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CHALLENGES AND APPROACHES ON FORMULATION AND MANUFACTURING OF ORALLY DISSOLVING TABLET DOSAGE FORMS

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Abstract: Orally dissolving tablets (ODTs) offer a significant advantage in terms of patient compliance and convenience, particularly for populations with swallowing difficulties or aversions to traditional solid dosage forms. ODTs dissolve rapidly in the mouth, reducing the risk of choking in patients with dysphagia and ensuring safer administration. However, their formulation and manufacturing pose unique challenges that require specialized approaches to ensure efficacy, palatability and stability. Excipient selection like super disintegrants, fillers and manufacturing processes are crucial for enhancing the disintegration and dissolution of ODTs leading to faster onset of action and improved therapeutic efficacy. Many new molecules and other drugs with unpleasant tastes can negatively impact patient compliance hence it is mandatory to use and optimize taste modifiers, such as sweeteners or flavoring agents to improve palatability and patient acceptability. Coprocessed excipients offer synergistic benefits by combining the advantages of multiple excipients into a single formulation to optimize ODT's quality parameters such as disintegration, dissolution and tablet hardness, while simplifying the formulation and manufacturing process. Advanced manufacturing technologies, such as spray drying, lyophilization and direct compression, improve the uniformity and stability of ODTs. The utilization of patented technologies offers unique advantages such as rapid dissolution, taste masking, improved mechanical strength, and enhanced drug delivery. It is necessary to understand the importance of ODT platform technologies in enhancing patient adherence, especially for vulnerable populations. Furthermore, ongoing research and innovation in this field continue to drive advancements in ODT technology and offer advantages in terms of simplicity, cost-effectiveness and scalability to enhance its therapeutic potential and market viability. This review outlines various strategies employed to address these challenges and optimize ODT formulations and manufacturing processes.

Index Terms **- patient compliance, disintegration, taste, excipients, dissolution, stability**

I. INTRODUCTION

Oral administration of medication is thought to be the most common method [1] and >60% of the drugs can be accepted via oral routes of administration [2]. In oral drug delivery, due to easy production, compact size and ease of self-administration, tablets are the most widely used dosage form on the market currently. A key consideration in the design and composition of dosage forms is patient convenience of administration and cost-effective manufacturing process.

The primary drawback of techniques of regularly used oral medicine delivery such as tablets and capsules is dysphasia or difficulty in swallowing. It may be challenging to swallow regular tablets in some situations, such as motion sickness, sudden allergic reactions, coughing fits and dehydration [3]. This condition

primarily affects pediatric and elderly patients, who find it difficult to take the tablets and capsules as recommended. Also due to hand tremors, fear of swallowing, delayed muscles and nervous system functioning, and schizophrenia, swallowing difficulties are widespread in elderly patients and often result in poor patient compliance. Due to poor adherence to oral tablet drug therapy, which occurs in about one-third of the population (mostly adults and children), the overall effectiveness of the therapy is reduced.

To address this issue an alternate approach known as the orally dissolving drug delivery system was developed and patient convenience improved using the same oral route [4,5]. When the tablet dosage form placed in the mouth, dissolves in a few seconds, the active ingredient released comes into contact with saliva and starts to act therapeutically [6]. The unique ability of orally dissolving tablets (ODTs), also referred to as orally disintegrating tablets (ODTs), fast dissolving/disintegrating tablets (FDTs) is to dissolve in the mouth in a matter of seconds without the need for chewing or water. A solid dosage form that dissolves or disintegrates fast in the oral cavity without requiring an intake of water is called an orally dissolving tablet (ODT). European Pharmacopoeia defined it as ‘uncoated, customized tablets that are intended to dissolve in the mouth in three minutes or less and are intended to break down rapidly for quick absorption’ [7]. In the "Orange Book" by the US Food and Drug Administration - Center for Drug Evaluation and Research,. ODT is described as "a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of 30 seconds when placed upon the tongue [8, 9]. Furthermore, patients who are traveling with little or no additional water should minimize the use of conventional tablets. ODT causes rapid absorption and breakdown, which leads to an early start of therapeutic activity [10]. Additionally, when packaged as ODTs, medication candidates that experience pre-gastric absorption may exhibit higher oral bioavailability. It provides easy manufacture, accurate dosing and good stability [11].

