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A REVIEW ON ORAL DISINTEGRATING TABLETS

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ABSTRACT

Oral disintegrating tablets are the solid dosage forms consist of drugs that disintegrate in the oral cavity with in less than one minute leaving an easy to swallow residue. Now a days the formulation of oral disintegrating tablets is emerging and gaining popularity because it is easy to administer and leads to better patient compliance. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva. Then the drug releases as soon as they come in contact with the saliva, thus obviating the need for water during administration. Oral disintegrating tablets (ODTs) are an innovative dosage forms over comes the problems of swallowing and gives onset of action. This review describes the various formulation technologies developed for ODTs, patent technology and marketed formulations. However, ODTs may also be used to deliver drugs to the oral cavity, for local action or, in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake, and reducing undesirable metabolites," The potential for such pregastric absorption rests largely in the physicochemical characteristics of the drug molecule. The intrinsic taste of the drug is also a significant consideration for all ODT formulations.

KEYWORDS: Oral disintegrating tablets (ODTs), oral cavity, patient compliance.

INTRODUCTION

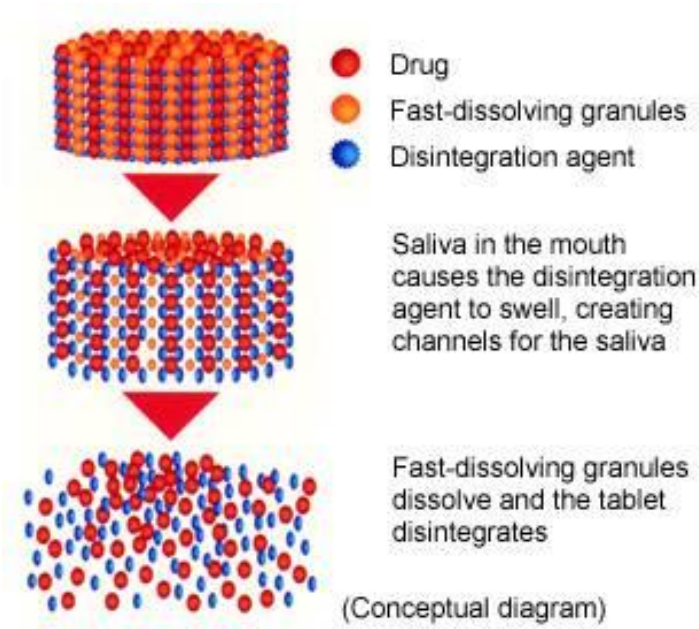
The concept of Fast dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with

prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. The center for drug Evaluation and Research states an ODT to be: "A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue."

These tablets are distinguished from conventional, sublingual tablets, lozenges and buccal tablets which require more than a minute to dissolve in the mouth. In the literature these are also called orally disintegrating, Oro disperse, Mouth dissolving, Quick dissolving, Fast-melt and rapidly disintegrating tablets and freeze- dried wafers.

Disintegration Mechanisms of ODTs

In the tablet disintegration process, several factors may affect the¬ disintegration. They include the rate of water absorption, porosity of the tablet, processing parameters, and effect of active ingredients, surfactants, binders, and lubricants. Fast disintegration always requires fast absorption of water into the center of the tablet. Thus, having open pore structures inside the tablets is very important for making fast dissolving tablets.



Water Absorption: Fig: 1- Disintegration Mechanisms.

Absorption of water into the tablet is important for binding between granules through liquid bridges and for disintegration of the tablet through swelling or dissolution of excipients & through water solid interactions. The affinity of a substance to water in its vapor state is generally referred to as hygroscopicity.

Types of ODTs

For ease of comparison, ODTs may be categorized into two main groups:

1) Lyophilized formulations

2) Loosely compressed tablets.

Advantages

a) Clinical benefits

- Improved oral absorption.
- Faster onset of action.
- Minimized first pass effect.
- Improved bioavailability.

b) Medical/ Patient benefits

- better taste
- No water required.
- Improved safety and efficacy
- Improved compliance

c) Technical benefits:

- Accurate dosing compared to liquid products
- Contains sugars and GRAS (Generally Regarded As Safe) excipients
- improved stability due to better packaging.
- Employ common process and convenient equipments

d) Business benefits

- Unique product differentiation
- Provide exclusive marketing

-Extend patent protection.

