

Orodispersible tablets: A review

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ABSTRACT

Now day's formulation research is breaking barriers of conventional methods. Today, active ingredients can be delivered with a level of convenience, performance and bioavailability never seen in the market place. Fast disintegrating or Mouth dissolving tablet (ODTs) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self administration without water or chewing. This novel type of delivery system offers convenience for treatment-resistant population who have difficulty in swallowing unit oral dosage form, namely Tablets and Capsules. These formulations are particularly beneficial to pediatric and geriatric patients. It is estimated that 50 % of the population is affected by dysphagia which results in high incidence of non-compliance and ineffective therapy. The aim of this article is to review the ideal properties, significance, characteristics, limitation, choice of drug candidates, challenges in formulation, approaches for preparation of ODTs, Patented technologies on ODTs, Suitable drug candidates for ODTs, and Evaluation tests of ODTs.

Key words: Orodispersible, Tablets, Delivery system, Technologies, orally, Compression.

1. INTRODUCTION

Oral drug administration has been one of the most suitable and widely accepted by the patients for the delivery of most therapeutically accepted drug. Various dosage forms like tablet, capsule and liquid preparations have been administered by oral route. But, due to some unsuitable physiological conditions of gastro-intestinal tract like relative poor absorption, presence of various digestive enzymes in gastro-intestinal lumen and epithelium, poor absorption efflux (i.e. by p-glycoprotein) and first pass metabolism by hepatic enzymes, the administration of some drug is affected. Also, it limits many drugs to reach into the therapeutic level. Hence to minimize the problems associated with drug absorption through gastro intestinal membrane, researchers have been developing intra oral drug delivery system that will enhance drug level, avoid first pass and gut wall metabolism, increases the bioavailability of active medicament or improve convenience of dosing [1, 2].

1.1. Oro dispersible tablet

The demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common

among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population [3].

Orally disintegrating tablets are also called as:

- Oro dispersible tablets.
- Quick disintegrating tablets.
- Mouth dissolving tablets.
- Fast disintegrating tablets.
- Fast dissolving tablets.
- Rapid dissolving tablets.
- Porous tablets.
- Rapid melts.

However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs.

1.2. Definition

European Pharmacopoeia has used the term ore dispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing [3].

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute.

The Center for Drug Evaluation and Research defines ODT as solid dosage forms containing medical substances which disintegrate rapidly, usually within a matter of second, when placed upon the tongue.

1.3. Ideal properties of odt's [1]

- The performance of ODTs depends on the technology used during their manufacture.
- The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water.
- Various technologies have been developed that enable ODT to perform this unique function.

An ideal ODT should meet the following criteria:

- Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds.
- Sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling allow high drug loading.
- Pleasant mouth feel.
- Insensitive to environmental conditions such as humidity and temperature.
- Adaptable and amenable to existing processing and packaging machineries
- cost effective.

1.4. Significance [4]

Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include.

- As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.

- Easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients).
- Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- Medication as "bitter pill" has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.
- Bioavailability of drugs that are absorbed from mouth, pharynx, and esophagus is increased. Larger contact area of oral cavity contributes to rapid and extensive drug absorption.
- Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.
- Drug is protected from its degradation due to pH and GIT enzymes.

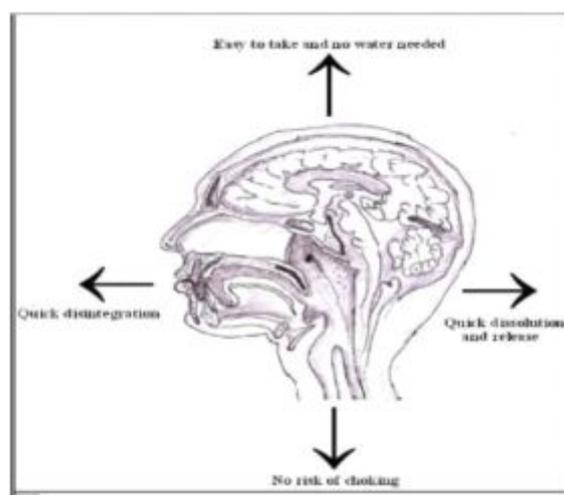


Figure - 1: Advantage of ODT

1.5. The need for development of ODTs

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

1.5.1. Patient factors

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.

- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H₂-blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water
- A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form.
- This leads to increased revenue, while also targeting underserved and under-treated patient populations.
- As examples, Eisai Inc. launched Aricept ODT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin ODT), a line extension of its block-buster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004.
- Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient population.

1.5.2. Effectiveness factor [7,8]

- Increased bioavailability and faster onset of action are a major claim of these formulations.
- Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs.
- Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism.
- Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT.

1.6. Manufacturing and marketing factors [9 - 11]

- Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size.
- As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form.

1.7. Challenges to develop ODT

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as [4]:

1.7.1. Palatability

As most 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 the drugs becomes critical to patient compliance.

1.7.2. Mechanical strength

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft molded 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 Wow tab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs [12].

1.7.3. 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 [13].

1.7.4. Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers [14].

1.7.5. 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 of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite [15].

1.7.6. 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 [16].

1.7.7. Taste masking

Many drugs are bitter in taste. A tablet of bitter drug dissolving/ disintegration in mouth will seriously affect patient compliance and acceptance for the dosage form. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity [17].

1.7.8. Mouth feel

ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODTs should be as small as possible. ODTs should leave minimal or no residue in mouth after oral administration. Moreover addition of flavors and cooling agents like menthol improve the mouth feel [17].

1.7.9. Sensitivity to environmental conditions

ODTs generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the

materials used in ODTs are meant to dissolve in minimum quantity of water [17].

1.7.10. Cost

The technology used for ODTs should be acceptable in terms of cost of the final product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent [17].

1.8. Ideal characteristics of drug candidate [2, 11]

- No bitter taste.
- Dose lower than 20 mg.
- Small to moderate molecular weight.
- Good solubility in water and saliva.
- Partially non ionized at the oral cavity's 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.

1.9. Limitations to orodispersible tablets [17, 18]

- Drugs with relatively larger doses are difficult to formulate into ODTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for ODTs.

1.10. Formulation methods

Various processes employed in formulating ODTs include.

- Freeze-drying.
- Cotton candy process.
- Molding.
- Spray drying.
- Mass extrusion and Compaction.

1.10. 1. Lyophilization or freeze-drying [19]

Formation of porous product in freeze-drying process is exploited in formulating ODT.

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.

1.10.2. Molding

Molding process includes moistening, dissolving, or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution, or suspension at ambient pressure (no vacuum lyophilization), respectively.

The molded tablets formed by compression molding are air-dried. As the compression force employed is lower than conventional tablets, the molded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. Molding process is employed usually with soluble ingredients (saccharides) which offer improved mouth feel and disintegration of tablets.

However, molded tablets have low mechanical strength, which results in erosion and breakage during handling [12].

1.10.3. Cotton candy process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy.

Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning.

The matrix formed is partially recrystallized 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 ODT.

This process can accommodate high doses of drug and offers improved mechanical strength.

However, high-process temperature limits the use of this process [20].

1.10.4. Spray drying

Highly porous, fine powders are obtained by this method. Allen et al. utilized this process for preparing ODT.

The ODT formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and

sodium starch glycolate or cross-carmellose sodium as disintegrating agent.

Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray-dried to yield a porous powder.

The ODT made from this method disintegrated in <20 s [21-23].

1.10.5. 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 [24].

1.10.6. Melt granulation

Abdelbary et al. prepared ODT by incorporating a hydrophilic waxy binder (superpolystate) PEG-6-stearate. Superpolystate is a waxy material with an M.P. 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 the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue [25].

1.10.7. Phase transition process

Kuno *et al.* investigated the disintegration of ODT by phase transition of sugar alcohols using erythritol (m.p. 122°C), xylitol (m.p. 93-95°C), trehalose (97°C), and mannitol (166°C) [26].