The present review describes in detail on challenges in the development of orally dissolving tablets, various formulations technologies developed to achieve fast dissolution or dispersion of tablets in the oral cavity for better absorption and improved bioavailability with patient compliance and evaluation methods necessary to be adopted in analyzing various quality attributes of ODT formulations. Table 1 describes the advantages, disadvantages and challenges of ODTs.

Table 1. Advantages, disadvantages and challenges of orally dissolving tablets.

Advantages [12,13]
• Administration to patients who refuse to swallow, including pediatric, geriatric and mental patients, as well as those who are bedridden, elderly, suffering from renal failure or who are unable to swallow. • Increased bioavailability and faster absorption via pre-gastric medication absorption from the mouth, throat, and esophagus as saliva flows down to attain a quick therapeutic result. • Treating disabled patients who are confined to their beds, as well as people with hectic schedules or frequent travelers who might not always have easy access to enough water. • Better mouth feel qualities help to change people's negative perceptions of medications, especially important for kids to make bitter medication taste pleasant. • Provides effective dosing and convenience of administration in comparison to liquid dose forms, • Pre-gastric absorption has the potential to enhance bioavailability and, due to lower dosage requirements, improve clinical performance by minimizing side effects
Disadvantages [14]
• Mechanical Strength - More likely to break or fragment since they don't have the strength required in some formulations. • Hygroscopicity - Moisture can cause them to degrade; hence specialized packaging is necessary to preserve the physical integrity of this under typical circumstances. • Brittleness - Because of its brittleness, sophisticated peel-off blister packaging is required, which poses problems with manufacturing. • Bitter drugs or unpleasant odors - Formulating bitter medications or those that have unpleasant smells medications, additional precautions need to be taken to improve patient acceptability.
Challenges [15,16].
• Preparation of tablets that disintegrate quickly without sacrificing their mechanical strength • The biggest challenge in the formulation is striking a balance between the necessity to avoid excessive tablet size expansion and the goal of quick disintegration. • For successful formulation, a compromise must be struck between achieving fast disintegration and maintaining appropriate tensile strength.

- Creating tablets that leave little to no residue in the mouth after administration while maintaining a pleasant patient experience is a challenge.
- To preserve stability and stop degradation, it is necessary to implement efficient moisture protection techniques due to the hygroscopic nature of certain formulations.
- One of the challenges is creating packaging that is both protective and convenient to administer.
- Effective taste masking qualities must be included in the formulations to ensure patient acceptance, particularly for bitter medication formulations.

II. COMPONENTS OF ORALLY DISSOLVING TABLET FORMULATIONS

In Table 2, the major commonly used components to develop an orally disintegrating tablet of different therapeutic categories, ideal characteristics with examples are described [17, 18, 19].

