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Orally Disintegrating Tablets: A ShortReview

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ABSTRACT:

This article provides an overview of the benefits of orally disintegrating tablets (ODTs), as well as important considerations when evaluating ODTs, including bioequivalence, obstacles and restrictions, and lastly the present and future of ODTs. ODTs are in high demand, and the field is one that the pharmaceutical industry is developing quickly. These tablets melt or disintegrate in the mouth when placed there without the need for extra water. ODTs degrade when placed on the tongue. the medicine is instantly released, dissolving or dispersing in the saliva. As saliva descends into the stomach, some medications are absorbed from the mouth, pharynx, and oesophagus. When this occurs, a drug's bioavailability is much higher than what is seen from are becoming more and more respected in both business and academics. Their increasing significance was recently shown when the European Pharmacopoeia introduced the "Orodispersible Tablet" refers to a tablet that must be placed in the mouth for quick dispersion before being swallowed. ODTs face some difficulties, but this study demonstrates ways to deal with them.

KEY WORDS: ODT'S, Geriatric, superdisintegrent etc.

INTRODUCTION:

Formulation of drugs into a presentable form is the basic requirement and need of today. The dosage form is a mean of drug delivery system, used for the application of the drug to a living body. Various type of dosage forms are available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having a different type of drug delivery mechanisms. These classical/ modern dosage forms have some advantages and disadvantages. Therefore, the development of an ideal drug delivery system is a big challenge to the pharmacist in the presence scenario.Oral routes of drug adFominister have wide accept. Oral drug delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, the most convenient and most economical method of drug delivery with the highest patient compliance. Oral route is the most preferred route of administration and tablet and capsules are the most preferred dosage forms, but several limitations of that kind of dosage forms like chocking and swelling discomfort in geriatric and pediatric patients. Orally disintegrating tablets have been developed
and new ODT technologies compensate many pharmaceuticals and patients' needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphasia. Over the past 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 being named as ordispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. (1)

There are some definitions that made by pharmacopeias and agency as follows:

Orodispersible tablets have been placed in the mouth where they disperse ODTs are oral solid dosage forms that disintegrate rapidly in the oral cavity releasing the drug. They contain superdisintegrants that helps in dissolving the ODT without water intake within three seconds (s) to three minutes (min). This makes ODTs advantageous to many populations of patients including geriatrics and also increases their compliance. Because the oral cavity is rich in blood supply, drugs are directly delivered to the systemic circulation resulting in rapid absorption, enhanced bioavailability and reduced side effects. In the current study, formulations are prepared by the direct compression technique. It is the most simple and economic method for conventional tablet press. However, achieving robust disintegration and enhanced tablet porosity together with sufficient mechanical strength is a critical challenge. Among the various strategies employed to produce adequately hard ODTs without impairing disintegration time is "co-processing of
excipients". Co-processing methods include mixing, co-grinding and spray drying. These processes produce ODTs incorporable excipients, having enhanced mechanical properties with preserved disintegration times. Mannitol-based co-processed excipients are one of the most common ODTs excipients that are commercially available in the pharmaceutical market and that are ready to use. Although these excipients may be very similar in composition yet, different fabrication methods, as well as minor changes in the characteristics of their components make them react otherwise after ODT formation. Examples of active pharmaceutical ingredients (APIs) that were formulated as ODTs using co- processed excipients include sertraline hydrochloride, chlorpeniramine maleate and chlorzoxazonese fast before being swallowed and they are uncoated tablets. Oro dispersible tablets disintegrate within 180 seconds when the disintegration tests have been conducted up to the test for disintegration of tablets.
Accurate dosing and stability makes it a better dosage form than liquids. [10-11] Pre-gastric absorption makes the drug bypass first pass metabolism resulting in better blood plasma concentration with improved efficacy making it a suitable formulation for drug that undergo extensive presystemic metabolism.Exception of the pre-gastric absorption would be ODTs whose bitter taste API has been coated with a pH sensitive polymer i.e. Eudragit EPO, which release the drug substance in the stomach, even if the tablet disintegrates in the mouth.Two critical aspects in formulating this dosage form are proper addition of superdisintegrants Key to disintegration time and concealing the bitter taste of drugs significant for patients‟ compliance. (5) (6)