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.

1.10.8. Sublimation

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODT. 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 the tableting process, which sublimated from the formed tablet [27].

Koizumi *et al.* developed ODT 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.

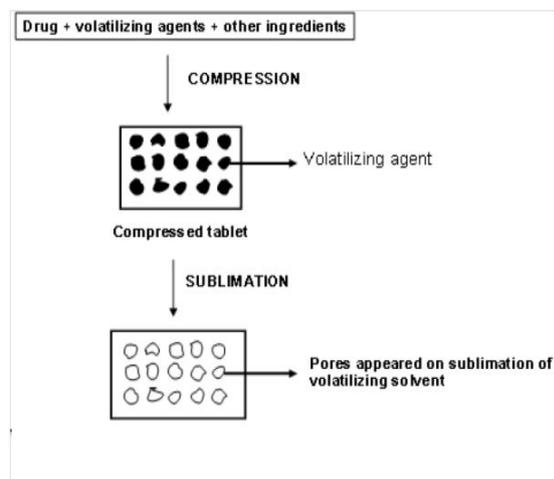


Figure - 2: Sublimation

1.11. Conventional methods

Conventional methods in formulating tablets such as dry granulation, wet granulation, and direct compression methods were adapted to produce ODTs [28,29].

1.11.1. Patented Technologies

1.11.1.1. Zydis technology

Zydis is patented by R.P. Scherer. This technology includes physical trapping of the drug in a matrix composed of a saccharide and a polymer. Polymers generally employed are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, polyvinyl alcohol, polyvinyl pyrrolidone, acacia, and these mixtures. The methodology involves solution or dispersion of components is prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers. Peelable backing foil is used to pack Zydis units. Zydis formulation is sensitive to moisture and may degrade at humidity greater than 65% [30-32].

Desired characteristics of Zydis technology

- Drug should be chemically stable.
- Water insoluble.
- Particle size should be smaller than 50 μm .
- Dose for water-soluble drugs is limited (60 mg).

Lyoc³³

Lyoc technology is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Nonhomogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

1.12.1.2. Quick solv

This technology is patented by Janssen Pharmaceuticals. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion 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 [34].

1.11.1.3. Nanocrystal technology

This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug [35].

1.11.1.4. Flashtab technology

This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types [36].

Disintegrating agents include reticulated polyvinylpyrrolidone or carboxy methylcellulose. Swelling agents include carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

1.11.1.5. Orasolv technology

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the ODT. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight.

As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv, a special

packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression. Paksolv offers moisture, light, and child resistance packing [37-39].

1.11.1.6. Durasolv technology

This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, nondirect compression fillers, and lubricants.

Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in bottles and blisters. Nondirect compressible fillers generally used in the range of 60-95%, lubricant in 1-2.5% [40].

1.11.1.7. WOW tab technology

Yamanouchi patented this technology. WOW means without water. This technology utilizes conventional granulation and tableting methods to produce ODT employing low- and highmoldability saccharides.

Low moldability saccharides are lactose mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, mannitol, orbital, and oligosaccharides. When these low- and high-moldable saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used. This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration [41,42].

1.11.1.8. Dispersible tablet technology

Lek, Yugoslavia patents this technology. It offers development of ODT with improved dissolution rate by incorporating 8-10% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration.

Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improved disintegration of tablets usually less than 1 min [43].

1.11.1.9. Pharmaburst technology

SPI Pharma, New Castle, patents this technology. 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. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles [44].

1.11.1.10. Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

- Porous and plastic material.
- Water penetration enhancer.
- Binder.

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet [45].

1.11.1.11. Oraquick

This technology is patented by K.V Pharmaceuticals. It utilizes taste masking microsphere technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. 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. Oraquick product dissolves within few seconds [44].

1.11.1.12. Zipllets/advatab

This technology is patented by Pessano con Bornago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles [46].