Table 2: Components of orally dissolving tablet

Ingredient and it's proportion	Ideal Characteristics	Examples
Active drug moiety 1- 25%	Low doses of highly stable drugs with acceptable organoleptic properties	Antihypertensives, antidepressants, antipsychotics, antiepileptics, antiemetics, etc.,
Super disintegrants 1- 10%	Super disintegrants with higher disintegration efficiency at lower concentrations which produces hydrostatic pressure and volumetric expansion required for rapid disintegration in the mouth, saliva must be rapidly wicked into the tablet.	Crospovidone, croscarmellose sodium, microcrystalline cellulose, sodium starch glycolate, sodium carboxy methyl cellulose, calcium carboxy methyl cellulose, modified corn starch.
Binders 5 - 10%.	In addition to providing low active dosage tablets with volume, binders ensure that tablets and granules can be made with the minimum mechanical strength.	Mono/di/polysaccharides and their derivatives, starches, microcrystalline cellulose and hydroxy propyl cellulose, xylitol, sorbitol, maltitol, gelatin, polyvinyl pyrrolidone, polyethylene glycol.
Diluents/Fillers 10 - 90%.	Fillers increase the volume and decrease the concentration of the active ingredient in the formulation. Also improving tablet texture and disintegration in the mouth.	Dibasic calcium phosphate, mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pre-gelatinized starch, magnesium trisilicate, aluminium hydroxide.
Sweetener 3 - 6%	It provides a pleasant mouthfeel and taste masking ability.	Natural: sucrose, maltose, steviosides, dextrose, glucose, xylose, ribose, fructose and isomaltose; Artificial: sucralose, saccharin sodium, acesulfame potassium, neotame, altitame, aspartame.
Flavor 0 to 10%.	It promotes patient acceptance and compliance.	Vanilla, mint, cherry, anise, peach, apricot, liquorice, raspberry, strawberry and peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil thyme oil, oil of bitter almonds.
Color 0 - 10%.	Improves the appearance and organoleptic characteristics.	Amaranth, red iron oxide, sunset yellow or approved colors
Emulsifying agents 0.05 - 15%	Helps the drugs to dissolve quickly and release without the need for chewing, swallowing or water consumption. Improve bioavailability and stabilize immiscible mixtures.	Lecithin, sucrose esters, sodium doecylsulfate, sodium lauryl sulfate, alkyl sulfates, propylene glycol esters.
Lubricants 1- 5%	Prevent ingredients from sticking to tablet punches or capsule filling machines and from clumping together.	Magnesium stearate, stearic acid, polyethylene glycol, liquid paraffin, colloidal silicon dioxide.
Preservatives qs.	Improves the stability and reduces impurities	Methylparaben, propylparaben, citric acid and sodium citrate.

Surfactants qs.	Decreases interfacial tension, therefore enhances solubility.	Sodium lauryl sulfate, sodium dodecyl sulfate, tweens, spans.

III. FORMULATION APPROACHES

The choice and selection of suitable excipients is crucial for formulating ODTs. Excipients such as superdisintegrants, filler-binders, lubricants, and taste modifiers play a significant role in enhancing disintegration, dissolution and other quality characteristics.

3.1 Super disintegrants

Crospovidone, croscarmellose sodium and sodium starch glycolate are commonly used super disintegrants in pharmaceutical formulations, especially in solid oral dosage forms like tablets and capsules. These excipients promote rapid disintegration of the dosage form upon exposure to aqueous environments, facilitating drug dissolution and subsequent systemic absorption.

Crospovidone - Synthetic polymer crospovidone is made from polyvinyl pyrrolidone (PVP) and cross-linked to enhance swelling and water absorption. Crospovidone absorbs water quickly, which causes substantial swelling and the tablet matrix to be disrupted, which causes the tablet to disintegrate quickly. Because of its superior disintegration efficiency and compatibility with a wide range of medicinal ingredients and excipients, it is frequently employed in pharmaceutical formulations.

Croscarmellose sodium - Chemically, croscarmellose sodium is a cross-linked sodium carboxymethylcellulose that is produced through carboxymethylation. Similar to crospovidone, croscarmellose sodium rapidly absorbs water upon exposure, leading to swelling and subsequent disintegration of the dosage form. Preferred for its high-water absorption capacity and effectiveness in promoting rapid disintegration.

Sodium starch glycolate - Sodium hydroxide or other reagents are used to cross-link starch to create sodium starch glycolate, a modified starch derivative. Sodium starch glycolate like crospovidone and croscarmellose sodium, exhibits rapid swelling properties when it comes into contact with water, which causes the tablets to disintegrate. Because of its effectiveness and compatibility with a variety of drug substances and excipients, it is frequently used as a super disintegrant in pharmaceutical formulations [20].

3.2 Filler-Binders

Filler-binders are essential components in the formulation of solid oral dosage forms like tablets and capsules. They serve two main functions:

As a bulking agent, providing the tablet or capsule with the required volume and bulk, filler-binders serve as bulking agents. Through this, the dosage form can reach the appropriate weight and size for handling and administration. Without filler-binders, tablets or capsules might be too light weight or tiny, which would make them difficult to handle and might cause dosage problems.

As a binding agent, they have binding qualities that, in addition to their bulking ability, aid in keeping the active pharmaceutical ingredient (API) and other excipients together while compressing tablets or filling capsules. For the tablet to remain intact and have mechanical strength, this is essential. Tablets that aren't properly bound may crumble or dissolve too soon, which could affect the stability and precision of dosage.