ADVANTAGES OF ODT's:

- No need of water to swallow the tablet.
- It is easy to administered for paediatric, geriatric and mentally ill patients.
- It have higher bioavalability than other dosage form.
- Appropriate dose can be given as compered to the liquid.
- It can have unit dose packaging therefore it can have less chance of contaminatiom.
- It can be suitable for sustain and controlled release activity.
- These doses form can required less expanses because it have required few sterility testing.
- It required minimum number of ingredients and it cost saving doses form. ,(2,3,4)

LIMITATION OF ODT's:

- Some drugs have unpleasant or bitter taste drug can't formulated by Odt's.
- Hygroscopic material can't be formulated by these doses form.
- Patient who simultaneously taking anticholinergic drugs are not suitable for Odt's.
- Drugs which have large doses so it can have difficulty to formulate into Odt's.
- The Tablet may be evaluated as a first option for geriatric and peadiatric patient .
- Drug candidates should be stable both in water and in saliva, should not ionize at oral cavity pH and should be able to permeate oral mucosal tissue to diffuse and partition in upper GI epithelium (logP > 1, or preferably > 2, not have short half-life). To optimize solubility problem of the active pharmaceutical ingredient some solid buffers and surfactants can also be chosen.(7,8)

PROPERTIES OF ODT'S:

- Be portable without fragility concerns.
- Allow high drug loading.
- Not required water to swallow.
- Have leave minimal no residue after the oral administration.
- Low manufacturing cost. (9,10)

Formulation approaches for orally disintegrating tablets :-

Formulation approaches begins with selection of excipients to be incorporated into the formulation then pre formulaion studies.

Selection of excipients :-

Excipients selected must ensure that the tablets prepared meet the objectives or purpose of this dosage form with shorter disintegrating time and good patient‟s compliance to .specifications. Recent advances on ODTs formulation has emphasized also on quality by design during excipient selection. This will be discussed under formulation development. Some excipients may be specific to the preparation method employed e.g. acesulfame, a sweetener is used in the recently shown technique for taste masking. This will also be discussed under taste masking. The commonly used excipients areas follows

1. **Superdisintegrants:**

Superdisintegrants facilitate the breaking of the orally disintegrating tablet once it is placed on the tongue. Addition of these materials in the formulation is critical to the disintegration time, and they should be used at their optimal concentration. Superdisintegrants can be used alone or in combination in the formulation and they have concentration ranges within which they work effectively.

The following properties should be considered when selecting the superdisintegrant(s).

- Ability to flow and to be compressed.
- Poor gel formation
- Poor water solubility
- Good hydration
- Inability to form complexes with drugs

Synthetic superdisintegrants which are commonly used have included Sodium starch glycolate, Crosspovidone and carboxymethyl cellulose sodium (Croscarmellose sodium). Natural polymers which are used as superdisintegrants have included; Isapghula Husk Mucilage (Plantago ovata), Lepidium sativum Seed Mucilage, Fanugreek Seed Mucilage, www.wjpps.com Vol 9, Issue 1, 2020. 307 Juan et al. World Journal of Pharmacy and Pharmaceutical Sciences Gellan Gum, Chitin and Chitosan. Modification of polysaccharides have resulted in superdisintegrants with lower disintegration time. Mahaveer Pr. Khinchi et al (2011) study showed that modified treated agar as a superdisintegrant had lower disintegration time than treated agar and agar in Fenoxidine HCl tablets.n Finally, several factors have to be considered when choosing superdisintegrants including; percentage of disintegrants in the formulation, nature of drug, type of mixing and addition, hardening of tablets, presence of surfactant, ability to form less friable tablets, and good mouth feel. (12)

2. **Binders:**

Binders help to hold particles together in a formulation. Commonly used binders include cellulose or modified cellulose such as microcrystalline cellulose, Sucrose, lactose, starches, cellulose ethers such as hydroxypropyl cellulose (HPC), Hydroxy propyl methylcellulose (HPMC), Sugar alcohols such as xylitol, sorbitol or maltitol, proteins such as gelatin, synthetic polymers such as polyvinylpyrrolidone(PVP), polyethylene glycol (PEG), polyvinylalcohol (PVA).

