation, which dissolve the tablets within minute in the mouth, and release the drug in the saliva. The drug get absorbed from section of g.i.t as the saliva travels down from the mouth, and its bioavailability is greater that other conventional tablets dosage from.[4-7]

Advantage[8]

- It bypasses the GI tract and hepatic portal system.
- It improves Patient compliance.
- Rapid drug therapy intervention.
- Useful for pediatric, geriatric and psychiatric patients.
- Suitable during traveling where water is may not be available.
- The large contact area of the oral cavity contributes to rapid and extensive drug absorption.

Disadvantage[9,10]

- When drugs are Hygroscopic in nature.
- Small amount of drug can used.
- Specific packaging are needed for stabilization and safety of stable product.
- Eating and drinking may become restricted.

Desired characteristic for ODTs[11]

- It should possess following characteristics.
- Disperse in mouth within in seconds.
- Pleasing mouth feel and task masking
- Cost effective production method
- Be portable without forgility concern
- Not residue in mouth after administration.

Points to be Consider During Formulation of ODTs:[12]

1. **Disintegration time and mechanical strength:** ODTs are usually disintegrate less than a minute. But it's good mechanical strength is a prime challenge. Tablets which are formed on the basis of Zydis technologies require special type of packaging. If we increasing the strength that disintegration time will delay. Therefore a food relation between these parameters is always essentials.
2. **Environmental Conditions:** ODTs exhibits low sensitivity to environment condition such as temperature and humidity because material used in ODTs are dissolve in less quantity of water.
3. **Task Masking:** Most of drugs are bitter in taste. Effective task masking of bitter drugs increase the patient compliance and its acceptance. Many numbers of techniques are used for making the tablets of bitter drugs, like formulation of pallets by extrusion, mass extrusion or spheronization[13], Polymer used to coating of drug[14] , spray drying , the drug dispersed in a solution of polymer[15] , complexation of drug by using cyclodextrin[16], and microencapsulation of drug, etc
4. **Mouth feel:** ODTs should generate small particle after disintegration in mouth and leave the no residue in mouth. Flavour and cooling agents use to improve the mouth feel.
5. **Cost:** ODTs should be formulated by technology which is accepted in terms of cost.

Drug Release from ODTs: OTD should be disperse in less than three minutes. The main approach used to develop the ODT is the use of super disintegrants like sodium starch glycolate, carboxymethlcellulose, polyvinylpyrolidone etc which release the drug in saliva after putting into mouth. The drug which is subject to undergo first ass metabolism is reduce by development of DTDs.

Super disintegrants : [18] Super Disintegrants are used in ODT for faster disintegration and effective at low concentration. But it have one drawback that is hygroscopic character. So that not used with moisture sensitive drug. Super disintegrants act by swelling and due to this pressure, it causes tablet to burstor leading to an increase in the volume of granules to promote disintegration.

Mechanism of action of super disintegrants:[19]

a. **Swelling :** All the disintegrants not swell in contact with water, it is believed that swelling is a mechanism in which disintegrating agents produce the disintegrating effect. By swelling, the adhesiveness of other ingredients is overcome causing the tablet to fall apart.

b. **Wicking (Porosity and capillary action):** When tablet placed in the aqueous medium leads to Penetration of the aqueous medium into the tablet and replaced the air absorbed resulting in weakening of intermolecular bond and tablet breaks into five particles.

c. **Particle-Particle repulsive forces:** Particle-Particle repulsive forces bond on that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the reason behind disintegration. Water is also required for this.

d. **Due to deformation:** When tablet are formed during compression, disintegrated particles become deformed and it return back to normal size or structure when they contact with aqueous medium.

Techniques used for preparation of ODTs:[20]

1. Lyophilization or freeze drying.
2. Spray drying.
3. Sublimation
4. Melt Granulation
5. Mass extrusion
6. Molding
7. Direct compression
8. Nanonization
9. Cotton candy process
10. Phase transition process.