1.11.1.13. Flash dose

Fuisz has patented Flashdose technology. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flashdose

technology is the first commercial product launched by Bioavail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as "floss." Shear form matrices are prepared by flash heat processing [47,48].

1.12. Evaluation of oro dispersible tablets

The mixture of powder was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for thickness, hardness, friability, weight variation test, drug content and In-Vitro release rate studies.

1.12.1. Pre compression parameters evaluation

The mixture of drug and excipient (i.e. blend) prepared for tablet compression is evaluated for following parameters.

- Bulk density.
- Tapped density.

Percentage compressibility or Carr's index:

- Hausner's ratio.
- Angle of repose.

1.12.2. Post compression parameters evaluation

All prepared tablets were evaluated for the following official and unofficial parameters.

1.12.2.1. Hardness

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet was placed between the plungers, and was tightened from one end, and pressure required to break the tablet was measured. It was expressed in kg/cm².

1.13.2.2. Friability

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The friability was then calculated using the formula:

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

1.12.2.3. Dimensions

A compressed tablet's shape and dimensions were determined by the tooling during the compression process. Thickness was

the only dimensional variable related to the process. The dimensions of tablets were measured using the vernier caliper scale. Tablet thickness should be controlled within a $\pm 5\%$ variation of the mean value.

1.12.2.4. Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual tabletweights deviate from the average weight by more than the percentage shown in Table 1 and none deviate by more than twice the percentage shown.

Table - 1: Weight variation tolerance for uncoated tablet

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10.0
130-324	7.5
More than 324	5.0

1.12.2.5. Stability study

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period.

The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications.

Stability is an essential factor of quality, safety and efficacy of a drug product. A drug product, which is not of sufficient stability, can result in changes in physical (like hardness, dissolution rate, phase separation etc) as well as chemical characteristics (formation of high risk decomposition substances).

Stability evaluation of drug substance or drug product is the key to drug quality as it determines the efficacy of any drug or dosage form. Stability assessment of drug products and drug substances are mandated by regulatory agencies across the globe.

Stability testing provides evidence that the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as temperature, relative humidity etc.

The stability study consists of a series of tests in order to obtain an assurance of stability of

a drug product, namely maintenance of the drug product packed in its specified packaging material and stored in the established storage condition within the determined time period.

The ICH Guidelines have established that long term stability testing should be done at 25°C/60%

RH; stress testing should be done at 40°C/75%RH for 6 months. If significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition i.e. 30°C/65%RH.

Table - 2: ICH guidelines for stability study

Study	Storage condition	Time period
Long term*	25°C±2°C/60%RH±5%RH 30°C±2°C/65%RH±5%RH	12 month
Intermediate**	30°C±2°C/65%RH±5%RH	6 month
Accelerated	40°C±2°C/75%RH±5%RH	6 month

The stability study was carried out for the optimized formulation for following condition and time period,

Initial sample at room temperature. 40°C/75% RH for 4 weeks, 50°C/80% RH for 4 weeks, 60°C/80% RH for 4 weeks, 2-8°C for 4 weeks.

1.13. APPLICATION

1.13.1. ODT technologies for sparingly soluble drugs

An ODT can also serve as a preferred delivery system for sparingly soluble compounds or compounds where absorption is solubility limited (BCS class II). With proper selection of formulation excipients

(solubilizers, resins, disintegrants, etc.) and processing technology, any issues relating to wettability, solubility and absorption could be overcome to obtain a product with good organoleptic properties that still meets bioequivalency criteria [49].

1.13.2. Granulation with rapidly disintegrating agents

The formulation comprises an API with appropriately selected solubilization excipients and rapidly disintegrating agents that aid drug disintegration in the mouth and dissolution in the GIT, thus overcoming bioequivalence problems. Examples of disintegrating agents include cross

carmellose sodium, croscopolvidone and sodium starch glycolate.

Loosely compressed ODTs usually rely on water-soluble excipients and/or super disintegrants to achieve rapid disintegration. However, to produce a less friable ODT, a stronger binder is required, which in turn requires a more effective disintegrating agent for the tablet to release its contents. Thus, the appropriate selection of formulation excipients and process can give a faster disintegrating tablet.