Lactose - Because of its exceptional compressibility, flowability and compatibility with a range of active substances, lactose is a commonly utilized filler-binder in pharmaceutical formulations. It works especially well for wet granulation and direct compression procedures. Additionally, lactose facilitates better pill dissolving and disintegration.

Microcrystalline cellulose - Also, a popular filler- binder, microcrystalline cellulose or MCC is known for its excellent compressibility, flowability and binding qualities. It contributes to the quick disintegration and dissolving of tablets and offers superior stability and hardness.

Dicalcium phosphate - As it works well with a variety of APIs and other excipients, dicalcium phosphate, particularly dibasic calcium phosphate dihydrate (DCPD), is used as a filler-binder. In addition to increasing the mechanical strength of tablets and improving their dissolution and disintegration, it has good flow and compressibility characteristics.

Mannitol - Mannitol is a sugar alcohol. Because of its sweet flavor, low hygroscopicity and compatibility with a variety of APIs, it is frequently employed as a filler-binder in orally disintegrating tablets (ODTs). It imparts a pleasant mouth feel and has taste-masking capabilities in addition to contributing to the overall hardness of the tablet [21].

3.3 Lubricants

To prevent sticking and ensure smooth tablet ejection, lubricants are added to ODT formulations to reduce friction between the tablet grains and the surfaces of the tablet press equipment. One lubricant that is frequently utilized in ODT formulations is magnesium stearate. However, to prevent negatively impacting tablet breakdown and disintegration, the choice and concentration of lubricants need to be carefully screened.

3.4 Taste-Masking agents

The use of taste-masking agents is crucial in pharmaceutical formulations, particularly in orally dissolving tablets, to improve patient compliance by masking the unpleasant taste of drugs. Taste-masking agents such as sweeteners and flavors enhance the palatability of ODTs, making them more acceptable to patients, especially pediatric and geriatric populations who may have difficulty in swallowing with conventional tablets.

Sweeteners - To provide medications a sweet taste and mask away the bitter or unpleasant taste, sweetening agents are frequently utilized as taste-masking agents in ODTs. Depending on their flavor, solubility and compatibility with the recipe, different natural and artificial sweeteners can be used. Common sweeteners include artificial sweeteners like sucralose, aspartame and saccharin, as well as sucrose, glucose, fructose and sorbitol. These sweeteners improve the overall palatability of ODTs while also masking the undesirable taste of medications, which encourages patient acceptability and compliance [22].

Flavors - Another class of taste-masking compounds utilized in ODTs to further mask the unpalatable taste of medications is flavoring agents. To improve taste and increase patient acceptability, a wide range of artificial and natural flavors, including fruit tastes (cherry, orange, strawberry), mint flavors (peppermint, spearmint) and other flavoring compounds can be added. The bitter or disagreeable taste of medications is largely masked by flavors, which enhances the patient's sensory experience entirely [23].

3.5 Incorporation of co-processed excipients

Co-processed excipients are a class of multifunctional excipients that are designed to address specific challenges encountered in pharmaceutical formulation. These excipients are created by combining two or more individual excipients in such a way that they exhibit synergistic properties, providing advantages that exceed those of the individual components alone. The incorporation of co-processed excipients in orally dissolving tablet (ODT) formulations offers several benefits, including improved flow properties, compressibility and disintegration characteristics.

Better Flow Properties - Considering it influences the homogeneity and consistency of tablet formulations, flowability is a crucial characteristic in the pharmaceutical production process Co-processed excipients are designed to improve particle packing and decrease interparticle friction in order to improve flow characteristics. As an illustration, co-processed excipients that combine various grades of microcrystalline cellulose (MCC) with appropriate lubricants or glidants can enhance flow characteristics, which in turn improves content and tablet uniformity [24].

Enhanced Compressibility - Excipients that have been co-processed are made to have the best possible compressibility, which makes tableting procedures more effective. Co-processed excipients can reduce the possibility of tablet defects such as capping and lamination during compression and increase tablet strength by combining excipients with complementary qualities, such as binders with fillers or disintegrants with binders.