During tablet disintegration, the binding forces between particles are overcome and the tablet disperse.Some binders, especially starch and its derivatives are enzyme labile especially to amylase in the saliva thereby reducing the effect of

binding making tablet disintegration easier for ODTs.

Binders are categorized according to their usage as solution binders which are employed in wet granulation (e.g. starch, gelatin, cellulose and their derivatives) and dry binders whose addition to the formulation is to the powder mix after completion of wet granulation process or to the powder mixture for direct compression formula. Some examples of dry binders include cellulose, methyl cellulose, Poly vinyl pyrrolidone.

During ODT preparation, increasing the concentration of the binder results in less friable tablets. The study by Chikwuma O. Agubata, et al (2012) on the physical and mechanical effects of binder mixtures on sodium salicylate tablets showed that as the binder concentration was increasing, the crushing strength or hardness was generally increasing, and the friability was decreasing.

However, it is important to note that tablet hardness resulting from either increasing the concentration of binders in formulation or compression force can prolong the disintegration time, defeating the whole purpose of this dosage form. www.wjpps.com Vol 9, Issue 1, 2020. 308 Juan et al. World Journal of Pharmacy and Pharmaceutical Sciences (14,15)

3. **Test Masking:**

Orally disintegrating tablets disintegrate in the saliva and during the process the drug may be exposed to taste buds imparting an acrid taste which can lead to poor patient compliance. This makes masking of unpleasant taste of therapeutic agents paramount when developing this dosage form. Several methods have been used in drug dosage formulation to improve taste. Examples include polymeric coatings strategies, complexation with cyclodextrin, ion exchange resins, salt formations, using liposomes, microencapsulation technique and coating or granulation. The use of sugar based excipients as diluents is also one of the approach used. Some examples of these excipients include mannitol, maltose, dextrose, sorbitol, fructose, etc. These improve the mouth feel as they dissolve in saliva. Aspartame and Saccharine have been widely used as sweetening agents in formulations of orally disintegrating tablets. With reference to sucrose, Aspartame is 200 times sweeter while Saccharin is 450 times sweeter. Sugar based excipients which can be used as diluents, for example mannitol and lactose are 0.60 times and 0.16 times sweeter than sucrose respectively. Addition of sweetening agents and flavoring agents is the easiest way of masking the distasteful sensation, though the approach may not be sufficient for very bitter drugs. In combating the bitter taste, artificial sweetening agents and flavoring agents should generally be used alongside other bitter taste masking approaches. (19,20,21)

4. **Diluents:**

Diluents function as bulking agents especially for drugs with role doses. This is necessary to facilitate exact material handling when preparing the dosage form and subsequent compression. When smaller amount of the drug is involved, a larger amount of the diluent/filler will be necessary. Apart from being pharmacologically inert, compatible with drug and other excipients, not hygroscopic, good flowability and compressibility properties, diluents for ODTs should have a pleasant taste. Mannitol, microcrystalline cellulose, Lactose starch, pregelatinezed starch, sorbitol sucrose, and calcium phosphates are commonly used diluents and are classified based on their chemical nature and solubility. Mannitol, Lactose and Microcrystalline cellulose have been widely used as diluents in the preparation of orally disintegrating tablets by direct compression because of good compressibility and flowability properties. Microcrystalline cellulose has also been used as a binder, and it has disintegrant properties in tablets prepared by direct compression process because of its swelling properties when in contact with water.(24,25,15)

5. **Lubricants:**

Lubricants help reducing die wall friction (true lubricants role), preventing sticking of powders to punch faces (anti-adherent role), and to aid flow of granules (glidants role) during ODT preparation.Poor powder (granule) flow may results in tablets with variations in weight and content. It is important to determine the concentration of the lubricant, and the manner into which it is incorporated into the ODT formulation. Mainly, the addition of lubricants should be in a dry form when other ingredients in the formulation are uniform. Addition and mixing should be within 2 to 5 minutes as opposed to the 10 to 30 minutes which is usually the case for complete mixing of powder for granulation. Very low concentration of lubricants and insufficient powder mixing may result in sticking, binding in the die cavity, punch filming, and picking. Higher concentration of lubricants in the formulation, or prolonging mixing time may result in tablets with reduced strength and incompressible powder blend because of particle coating which in turn reduce particle-particle binding forces. Increased tablet disintegrating time, as well as a reduction in the dissolution rate may result if there is higher lubricant concentration in

the formulation. (15,19,27,28)

