

Overview Of Oral Dispersible Tablets

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Abstract: 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 addition they give pleasing mouth feeling. ODT has advantages such as patient compliance, quick onset of action, improved bioavailability, etc. Therefore, mouth dissolving tablets are attractive alternative to liquid and conventional tablet dosage forms. 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. Once the mouth dissolving tablets are prepared they are required to be evaluated for various parameters so as to have long term stability and better therapeutic efficacy.

Keywords: Fast Dissolving Tablets, Superdisintegrants, Oral Route.

INTRODUCTION

The oral route of drug administration is the most and convenient for patient use. Novel oral drug delivery systems that dissolve or disperse quickly in a few seconds after placement in the mouth without water can alleviate the problem of swallowing tablets. The potential for improved compliance in patients. The dispersible systems are defined as systems that dissolve or disintegrate within seconds to a few minutes placement. In these cases, the bioavailability of drugs from these formulations might be greater compared to the conventional oral dosage forms. This creates porous Structure and results in rapid disintegration. Basic approaches to develop dispersible tablet include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation, dispersible tablet can be achieved by various direct compression technique. In this way, or dispersible tablets provide a rapid onset of action and prevent hepatic first-pass metabolism. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make

these tablets popular as a dosage form of choice in the current market. Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). Conventional method used in Preparation of orally disintegrating tablet includes: Freeze drying , tablet molding , spray drying , mass extrusion , sublimation and direct compression.^{1,2,3}

Advantages⁴

1. It bypasses the GI tract and hepatic portal systems, increase the bioavailability of orally administered drugs which can otherwise undergo hepatic first-pass metabolism.
2. Apart from it the drug is protected from degradation due to pH and GIT enzymes.
3. It improves patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.

4. It provides rapid drug delivery from the dosage forms.
5. A relatively rapid onset of action can be achieved as compared to the oral route, and formulation can be removed after discontinuation of therapy.
6. Drug administration through buccal mucosa is easy.
7. Buccal mucosa is less permeable than the sublingual area, the buccal mucosa is having rich blood supply, and drugs can be rapidly absorbed into the circulation system underneath the oral mucosa.
8. The large contact area of the oral cavity contributes to rapid and extensive drug absorption.
9. Patient compliance is more.
10. Having rapid onset of action which may leads to an improved bioavailability.
11. Patient having difficulty in swallowing tablet can easily administer this type of dosage form.
12. Useful for pediatric, geriatric and psychiatric patients.
13. Suitable during traveling where water is may not be available.
14. Gives accurate dosing as compared to liquids.
15. Good chemical stability.
16. Free of need of measuring, an essential drawback in liquids.

How it beneficial for patients²¹

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients.
- Convenience in administration of drug and accurate dosing as compared to liquid formulations.
- Water is not required for swallowing the dosage form, which is convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feels properly of ODTs helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Fast dissolution of medicament and absorption which will leads to rapid, onset of action.
- Some drugs are absorbed from the mouth pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- It provides advantages of liquid formulations in the form of solid dosage form.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

Pathway of drug release from odt.