Lyophilization or freeze drying:[21] Lyophilization is a process in which water are removed by sublimation under low temperature. This process produces an amorphour porous structure which is dissolve rapidly. Freeze drying consist of three steps:

1. Material is Frozen
2. Moisture reduce around 1 % w/w of dry product.

3. Called primary drying.
4. Moisture reduce up to required final volume called secondary drying.

Spray Drying: [20]Spray drying mostly used in biochemical process. Spray drying produce highly porous, or fine powder because solvent is evaporated quickly. Spray drying is based on particulate support matrix, which is formed by spray drying an aqueous composition containing support matrix and other material to usage a highly porous or fine powder. The ODTs made from this technology are disintegrate within 20 seconds.

Sublimation:[22]The subliming material like ammonium carbonate, urea, ammonium bicarbonate, camphor, Naphthalene and benzoic acid are removed by this technique from compressed tablets and porosity increased by formation of many pores. These tablets have high porosity and quickly dissolved within 15 seconds in saliva.

Melt Granulation: [23] In Melt Granulation process providers are agglomerated efficiently by meltable binder. Water or organic solvents is not necessary in this techniques. Drying step is not required that's why it is less time consuming process. It is also to enhance the dissolution rate of many drugs like griseofuluin.

Mass Extrusion:[24,25] In this technique, softening of active blend by using mixture of solvents like water soluble polyethylene glycol and methanol and then expulsion of softened mass through the extruder, which are finally cut into small segment by heated blade to form tablets. The taste of bitter drug are masked by coating the granules. This process involves embedding the drug in a polymeric carrier and shaping it to form a pharmaceutical product. Many super disintegrate are used in this process.

Molding:[26] In this process tablets are formed by water soluble material so that it dissolve completely and rapidly. Hydro alcoholic solvent are used to moisture the powder blends and is molded into tablets under the low pressure. Solvent is removed by air drying. In this techniques the dissolution rate increased due to porous structure is formed.

Direct Compression:[27] In direct compression tablets are compressed directly from blends of the drug and excipients without any previous treatment. It delivers high efficiency than other process like wet granulations. The blends to be compressed need have satisfactory flow properties. The selection of a suitable and optimal amount of disintegrates is important for high disintegration rate.

Nanonization:[28] Nanonization process contains reduction in the particle size of drug to nano size by milling technique. The drugs are stabilized against agglomeration by surface absorption on selected stabilizers. This process is suitable for poorly water soluble drugs.

Cotton candy Process:[29] This process contains formation of matrix of polysaccharides by simultaneously action of flash melting and spinning. To improve the flow properly and compressibility the matrix formed is then milled and blended with drugs and excipients and subsequently compressed. It provides high mechanical strength. However this process is limited because of high process temperature.

Phase transition process:[30] In this process, a combination of low and high melting point super alcohol, as well as a phase transition used in the manufacturing process. ODTs was produced by compressing blends containing (122 C) erythritol and xylitol (-92 C) and then heating at about 93 C for 15 min. The increase of the tablets hardness with heating did not depend on the crystal of the lower melting point sugar alcohol.

IMPORTANT PATENTED TECHNOLOGIES IN ODTs:[31,32]

1. **Zydis Technology:** Zydis technology contain softening the active drug using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder to get a even segment using heated blade to form tablets. The even segments can also be used to coat granules of bitter drugs and masking their taste.
2. **Orasolv Technology:** CIMA Labs developed Orasolv Technology . In this process active drug is taste masked. It contains effervescent agents. Direct compression techniques are used to formed tablets at low compression force in order to minimize oral dissolution time. The soft and friable tablets are produced and packed in specially designed pick and place system.
3. **Durasolv Technology:** This technology is patented by CIMA Labs. This process consist a drug, diluents and lubricant tablets are prepared by this process have good rigidity. Tablets are packed into

conventional packaging system. This technology is appropriate for products requiring low amount of active drugs.