MANUFACTURING METHODS OF ODT'S:

1. **SPRAY DRYING**:

Spray drying methods are used to a great extent in pharmaceutical and biochemical procedures. Spray drying provides a rapid and economically efficient way to eliminate solvents and produces highly porous and fine powders. Allen et al utilized this process for preparing ODTs. These formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescentcomponents, i.e. citric acid and sodium.

CHARACTERISTICS: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous mediumbicarbonate. The formulation was finally spray dried to yield a porous powder.(35,36,37)

2. **FREEZE DRYING (Lyophilization):**

Lyophilization process involves removal of solvents from a frozen drug solution or a suspension containing structure-forming excipients. The tablets formed by this process are usually very light and have highly porous structures that allow, rapid dissolution or disintegration. Glassy amorphous porous structure of excipients as well as the drug substance produced with freeze drying results in enhanced dissolution.

Freeze drying process normally consists of three steps:

- Material is frozen to bring it below the eutectic point.
- Primary drying to reduce the moisture around 4% w/w of dry product.
- Secondary drying to reduce the bound moisture upto required final volume. (33,34,35)

3. **SUBLIMATION :**

Compressed tablet which contains highly water-soluble components can show slow dissolution behaviour, due to the low porosity of the tablets that reduces water penetration into the matrix. By conventional methods, volatile materials are compressed into tablets, these volatile materials can be removed by sublimation, which results in extremely porous structures. The volatile materials which can be used are ammonium carbonate, urea, ammonium bicarbonate, camphor and hexa methylene tetramine. In a few cases, thymol, menthol, camphor, an organic acid such as adipic acid and fatty acid such as arachidic acid, myristic acid, capric acid, and palmitic acid were used as the volatile materials and the sublimation temperature ranged from 40 ^{0}C to 60 ^{0}C. The disintegration time in the oral cavity was found to be about 25 s.

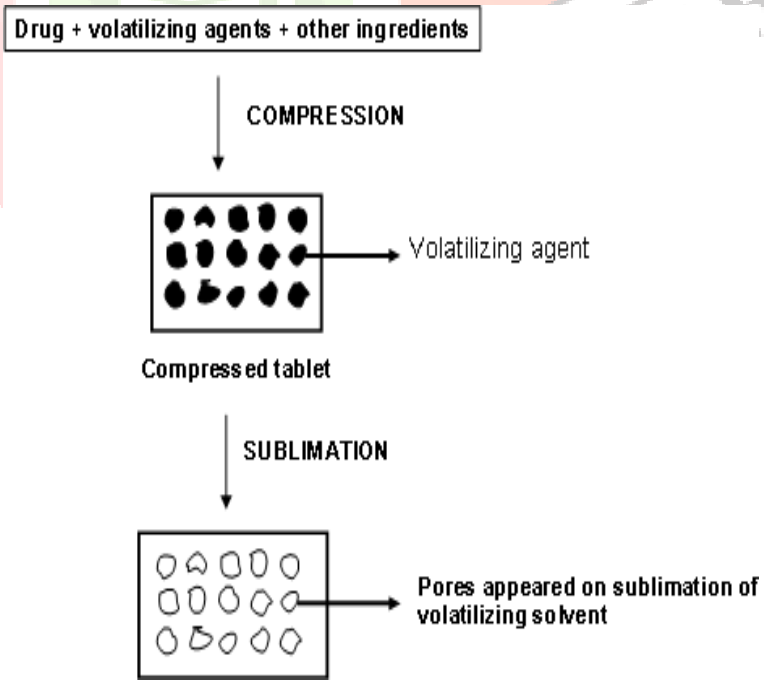

Figure 1: Steps involved in sublimation process (38,39)