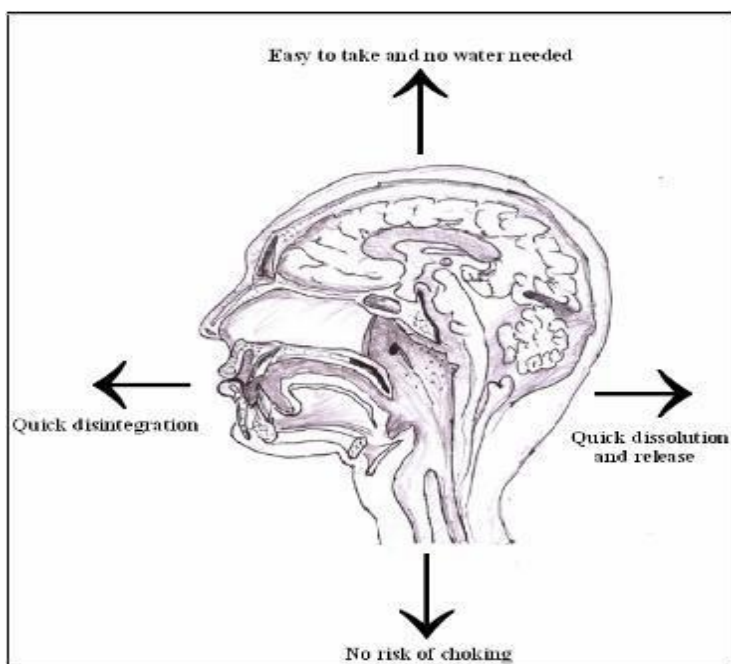


Diagram Showing Advantages of ODT⁴

Criteria of selection of drug ODT⁹:

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

- No bitter taste
- Dose lower than 20mg
- 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 (log P>1, or preferably>2)
- Ability to permeate oral mucosal tissue
- Passive diffusion drug absorption
- Bcs-class 2
- Molecular weight below 500 da.

MECHANISM OF DRUG RELEASE:

Overall Mechanism of drug release of ODT:

According to official publication European Pharmacopoeia the ODT should be disperses or disintegrates in less than three minutes. The fundamental approach used in development of ODT is the use of superdisintegrants like sodium starch glycol ate (Primo gel, Explotab) carboxymethylcellulose (Croscarmellose), Poly vinylpyrrolidone (Polyplasdone) etc. which

provides rapid disintegration of tablet after putting in mouth, and release the drug in saliva. Bioavailability of certain drugs may be increased due to absorption of drugs in oral cavity and may be due to pregastric absorption of saliva which contains dispersed drugs which pass down into the stomach. The amount of drug which is subject to undergo first pass metabolism is reduced.

1. Superdisintegrants¹

As ODT require faster disintegration. So, pharmacist needs to formulate Disintegrates i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

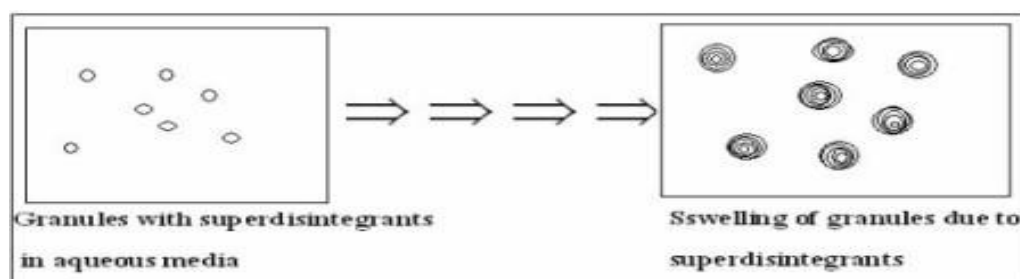


Table1. List of superdisintegrants

Example	Super-Disintegrants	Mechanism Of Action	Special Comment
Crosslinked cellulose	Crosscarmellose [®] Ac-Di-Sol [®] Primellose [®] Vivasol [®]	Swells 4-8 folds in < 10 seconds. Swelling and wicking both.	Swelling is in two dimensions. -Direct compression or granulation -Starch free
Crosslinked PVP	Crosspovidone	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Crosslinked starch	Sodium starch glycolate	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Cross linked alginic acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Natural super Disintegrates	Soya polysaccharides	Rapid Dissolving	Does not contain any starch or sugar. Used in nutritional products.

Selection of super-disintegrates.**The ideal superdisintegrant should have²²:**

- Poor solubility.
- Poor gel formation.
- Good hydration capacity.
- Good moulding and flow properties
- No tendency to form complexes with the drugs.
- Good mouth feel.
- It should also be compatible with the other excipients

And have desirable tableting properties.

