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A REVIEW ON ORAL DISINTEGRATING TABLETS

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Abstract: Oral drug delivery remains the most preferred route for administration of various therapeutic agents. The need for delivering drugs to patients efficiently with minimum side effects has prompted pharmaceutical industries to be engaged in development of new drug delivery systems. Pediatric and geriatric patients find it difficult to swallow solid dosage forms like tablets. Mouth dissolving tablet that dissolve or disintegrate rapidly in oral cavity result in solution, is an ultimate remedy for this problem. In recent past, several manufacturing technologies such as sublimation technique, spray drying technique etc. are employed to overcome the limitations of conventional tablet dosage forms. This review depicts the various aspects of Oral dispersible tablet formulation; advantages, disadvantage, technologies developed for Oral dispersible tablets, along with various drugs explored, evaluation tests and marketed formulations in this field.

Keywords: Disintegration, Oral disintegrating tablets, Advantages, Challenges,



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INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water ^[1].

Most of the pharmaceutical dosage forms are formulated for oral administration where, direct ingestion is intended. In such cases like those with conventional dosage forms, chewing imposes issue in pediatric and the geriatric patients form in. Further psychiatric patients, hospitalized or bedridden patients with chronic diseases finds difficult to swallow solid oral dosage. It is expected that Orally disintegrating tablets (ODTs) can address such critical issues. ODTs are solid dosage form that provides the rapid disintegration or dissolution of solid to present as solution or suspension form even when placed in the mouth under limited bio-fluid. These Orally disintegrating tablets have various synonyms such as or dispersible tablets, quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. The excipients which are used in ODT technology are usually hydrophilic in nature that could be selected on the basis of drug's physicochemical properties, especially, hydrophilicity or hydrophobicity. If the drug is hydrophobic then dosage form is termed disintegrating tablets whereas, if the drug is hydrophilic then it is called fast dissolving tablets ^[1, 2].

IDEAL CHARACTERISTICS OF ODTs

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include

1. It should dissolve or disintegrate in the mouth usually within fraction of seconds. There is no requirement of water for swallowing purpose.
2. It should provide pleasant feeling in the mouth.
3. It should be compatible with taste masking agents.
4. It should be portable without fragility concern.
5. ODTs leave negligible or no residue in the mouth after oral administration.
6. ODTs exhibit low sensitivity to altered environmental conditions such as humidity and temperature.

7. ODTs allow high drug loading.

8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.

ADVANTAGES OF ODTs

1. ODT can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance.
2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric
3. Absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
4. ODT is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.
5. Good mouth feel property of ODT helps to change the perception of medication.
6. As bitter pill particularly in pediatric patients.
7. The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
8. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
9. Suitable during traveling where water may not be available.
10. No specific packaging required can be packaged in push through blisters.
11. Allow high drug loading.
12. No chewing needed.
13. Provides rapid drug delivery from dosage forms.

DISADVANTAGES OF ODTs

1. ODT is hygroscopic in nature so must be keep in dry place.
2. It is also shows the fragile, effervescence granules property.

3. ODT requires special packaging for properly stabilization & safety of stable product
4. The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
5. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly [2, 3, 4].

SUITABILITY OF DRUGS FOR ODTs

For developing ODT of a specific drug several factors should be kept forth while selecting drug, excipients and formulation method. These are as follows:

1. Drugs to be used for sustained action are not suitable candidate for ODT.
2. Drugs having very disagreeable taste are not suitable like clopidogrel.
3. Patients suffering from Sjogren's syndrome and those with less saliva secretion and not suitable for FDT dosage form.
4. Drugs of very short half life and requiring frequent dosing are not appropriate candidate. Patients on anticholinergic therapy are not suitable for ODT.
5. Drugs showing altered pharmacokinetic behavior if formulated in such dosage form with respect to their conventional dosage form are not suitable, like selegiline, swallowing bulky conventional dosage forms.

EXCIPIENTS REQUIRED IN FORMULATING ODTs:

Excipients used in ODTs contain one superdisintegrant, a diluent/bulking agent, a lubricant and optionally swelling agent, a permeabilizing agent (depending upon drug nature), sweeteners and flavoring agents [5].

CRITERIA FOR EXCIPIENTS USED IN FORMULATION OF ODTs

1. It must be able to disintegrate quickly.
2. Their individual properties should not affect the ODTs.
3. It should not have any interaction with drug and other excipients.
4. It should not interfere in the efficacy and organoleptic properties of the product.
5. When selecting binder (a single or combination of binders) care must be taken in the final integrity and stability of the product.

6. The melting point of the excipients used should be in the range of 30-35°C.

7. The binder may be in liquid, semi solid, solid or polymeric in nature ^[6].

TECHNOLOGIES USED FOR MANUFACTURING OF ODTs

1. Lyophilization / Freeze-drying

Formation of porous product in freeze-drying process is exploited in formulating ODTs. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug. However, the ODTs formed by Lyophilization have low mechanical strength, poor stability at higher temperature, and humidity.

2. Molding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that increase dissolution.

3. Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimics cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharine by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to ODTs.