4. **Flash Dose Technology:** This process patented by Fuisz. It is now owned by Biovail. This technology utilizing SHEARFORM matrix in which material containing substantial amount of fibrous polysaccharides, processed by simultaneous action of flash melting, centrifugal forces. Flash dose tablets contains a matrix of sugar fibers disintegrates very rapidly upon contact with saliva and disintegrate within a few seconds. Biovail corp. launched first commercial product Nurofen melted a new form of ibuprofen.
5. **Flashtab Technology:** Flashtab have been patented by Prograte pharm laboratories. Tablets are formed by this process contain of an active blend in the form of micro crystal micro granules prepared by using the conventional process like micro encapsulation, extrusion spheronisation. Flashtab tablets matrix consists of a swallable agent and a super disintegrant.
6. **Wonitab Technology:** This technology has been patented by Yamanoucchi pharmaceutical Co. Wow means without water. In this technology combination of high and low mouldability saccharides is used to obtain a rapidly melting strong tablet. The active drug is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

PREFORMULATION STUDIES[33,34,35,36]

1. **Bulk Density:** Bulk density was determine by pouring the 5gm of powder into a 100 ml of granulated cylinder. The bulk volume v poured drug was determined

The bulk density was calculated using formula

P_b =M/V

M- wt of powder

v- vol of powder

Bulkness increase with a decrease in article.

2. **Tapped Density**: It is the ration of total mass of the powder to the tapped volume of the powder. Weight 5gm of powder and placed in a meaning cylinder. The measuring was tapped for 100 times or fixed times. The minimum volute (Vt) occupied was measured. It expressed in gm/l

Pt=M/Vt

M- mass of powder

Vt- taped volume

3. **Compressibility Index:** It indicated powder flow properties. It is expressed in percentage and this is calculated by

% C.I= Pt-Pb/Pt * 100

Pt- tapped density

Pb- bulk density

The volume below 15% indicates a powder with size to good flow properties

4. **Hausner ration:** Hausner ration is an indirect index to indicate the powder flow. It is the ratio of tapped density to bulk density. Lower the value better is the flow property.

If Hausner ration less than 1-25 means good flow.

It is calculated by given formula.

H.R= Pt/Pb

Pt= tapped density

Pb= bulk density

5. **Porosity:** Porosity was obtained by apparent density (Papp) and true density (Ptrue). It is expressed in percentage like

E= (1- Papp/Pture)*100

6. **Voide Volume**: The volume of the spaces is know as the void volume. It was obtained by difference between bulk (Vb) and tapped volume (Vp). IT can be calculated by following formula.

V= Vb- Vp

7. **Angle of Repose:** The angle of repose was determined by using funnel method suggested by Newman. Funnel can be fit vertically without stand at 6.3 cam height. The Opening end of funnel are closed with thumb fill drug are poured. 5gm of powder poured into funnel and flow freely on the surface until a maximum cone height (h) was obtained. Radius of heap (r) was measured and the angle of repose was calculated by this formula

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

Angle of repose less than 30 degree shows the free flowing of the powder.

Evaluation of ODTs:[35,37,38,39,40]

1. **Thickness**: Thickness of tablet can be measured by simple procedure. Thickness of tablets were measured using Vanier caliper .
2. **Uniformity of weight:** According to I.P uniformity of weight of tablets were measured 20 tablets were selected from the

lot randomly and weighted individually to check for weight variation.

3. **Hardness:** Hardness is the force required to break a tablet by compression in the radial direction. A tablet is placed in the hardness taster and load required to crush the tabler is measured. The hardness of ODTs kept lower as increased hardness delays the disintegration of the tablet. Hardness is measured in kg.
4. **Friability:** Friability is a measure of mechanical strength of the tablet. Friability of the tablets was determined using Roche Friability. Roche Friability subjects the tablets to the combined effect of shock and abrasions in a plastic chamber that revolves at 25 rpm and dropping the tablets at a height of 6 inches in each rotation. The tablet are rotated in the friabilator for at least 100 revolutions. Tablet were dedusted using a soft muslin cloth and reweight.