MECHANISM OF ACTION OF DISINTEGRATES**a. Swelling⁵**

General mechanism of action for tablet disintegration is Swelling tablets through high porosity expression poor Disintegration due to lack of sufficient swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing Fraction is very high; fluid is unable to penetrate in the tablet and disintegration is again slows down.

b. Porosity capillary action (wicking)⁵

While we place the drug into appropriate aqueous medium, the Medium enters into the tablet and replaces the air absorbed on the particles, which softens the intermolecular bond and Breakdowns the tablet into fine particles. Water uptake by Tablet depends upon hydrophilicity of the drug/excipient and on tableting environments. For these types of disintegrates, Maintenance of porous structure and low interfacial tension towards aqueous fluid is essential which helps in Disintegration by manufacture a hydrophilic system around the Particles.

c. Heat of wetting (air expansion)⁵

When disintegrates through exothermic properties gets wetted, Localized stress is produced due to capillary air expansion, this helps in breakdown of tablet.

d. Due to release of gases⁵

Carbon dioxide released within tablets continuously wetting Due to contact between bicarbonate and carbonate with citric Acid or tartaric acid. The tablet disintegrates due to generation of pressure inside the tablet. As these disintegrates are highly Sensitive to small changes in humidity level and temperature, Strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added

Immediately prior to compression or can be added in to Separate fraction of formulation.

e. By enzymatic reaction⁵

These enzymes destroy the binding action of binder and helps In disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous Increase in the volume of granules to promote disintegration.

f. Due to disintegrating particle repulsive forces⁵ (Secondary to wicking)

The swelling of tablet made through 'non-swelling' Disintegrates. Guyot-Hermann has planned particle repulsion Theory based on the observation that non-swelling particle also Cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and Water is required for it.

g. Due to deformation⁵

During the tablet compression, disintegrated particles become deformed and these deformed particles get into their normal Structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch remained Improved when granules where extensively deformed during Compression.

Patented Technologies**a. Zydis Technology¹⁴**

A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds

b. Orasolv Technology¹⁴

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.

c. Durasolv technology¹⁴

The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters.

d. Wow Tab Technology¹⁵

It is patented by yamanouchi. Wow means "without water". Wow tab is an intra buccally soluble, compressed tablets consisting of granules made with saccharine of low and high mould ability. When low- and high-moldable saccharine are used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. It is used to obtain a tablet of adequate hardness and fast dissolution rate. The wow tab formulation is stable to environment due to its significant hardness than zydis and Orasolv. Wow tab product is suitable for both conventional bottle and blister package.

e. Oraquick¹⁶

This technology is patented by K.V Pharmaceuticals. It utilizes taste masking microsphere technology called as micro mask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. (Bandari S et al., 2008) This process involves preparation of micro particles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat-sensitive drugs.

f. Nano Crystal technology¹⁴

Elan's proprietary NanoCrystal technology (NanomeltTM) can improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

g. Pharmaburst technology¹⁴

SPI Pharma, New castle, patents this technology. The Pharmaburst ODT uses a proprietary disintegrate (Pharmaburst) that is based on mannitol blended with conventional tableting aids. It utilizes the co processed excipients to develop ODT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets.

h. Flash Tab¹⁴

Ethypharm, Saint Cloud, France has patented the Flash tab technology. This technology includes granulation of excipients by wet or dry granulation

method and followed by compressing into tablets. (Chang et al., 2000). This technology relays on the use of super disintegrates. Flashtab is a combination of wet and dry granulation before compression. Micro particles of taste-masked API are blended with conventional tableting aids and disintegrate such as pvp or crospovidone (cross-linked PVP), cross-linked sodium carboxymethyl cellulose and swelling agents such as starches or microcrystalline cellulose. Disintegration times are typically less than 1 min.

Frosta technology⁵³

Akina patents this technology. The frosta technology is based on the compression of highly plastic granules at low pressure to prepare fast melting tablets. The highly plastic granules are composed of three components: a plastic material, (Maltrin QD M580 and Maltrin M180 are maltodextrin and corn syrup solids) a water-penetration enhancer (Mannogem EZ Spray) and a wet binder (sucrose, polyvinylpyrrolidone and hydroxypropyl methylcellulose). Each of the three components plays an essential role in obtaining tablets with higher strengthened faster disintegration time.