Improved Disintegration Characteristics - To ensure quick drug release and patient compliance, tablets must rapidly disintegrate. Super disintegrants and other excipients that facilitate quick disintegration can be added to co-processed excipients to modify their disintegration properties. Co-processed excipients, for instance, can improve tablet disintegration while preserving tablet integrity by combining super disintegrants like crospovidone or croscarmellose sodium along with suitable diluents [25].

IV. MANUFACTURING PROCESS APPROACHES

Manufacturing technologies such as lyophilization, spray drying, direct compression etc., play a crucial role in facilitating the production of orally dissolving tablets with enhanced uniformity, stability and dissolution characteristics.

4.1 Freeze-Drying or Lyophilization

The process of reducing water out of a frozen product is called freeze drying. With this method, an amorphous porous structure that dissolves quickly is produced. A carrier/polymer is dissolved or dispersed in an aqueous solution containing the active medication. After weighing the mixture, it is added to the walls of the blister packs that have already been created. To freeze the drug solution or dispersion, the trays containing the blister packs are put through a liquid nitrogen freezing tunnel. The freeze-drying process is then carried out by keeping the frozen blister packs in refrigerator cabinets. Using a blister-sealing machine, the aluminium foil backing is attached after freeze-drying. The blisters are finally wrapped and shipped. The process of freeze-drying has been shown to boost bioavailability and improve absorption. The primary drawbacks of the lyophilization process are its high cost and long duration; these items fragility makes traditional packaging appropriate for them and their poor stability in pressured environments [26]. The manufacturing process of lyophilization/freeze drying is described in Figure 1.

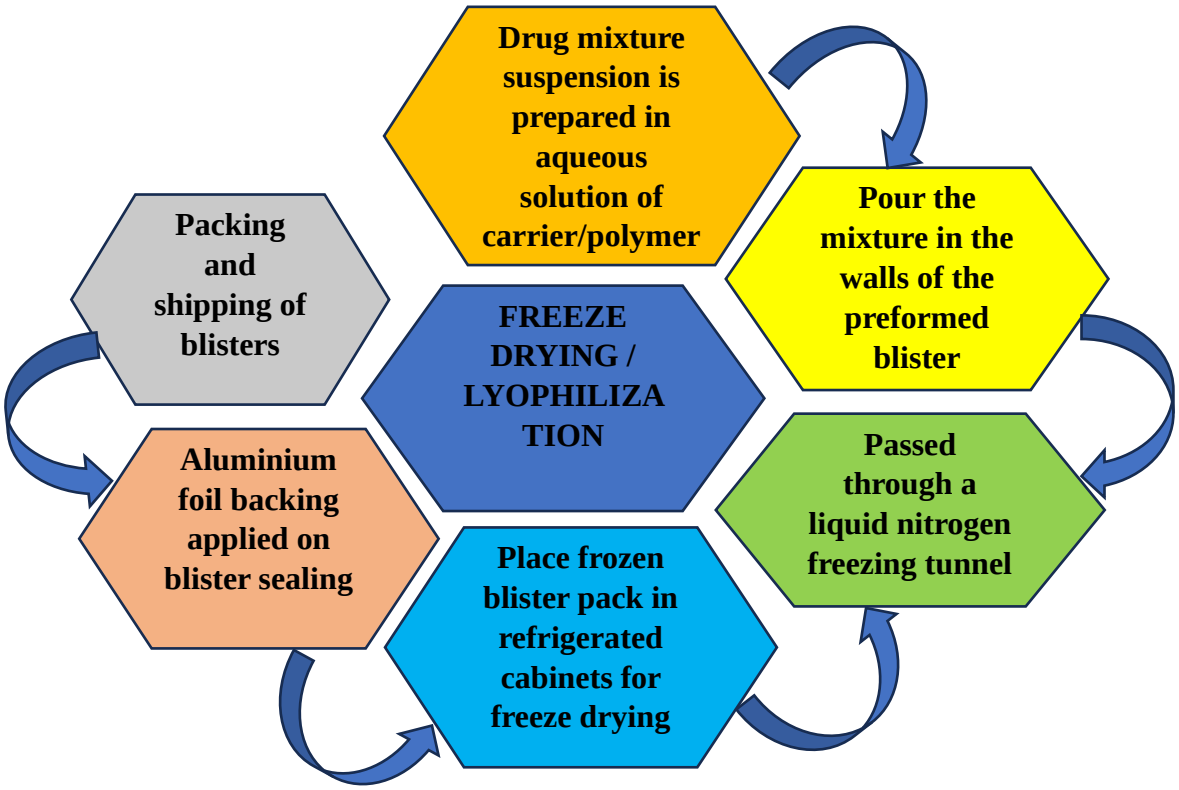

Figure 1: Lyophilization or Freeze-drying process.