4. DIRECT COMPRESSION :

Direct compression is one of the popular techniques for preparation of these dosage forms.Direct compression is the easiest and cost effective tablet manufacturing process. This method can be applied to manufacture ODT by selecting appropriate combinations of excipients, which can provide fast disintegration and optimum physical resistance. Sugar-based excipients are widely used as bulking agents because of their aqueous solubility, sweetness, pleasing mouth feel, and good taste masking. Tablets obtained by conventional compression method are less friable, but disintegrate more slowly. The compression method, with or without wet granulation, is a convenient and cost effective way to prepare tablets with sufficient structural integrity. The basic principle involved in development of these dosage forms using this technique is addition of superdisintegrants in optimum concentrations so as to achieve rapid disintegration along with pleasant mouth feel . It is considered as the best method to prepare orally disintegrating dosage forms since the prepared tablets offer higher disintegration due to absence of binder and low moisture contents . This approach is also considered as disintegrant addition technology. Bi et al and Watanabe et al developed fast-dissolving tablets using microcrystalline cellulose and low substituted hydroxy propyl cellulose as disintegrating agents in the range of 8:2-9:1 . Shu et al also prepared rapid oral disintegrating tablets by direct compression using co-ground mixture of D-mannitol and crospovidone. (40,41,42,43)

5. MASS EXTRUSION :

The mass extrusion technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of softened mass through the extruder or syringe is carried out, to get a cylinder of the product which is then cut into even segments using a heated blade to form tablet. (45,46)

6. MOLDING :

Molded tablets are made up of water soluble ingredients. The powder mixture is sprinkled with a solvent (usually water or ethanol). The mixture is molded into tablets under pressure. Applied pressure should be lower than those used in conventional tablet compression. This process is also known as compression molding. This is achieved by complete and rapid dissolution of the tablet using water soluble ingredients. Moulded tablets disintegrate more rapidly and offer improved taste because of the dispersion matrix which is generally prepared from water soluble sugars.
Powdered blend (containing drug and excipients like binding agents - sucrose, acacia, PVP etc.)(44)

7. PATENTED TECHNOLOGICAL :

Rapid-dissolving characteristic of ODTs is generally attributed to quick penetration of water into tablet matrix resulting in its fast disintegration. Several technologies have been developed on the basis of formulation aspects and different processes. Resulting dosage forms vary on several parameters like mechanical strength, porosity, dose, stability, taste, mouth feel, dissolution rate and overall bioavailability. Table 1 represents the list of unique patented technologies, their scientific basis, patent owner along with significant advantages.

Active Ingredients	Local Brand Name	Category	anufacturing Technology	Technological basis	dvantages oftechnology
Loratadine	Claritin	Antihistaminic	Zydis®	Lyophilization	lisintegration (2-10 sn)
Mirtazapine	Remeron	Antidepressant	Orasolv®	Compressed tablets	Effervescent disintegration
Olanzapine	Zyprexa	Antipsychotic; Serotonin-Dopa- mine Antagonist	Zydis®	Lyophilization	lisintegration (2-10 sn)
Ondansetron	Zofran ODT	Nootropic; Antiemetic; Seroto- nin Receptor Antagonist	Zydis®	Lyophilization	lisintegration (2-10 sn)
Risperidone	Risperdal	Antipsychotic; Dopamine Receptor Antagonist; Serotonin-Dopamine Antagonist	Zydis®	Lyophilization	lisintegration (2-10 sn)
Rizatriptan	Maxalt	timigraine; Serotonin Recep- tor Agonist	Zydis®	Lyophilization	lisintegration (2-10 sn)
Tramadol	Ultram	Analgesic (Non-narcotic)	FlashDose®	Cotton Candy Process	Effectively taste maske
Zolmitriptan	Zomig	timigraine; Serotonin Recep- tor Agonist	DuraSolv®	Compressed tablets	Easy to formulate lowdose of active ingredient and higher me- chanical strength than Orasolv
Zolpidem	Ambien	Sedative/Hypnotic	FlashDose®	Cotton Candy Process	Effectively taste maske

Table 1: Some ODTs in the market and name of patented ODTs technologies, their basis and advantages (47,48,49,50)

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