4. Spray drying

Spray drying can be used to prepare rapidly dissolving tablets. This technique is based upon a particulate support matrix that 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 ingredient and compressed into tablet. Allen and Wang have employed spray drying technique to prepare Orodispersible tablets.

5. 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.

6. Melt granulation

In this process, ODTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Superpolystate is a waxy material with a melting point of 33-37°C and a hydrophilic-lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of ODTs by melt granulation method where granules are formed by the molten form of this material.

7. Phase transition process

Investigated processes for the disintegration of FDTs by phase transition of sugar alcohols using erythritol (m. pt. 122°C), xylitol (m. pt. 93-95°C), trehalose (97°C), and Mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

8. Sublimation

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet. Developed ODTs utilizing camphor, a subliming material that is removed from compressed tablets prepared using a mixture of Mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

9. Direct compression methods

This technique is easy way to formulate FDTs since limited number of processing steps, low manufacturing cost and also accommodate high dose the final weight of tablet can easily exceed that of other production method. The disintegration and dissolution of directly compressed tablets depends on single or combined effect of disintegrant, water soluble excipients and effervescent agents. Disintegrant efficacy is strongly affected by tablet size and hardness which can be optimized by medium or low tablet size, low hardness and low physical resistance. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure fast disintegration and high dissolution rates. The addition of water soluble excipients or effervescent agent can further increase dissolution or disintegration properties.

10. Superdisintegrants addition

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 hydroxyl propyl cellulose 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 [7, 8].

CHALLENGES IN THE PRODUCT DESIGN, FORMULATION AND MANUFACTURE OF ODTs:

1. 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.

2. 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/or 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.

3. 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 for insoluble drugs and less than 60mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films.

4. Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging .

5. 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.

6. Aqueous solubility

Water soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing point depression and the formation of a glassy solid that may collapse upon drying because loss of supporting structure during the sublimation process. This collapse can be prevented by using various matrix-forming excipients like Mannitol which induces crystallinity and hence impart rigidity to the amorphous composite ^[6].

EVALUATION OF MOUTH DISSOLVING TABLETS

1. Hardness

A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness test.

2. Friability

To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the percent friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

3. Wetting time and water absorption ratio

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (W_b). The wetted tablet from the petridish is taken and reweighed (W_a). The water absorption ratio, R can be the determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

4. Moisture uptake studies

Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a dessicator over calcium chloride at 37°C for 24h. The tablets are then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity is achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded.

5. Disintegration test

The time for disintegration of ODTs is generally <1min and actual the disintegration time that patients can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents.

6. Dissolution test

The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP type-2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher

Paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP type-1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile [4, 9, 10, 11, 12].

Table. 1. PATENTED TECHNOLOGY AND THEIR BRANDED PRODUCTS [2, 3, 13]

S. No.	Active Ingredients	Brand Name	Category	Manufacturing Technology	Patent Owner	Process Involved
1.	Loratadine	Claritin	Antihistaminic	Zydis	R.P.Scherer Inc.	Lyophilization
2.	Mirtazapine	Remeron	Antidepressant	Orasolv	Cima Labs Inc.	Compressed tablets
3.	Olanzapine	Zyprexa	Antipsychotic; Serotonin Receptor Antagonist	Zydis	-----	Lyophilization
4.	Ondansetron	Zofran ODT	Nootropic; Antiemetic; Serotonin Receptor Antagonist	Zydis	-----	Lyophilization

5.	Risperidone	Risperdal	Antipsychotic; Dopamine Receptor Antagonist; Serotonin- Dopamine Antagonist	Zydis	Jansen Pharmaceutical	Lyophilization
6.	Rizatriptan	Maxalt	Antimigraine; Serotonin Recep- tor Agonist	Zydis	-----	Lyophilization
7.	Tramadol	Ultram	Analgesic (Non- narcotic)	FlashDose	Fuisz Technology Ltd.	Cotton Candy Process
8.	Zolmitriptan	Zomig	Antimigraine; Serotonin Recep- tor Agonist	DuraSolv	Cima Labs Inc.	Compressed tablets
9.	Zolpidem	Ambien	Sedative/Hypnotic	FlashDose	Fuisz Technology Ltd.	Cotton Candy Process
10.	Cisapride monohydrate	Propulsid	Gastroprokinetic	Quicksolv	Jansen Pharmaceutical	Lyophilization
11.	Ibuprofen	Nurofen	NSAID	Flashtab	Ethypharm	Lyophilization
12.	Famotidine	Gaster D	Antihistamine	Wow tab	Yamanouchi Pharma Technologies, Inc.	Compressed Molded Tablets

CONCLUSION

ODTs has increased as it has significant impact on patient compliance and is used to improve the bioavailability and stability. The ODTs have potential advantages over conventional oral dosage forms as they improved patient compliance; convenience, rapid onset of action and bioavailability which drawn the attention of many manufactures. They are a very good alternative for drug delivery to geriatric and pediatric patients. They have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. As a result of the variety of technologies for its formulation, several commercial products are available in the market. Thus ODT has tremendous scope for being the delivery system for most of the drugs in near future.

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