j. AdvantolTM 200⁵³

AdvantolTM 200 is a directly compressible excipient system offering "Soft-Melt" functionality and specially formulated for nutraceutical applications. SPI Pharma's Advantol platform uses proprietary co-processing technology. Advantol requires no special manufacturing equipment or tooling. Advantol formulations utilize a standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions to make robust "soft-melt" tablets.

k. Advatab⁵³

AdvaTab tablets disintegrate rapidly in less than 30 seconds. These tablets are prepared using polymer-coated drug particles that are uniformly dispersed in an ultra-fine, low-water content, rapidly disintegrating matrix with superior organoleptic properties. AdvaTab tablets are compressed using a proprietary, patented, external lubrication system in which the lubricant is applied only to the tablet surface, resulting in robust tablets that are hard and less friable and can be packaged in bottles or blister.

• Quicksolv technology¹⁶

This technology is patented by Janssen Pharmaceuticals. It uses two solvents in formulating a matrix which disintegrates instantaneously. Methodology includes dissolving

medium components in water and the solution or suspension is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

- **Ziplet technology¹⁸**

In ziplet technology water insoluble drugs or drugs as coated microparticles are used. The addition of a suitable amount of water-insoluble inorganic excipients combined with

Disintegrants imparted an excellent physical conflict to the oral dissolving tablet (ODT) and the simultaneously maintained optimal disintegration. The use of water-insoluble inorganic excipients offer better enhancement of disintegration in comparison to the most commonly used water soluble sugars or salts. Tablets primarily of water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed which reduces the rate of water diffusion into the tablet core.

- **Oraquick¹⁹**

The oraquick fast-dissolving tablet preparation utilizes a patented taste masking technology. The taste masking method does not develop solvents of any kind, and consequently leads to faster and additional efficient production. Also, lower heat of manufacture than alternative fast-dissolving/disintegrating technologies makes Oraquick suitable for heat-sensitive drugs

Techniques for preparing ODTs⁷

The various techniques are being utilized or adopted to Prepare ODTs

- Freeze drying or Lyophilization
- Sublimation
- Mass extrusion
- Melt Granulation
- Spray drying
- Molding
- Nanonization
- Direct compression
- Cotton candy process
- Phase transition process

- **Freeze drying or Lyophilization¹⁹**

Freeze drying is the technique in which water is sublimed from the product when it is frozen. This technique creates an amorphous porous construction that can dissolve rapidly. A Typical process involved in the manufacturing of ODT using this technique. The active drug is dissolved/dispersed in an aqueous solution of a carrier or polymer. The mixture is dosed through weight and poured in the wells of the preformed Blister packages. 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. After Freeze-drying the aluminum foil backing is useful on a blister sealing Machine. Finally the blisters are packaged and shipped. Advantages of freeze drying the major advantage of using this technique is that the tablets Produced by this technology have a very low disintegration Time and have great mouth feel due to fast melting effect.

Disadvantages of freeze drying

This technique is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed condition.

- **Sublimation⁶**

The slow dissolution of the compressed tablet having even highly water soluble components is due to the fact that the low Porosity of the drugs reduces water dispersion into the matrix. After inert volatile solid ingredients like ammonium Bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetra mine, naphthalene, phthalic anhydride, urea and urethane were additional too along with other tablet excipients and the blend were compressed into a tablet which is finally subjected to a process of sublimation resulting in exceedingly porosity. These compressed tablets exhibition Good mechanical strength and have high penetrability quickly Dissolved within 15 seconds in saliva.

- **Mass extrusion⁷**

This technology contains softening the active blend using the Solvent mixture of water soluble polyethylene glycol, using Methanol and expulsion of softened mass through the extruder or syringe to get a cylinder designed extrude which finally cut into even segments using heated blade to form tablets. This Process can also be used to coat granules of bitter drugs to mask their taste. This method used for preparing taste masked Granules. The tablet was prepared with different Super disintegrate. E.g. sodium starch glycolate, croscarmellose Sodium and crosspovidone etc.