1.13.3. Complexation with ion-exchange resins

Ion exchange resins have been used in pharmaceutical formulations for several reasons, including tablet disintegration, taste-masking, stabilization and extended release. One of the most important properties of ion exchange resins is imparted by the functional groups that are attached to a polymer backbone that can exchange ions with drugs in solution. Examples of ion exchange resins include amberlite IRP88 and amberlite IRP64. These resins are practically insoluble in all solvents and at all pH levels, which, combined with their particle size, results in limited absorption by the body. Because of this, these resins are generally recognized as nontoxic and safe.

1.13.4. Cyclodextrin-based ODT

Cyclodextrins are a class of cyclic oligosaccharides made from starch. They usually have a truncated cone structure and a lipophilic cavity with a hydrophilic exterior. Cyclodextrin can form molecular inclusion complexes with a wide variety of drugs, incorporating the lipophilic moiety of the drug molecule in its cavity. The complex provides an effective means of increasing its solubility. The complex is prepared by solubilizing both the drug substance and cyclodextrin in a suitable medium.

The drug complex is converted into solid intermediates for tableting using techniques such as spray drying or layering onto pharmaceutical carriers and/or diluents. The solid intermediate is blended with disintegrants, sweeteners and other tableting excipients, and then compressed into tablets. The synergistic effect of disintegrants and complexation supports faster disintegration, dissolution and bioavailability enhancement.

1.13.5. ODT TECHNOLOGIES FOR BITTER DRUGS

Orally disintegrating tablet, which disintegrate or dissolve in the saliva and produce a positive or negative taste sensation. Most of the drugs have unpalatable taste in which taste masking plays a critical role in formulating ODT.

The negative taste sensation of drugs can be reduced or eliminated by various approaches studied, which include addition of sweeteners and flavors, encapsulating the unpleasant drug in to microparticles and adjustment of pH [49].

1.13.6. Incorporation of sweeteners and flavors

Maximum patient acceptability with ODT is seen if they provide pleasant taste and mouth feel. To provide this property in tablets various sweeteners and flavors are employed.

Usually sugar-based excipients are used as they are highly water soluble and dissolve quickly in saliva and provide pleasant taste and mouth feel to the final product.

Mannitol is most widely used excipient in formulating ODT. Aspartame and citric acid are most commonly used along with various flavors such as mint flavor orange flavor, strawberry flavor, peppermint flavor to produce pleasant taste, and mouth feel^[50].

1.13.7. Encapsulation or coating of drugs

Some of the unpleasant drugs cannot be masked by incorporation of sweeteners and flavors, in such cases alternative method of masking the taste is by encapsulating or coating the drug. In fact this process retards or inhibits dissolution and solubilization of drug, which allows time for particles to pass form mouth before taste is perceived in mouth^[51].

1.13.8. Various techniques utilized include^[36,45,52-54]

- CIMA'S taste masking technique uses coating of drug with dissolution retarding material.
- Phase separation approach for taste-masked microcapsules.
- Microcaps process used microencapsulation technology.
- Extrusion method.
- Micromask technology used casting or spin congealing melt dispersions or solution of drug in molten blend of materials.
- Flashtab technology.
- Solutab technology involves coating drug with sustained release agents, which are finally coated with enteric polymers and further with mannitol.
- Blending with cyclodextrins.

- Coating crystals, granules, and pellets with aqueous dispersions of meth acrylic acid polymers.

2. CONCLUSION

The techniques and technologies described in this article represent how recent advances in formulation development and processing technologies make the efforts to achieve orodispersible tablets. ODTs have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolve/disperse in saliva and can be administered without need of water. A number of ODT products based on various technologies are now commercially available in the international market. The basic approach followed by all the available ODTs technologies is to maximize the porous structure of tablet matrix to achieve rapid tablet disintegration in the oral cavity along with good taste-masking properties and excellent mechanical strength.

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