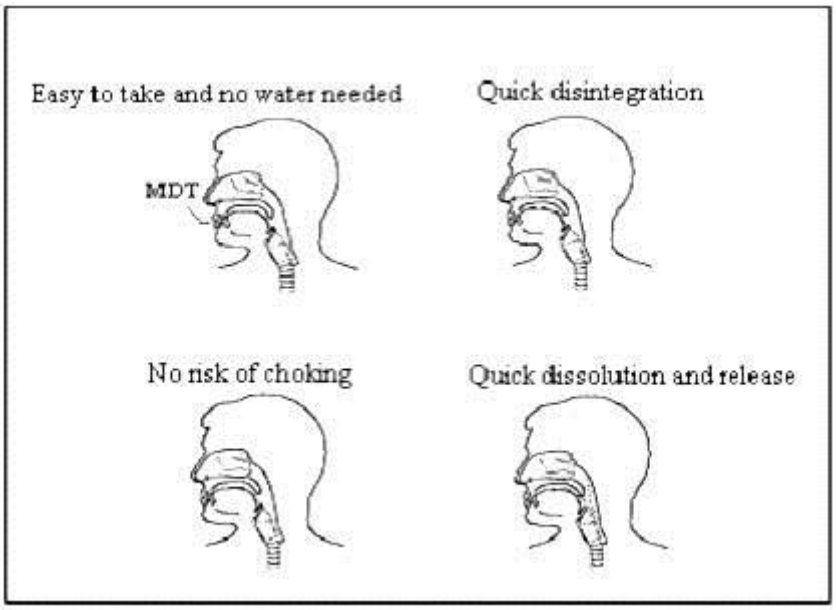


Figure 2: Diagram Showing Advantages of ODTS.

Selection of ODT drug candidates

The ideal characteristics of a drug for *in vivo* dissolution from an ODT include

- No bitter taste
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

Unsuitable drug characteristic for ODT.

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release.

Characteristics of Fast Dissolving Delivery Systems

1. Ease of administration

Fast Dissolving Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors

of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

2. Taste of the medicament

As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

3. Hygroscopicity

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.[11]

4. Friability

In order to allow fast dissolving tablets to dissolve in the mouth, 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 which are difficult to handle, often requiring specialized peel-off blister packaging. To overcome this problem, some companies introduced more robust forms of fast dissolving tablets.

5. Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

Approaches for Fast Dissolving Tablets

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

Conventional Techniques Used in the Preparation of Fast Dissolving Drug Delivery Systems

Various technologies used in the manufacture of Fast dissolving tablets include.

- Freeze –drying or lyophilization
- Tablet Molding
- Direct compression
- Spray drying
- Sublimation
- Taste masking
- Mass extrusion

a. Freeze drying or Lyophiliz ation

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilization to create an oral pharmaceutical preparation that not only dissolves rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomycin. Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug[18] on the basis of which US Patent 6,010,719 was granted. Tablets prepared by lyophilization, are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions.

b. Molding

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases is absorbed through the mucosal lining of the mouth.

The manufacturing process of molding tablets involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mold plates to form a wetted mass (compressing molding). The solvent is then removed by air drying. Thus the process is similar to what is used in the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

Molded forms are also prepared using a heat-molding process that involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at -30C under vacuum.

Another process used is called no-vacuum lyophilization, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure. Pebley et al., evaporated a frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth, or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol, or maltodextrin), and a solvent in a tablet shaped mould. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

c. Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen et al. have reported applying this process to the production of fast dissolving tablets. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatin as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 s in an aqueous medium.

d.Sublimation

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe, Knitsch et al., and Roser and Blair, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a

tablet. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

Koizumi et al. applied sublimation technology to manufacture tablets that rapidly dissolve in saliva. Mannitol is used as a matrix former, and camphor was used as a sublimating agent. The tablets dissolved in 10-20 s and displayed satisfactory handling properties. Makino et al. reported a method using water as pore-forming material[31]. A mixture of drug and a carbohydrate (e.g., erythritol, glucose, mannitol, sucrose, xylitol). The water was then removed, yielding highly porous tablets with satisfactory mechanical strength and a high dissolution rate.