4.2 Spray - Drying

By using hydrolyzed and nonhydrolyzed gelatins as supporting agents, mannitol as a bulkingagent, sodium starch glycolate or croscarmellose sodium as disintegrating agents and an acidic (like citric acid) or alkali (like sodium bicarbonate) material to improve disintegration and dissolution, the ingredients are integrated. The spray-drying methods characteristics that when the dosage form comes into contact with the aqueous medium, it dissolves quickly-within 20 seconds [27]. A flowchart for the spray drying method is described in Figure 2.

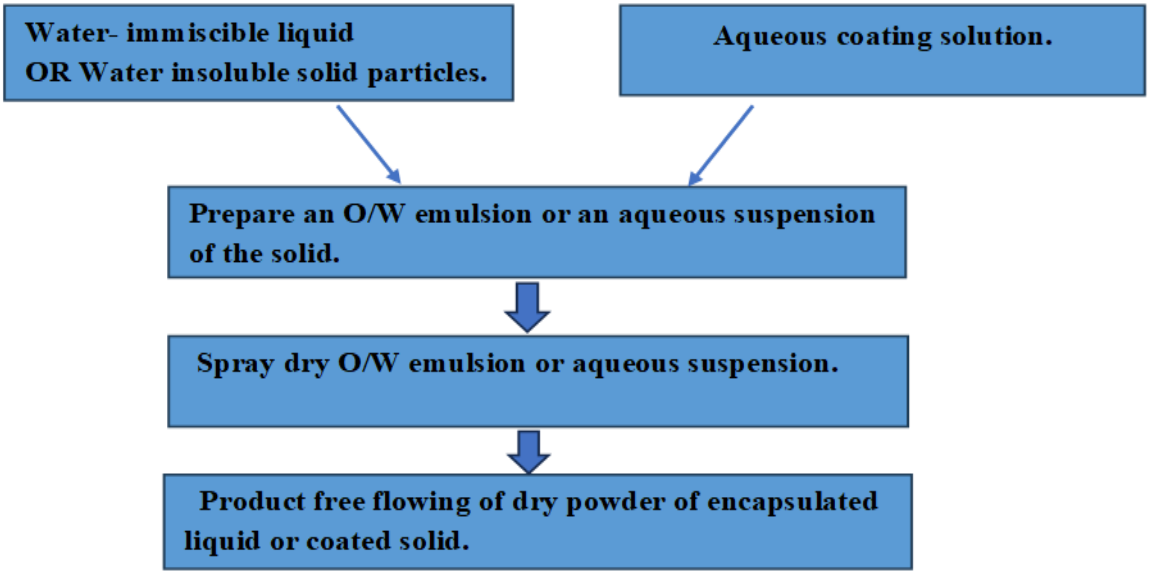

Figure 2: Flow chart for applying the coating to both liquid and solid particles using the spray drying method.

4.3 Direct compression

Direct compression represents the simplest stand most cost-effective tablet manufacturing technique. This technique can now be applied for the preparation of ODT because of the availability of improved excipients especially super disintegrants and sugar-based excipients.

4.3.1 Using super disintegrants

The presence of super disintegrants primarily influences the rate of disintegration and consequently, the dissolution in many orally disintegrating tablet technologies that rely on direct compression. Disintegration is accelerated by the addition of additional formulation ingredients such as effervescent agents and water-soluble excipients.