- **Melt granulation**

Melt granulation system is a process through which Pharmaceutical powders are efficiently agglomerated through a melt able binder. The benefit of this method associated to a Conventional granulation is that no water or organic solvents is necessary. For there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a

Useful technique to enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin 41. This methodology to prepare MDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (superpolystate, PEG-6-Stearate). Superpolystate is a waxy material with a melting point of 33-37°C and a HLB value of 9. So it determination not only act as a binder and increase the physical resistance of Tablets but will also help the disintegration of the tablets as it Melts in the mouth and solubilizes rapidly leaving no residues⁸.

• **Spray drying**⁷

Spray dryers remain widely used in pharmaceuticals and Biochemical processes. Due to processing solvent is evaporated quickly; spray drying can produce highly porous, fine powder. Spray drying can be used to formulate quickly Disintegrating tablets. This technique is based on a particulate Support matrix, which is equipped by spray drying an aqueous Composition containing support matrix and other components to usage a highly porous and fine powder this is then mixed with active ingredients and compressed into tablets. The Tablets made from this technology are claimed to disintegrate within 20 seconds.

• **Molding**⁹

In this method, molded tablets are prepared by using water soluble Ingredients so that the tablets dissolve completely and rapidly. The powder blends 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. They are very less compact than compressed tablets. In this process porous Structure is formed and enhances the dissolution rate.

Advantage:

As the dispersion matrix is made from water-soluble sugars, molded tablets disintegrate more rapidly and offer improved Taste. These properties are enhanced when tablets with porous Structures are produced or when components that are physically modified by the moulding process are used. In Comparison to lyophilization process, tablets produced by molding technique are easier to adapt to the industrial scale.

Disadvantage:

The molded tablets have poor mechanical strength, they may Undergo erosion and breaking during handling. Through Hardening can increase the strength of the tablets but it would be at the cost of their disintegration time.

• **Nanonization**²⁰

In this technology contains reduction in the particle size of Drug to nano size by milling the drug using a patented wet milling Technique. The nano-crystals of the drug are stabilized against agglomeration by surface absorption on selected Stabilizers which are then incorporated into mouth dissolving Tablets. This system is suitable for poorly water soluble drugs.

Sahu et al., Novel Science International Journal of Pharmaceutical Science (2012), 1(3):204-211208. Other advantages of this technology include fast Disintegration/dissolution of nanoparticles leading to better Absorption and hence higher bioavailability and reduction in Dose, cost effective manufacturing process, conventional Packaging due to exceptional durability and wide range of Doses i.e. 200 mg of drug per unit.

• **Direct compression**

This process by which tablets are compressed directly from Mixtures of the drug and excipients without any preliminary Treatment. It offers advantages over the other manufacturing Processes of tablets, such as wet granulation and delivers high Efficiency. The mixture to be compressed need have Satisfactory flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. In many cases, the superdisintegrants have a major role in the disintegration and dissolution process of mouth dissolving tablets made by direct compression. The choice of a suitable type and an optimal amount of disintegrates is vital for ensuring a high disintegration rate. The addition of other formulation mechanisms such as water soluble excipients or Effervescent agents can further enhance dissolution or disintegration properties¹¹.

• **Cotton candy process**^{12,23}

It is also known as the “candy floss” method and forms the basis of the technologies such as flash dose (Fuisz Technology). It utilizes an inimitable spinning mechanism to Yield floss like crystalline structure which mimics cotton candy. ODT is formed using a candy floss or shear form Matrix; the matrix is formed from saccharides or Polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallized to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and subsequently compressed into MDT. However the high processing temperature limits the use of this technology.

Characteristics: It can accommodate high doses of drug and offers improved mechanical strength.

• Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making MDTs without any special apparatus. MDT was produced by Compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93°, 95°C), and then heating at about 93°C for 15 min. after heating, the median pore size of the tablets was increased and tablet hardness was also Increased. The increase of the tablet hardness with heating and storage did not depend on the crystal state of the lower melting Point sugar alcohol¹³.

CONCLUSIONS

The ODTs have potential advantages over conventional dosage forms, with their improved patient compliance; convenience, bioavailability

and rapid onset of action had drawn the attention of many manufactures over a decade. The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of Fast dissolving tablets, which in turn prolongs the patent life of a drug. Keeping in view of the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular. Thus ODT may be developed for most of the available drugs in near future.

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