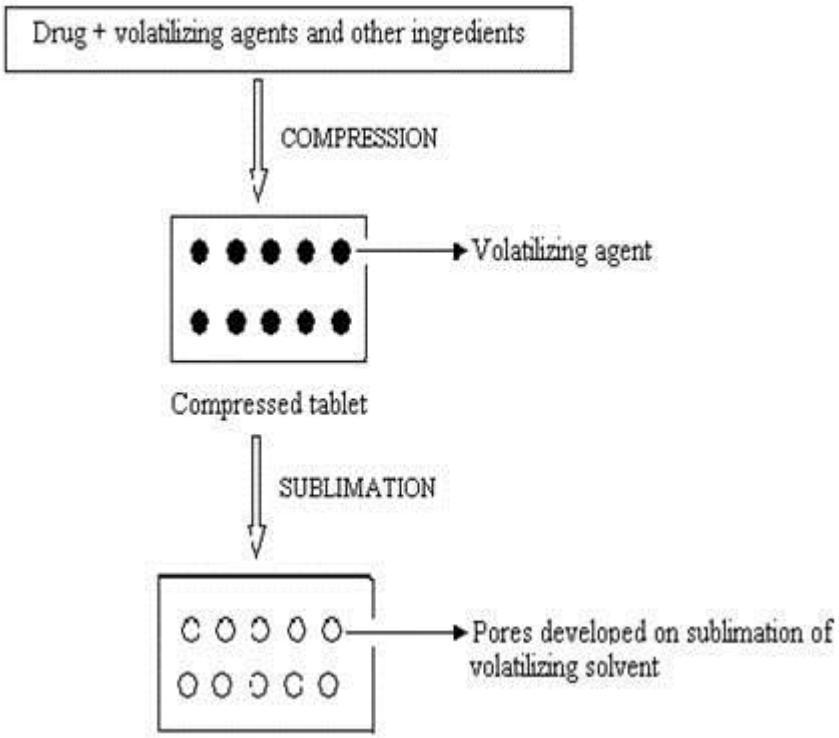


Fig 3: Schematic Diagram of Sublimation Technique for Preparation of ODTS./

e. Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar-based excipients.

Excipients used in direct compression ODT formulations

a) Super disintegrants: Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.

b) **Flavors,** c) **Sweeteners** d) **Fillers** e) **Lubricants.**

The ideal characteristics of a disintegarnts are

a) Poor solubility
b) Poor gel formation
c) Good hydration capacity
d) Good molding and flow properties
e) No tendency to form complexes with the drugs.

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.

There are three methods of incorporating disintegrating agents into the tablet.

a) Internal addition (Intragranular)
b) External addition (Extra granular)
c) Partly Internal and external addition

Mechanism of tablet disintegrants

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

1. By capillary action.
2. By swelling.
3. Because of heat of wetting.
4. Due to disintegrating particle/particle repulsive forces.
5. due to deformation.
6. due to release of gases.
7. By enzymatic action.

Table 1: Superdisintegrants employed in ODTs.

Superdisintegrant	Nature	Properties	Mechanism
Crosspovidone	Crosslinked homo polymer of N-vinyl-2-pyrrolidone	Particle size - 100µm. Insoluble in water. Gives smoother mouth feel.	Both swelling and wicking
Cross carmellose sodium	Cross-linked form of sodium CMC	Particle size - 200µm. Insoluble in water.	Swelling
Sodium starch glycolate	Crosslinked low substituted carboxy methyl ether of poly-glucopyranose	Particle size - 140mesh. Insoluble in organic solvents, disperses in cold water and settles in the form of a highly saturated layer.	Water uptake followed by rapid and enormous swelling.
Acrylic acid derivatives	Poly (acrylic acid) super porous hydrogel	Particle size - 106µm. DT – 15 + 2 s	Wicking action
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate.	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
L-HPC	Low hydroxy propyl cellulose	Particle size - 106µm. DT – 90 s	Both swelling and wicking

Table 2: ODT products available in international market.

Brand name	Active ingredient	Company
Alavert	Loratadine	Wyeth Consumer Healthcare
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	ETHEX Corporation
NuLev	Hyoscyamine sulfate	Schwarz Pharma
Fluoxetine ODT	Fluoxetine	Bioavail
Benadryl Fastmelt	Diphenhydramine	Pfizer
Nurofen flash tab	Ibuprofen	Boots Healthcare
Zomig ZMT & Rapimelt	Zolmitriptan	Astra Zeneca
Fluoxetine ODT	Fluoxetine	Bioavail
Excedrin Quick Tabs	Acetaminophen	Bristol-Myers Squibb
Claritin RediTabs	Loratadine	Sching Corporation
Remeron SolTab	Mirtazepine	Organon Inc
Feldene Melt	Piroxicam	Pfizer
Propulsid Quicksolv	Cisapride monohydrate	Janssen
Imodium Instant melts	Loperamide HCL	Janssen

CONCLUSION

Oral dissolving tablets establish an innovative dosage form which overcomes the difficulties of Swallowing and geriatric populations. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally within one minute. ODTs need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for individuals patients who are busy in travelling, patients who are not have access to water. The clinical studies show ODTs can

improve patient compliance, provide a rapid onset of action, and increase bioavailability. Considering the many benefits of ODTs, it is only a matter of time until a majority of oral formulations are prepared in ODT forms. The basic method followed by all the presently available technologies involved in the formulation of mouth dissolving tablets is to maximize the porous structure of the tablet matrix and incorporate super disintegrating agents in optimum concentration so as to achieve rapid disintegration and instantaneous dissolution of the tablet along with good taste masking possessions and excellent mechanical strength. The availability of the various technologies and manifold benefits of fast dissolving tablets will surely increase its popularity in the near future.

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