The friability can be measured by this formula

%F=(1-wo/w)*100

Wo- weight of tablet before test

W= weight of tablet after test

5. **In vitro dispersion time test:** To determine the dispersion time 10 ml measuring cylinder was taken in which 6 ml distilled water was added and tablet was dropped in it. Time required for complete dispersion was determined.
6. **Water absorption ratio:** A small piece of tissue paper folded twice is placed in a small petdidish containing 6 ml of water. Placed a tablet on the paper and time required for complete wetting is measured. Tablet is than reweighed . Water absorption ration, R is measured by

   R=100*wa-wb/wb

   Where wb= weight of tablet before test

   Wa= weight of tablet after test
7. **Wetting time**: Five circular size of tissue paper of 10 cm diameter are placed in a petridish with a 10 cm diameter. Water soluble dye like Eosin is added to petridish. Tablet placed on the surface of the tissue paper. When the water reach upper surface of the tablet is noted as wetting time.
8. **Disintegration time:** The Disintegration time was carried out on 6 tablet using the apparatus specified in I.P ODTs should disintegrate within 3 minutes without leaving any residue on the screen. Distilled water at 17 °C +- 2 °C was taken as a disintegration media.
9. **Dissolution test:** Dissolution test for ODTs is the same as conventional tablets. More suitable and common choice of apparatus used is USP 2 paddle, where the paddle speed is 50 rpm is used. The USP 1 apparatus have certain application for such tablets but is used less frequently due to specific physical properties of tablets.
10. **Mouth sensation:** ODTs should provide pleasant feel to the patient. Tablet from each batch is tested for the sensation by placing the tablet on the tongue. The healthy human volunteers are used for the evaluation of mouth sensation.

Future prospects: In Oral route remains the largest segment of the overall drug delivery market, presently valued at $49 billion and 10% growing every Year[41]. Fast dissolving drug delivery becomes a rapidly growing area in the pharmaceutical industry. Protein and peptide based therapeutics may be suitable for ODTs because these have limited bioavailability. When administered by convention tablets. These products usually degrade rapidly in the stomach. The development of enhanced oral protein delivery technology by ODTs may release these drug in oral cavity are very promising for delivery of protein and peptide of high molecular weight.

Conclusion: Based on the literature surveyed, it may be concluded that ODTs has solved the problem in administration o f drug to the pediatric and elderly patient. ODTs are provide rapid disintegration and instantaneous dissolution of the tablet along with pleasant taste and excellent mechanical strength because it contain super disintegrating agents in optimum concentration. Unpalatable drug may be incorporated in ODTs and research in still going on the area. These ODTs may be developed for most of the available drugs in next future.

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Declaration of Interest: It is hereby declared that this paper have any conflict of interest.

List of Super Disintegrants:

Super disintegrants	**Example**	**Mechanism of action**	**Comment**
Cross carmellose Primellose Ac-di-sol Vivasol	Cross linked cellulose	Swelling and wicking both. Swelles 4-8 folds in less than 10 second.	Direct compression Starch free Swells in two dimensions
Sodium starch Glycolate	Cross linked starch	Swells 7-12 folds in less than 30 seconds.	Swells in three dimension High conc. used as sustain release matrix.
Cross povidone	Cross linked PVP	Swells 7-12 folds in less than 30 seconds.	Swells in three dimension High conc. used as sustain release matrix.
Alginic acid NF	Cross linked alginic acid	Swells rapidly in aqueous medium or wicking action	Disintegrants in both dry and wet granulation.
Soya polysaccharides	Natural super disintegrants	Dissolve Rapidly	Used in nutritional products

Angle of repose as an indication of powder flow properties.

Sr No	Angle of Repose	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very poor

Weight variation specification s per I.P

Average weight of tablet	**% Deviation**
80 mg or less	±10
More then 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

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