Mechanism of super disintegrants: Swelling - This process disintegrates tablets when certain disintegrating ingredients, such as starch, come into contact with water and start to disintegrate. For example, Plantago ovata and sodium starch glycolate. **Porosity and capillary action (Wicking) -** Porosity and capillary action are the mechanisms that cause some super disintegrants to disintegrate. The broken-down particles combine to increase porosity, which creates pathways for the liquid to penetrate into tablets. The liquid is then exhausted through capillary action or wicking action, which causes the breakage of interparticulate connections and, in the end, tablet disintegration. Examples include Croscarmellose and Crospovidone [28]. **Deformation -** The starch grains deformed when pressure was applied, and they returned to their previous shape when the pressure was released. However, they are irreversibly damaged when compacted into tablets, releasing their energy upon contact with water [29].

Due to disintegrating particle/particle repulsive forces: The swelling of tablets created with non-swellable disintegrants has been tried to be explained by another disintegrant mechanism. The finding that no swelling particle also causes tablet disintegration led Guyot-Hermann to develop the particle repulsion theory. The mechanism of disintegration is caused by the electric repulsive interactions between particles [30].

4.3.2 Using sugar-based excipients

This is an additional method of producing ODT through direct compression the use of excipients derived from sugar, particularly bulking agents such as polydextrose, xylitol, fructose, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate and dextrose which have a pleasant mouth feel and high aqueous solubility. Mizumito et al have divided excipients made of sugar into two categories according to how quickly they dissolve and mold. (i) Low moldability and a high rate of dissolution characteristics of type 1 saccharides, such as lactose and mannitol. (ii) Low dissolution rate and high moldability are characteristics of type 2 saccharides, such as maltose and maltilol [31,32]. The process of direct compression is described in Figure 3.

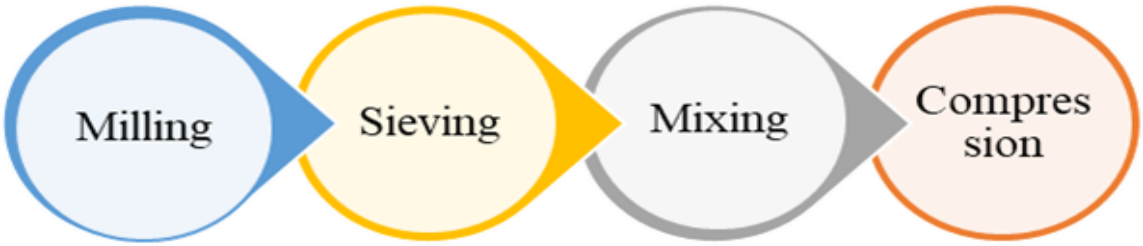

Figure 3: Direct compression method.

4.4 Tablet moulding

Although the chemicals in molded tablets dissolve quickly and fully in water, they are entirely soluble. There are two types of molding processes: solvent method and heat method. By using a hydro-alcoholic solvent to moisten the powder blend, the solvent method compresses the mixture at low pressures into molded plates to create a wetted mass (compression molding). After that, the solvent is eliminated by air-drying. The tablets produced in this way have a porous structure that speeds up dissolving and is less compact than compacted tablets. In the heat molding procedure, a suspension containing a medicine, agar and sugar (such as lactose or mannitol) is prepared, then the suspension is poured into blister packaging walls, the agar is solidified at room temperature to create a jelly and the mixture is dried at 30˚C under vacuum. One major challenge is the mechanical robustness of molded tablets. It is necessary to include binding agents, which boost the tablet's mechanical strength. One additional issue with this technique is taste masking. Spray congealing a molten combination of hydrogenated cotton seed oil, sodium carbonate, lecithin, polyethyleneglycol and an active component into a lactose-based tablet triturate form produced the taste-masked drug particles. The molding approach produces tablets that are easier to scaleup for industrial manufacture compared to the lyophilization method. To create an ODT with a disintegration period of roughly 20–60 seconds, Pebley et al evaporated the frozen mixture comprising a gum (such as Acacia, carrageenan, guar, tragacanth, and xanthan), a carbohydrate (such as Dextrose, lactose, maltose, mannitol or maltodextrin) and a solvent in a tablet-shaped mold [33].

4.5 Cotton candy process

There as on this method gets its name in that it uses a special spinning mechanism to create crystalline structures that resemble cotton candy and floss. The process of making cotton candy requires simultaneously spinning and flash-melting polysaccharides or saccharides to generate a matrix. The resulting matrix is partially recrystallized for better compressibility and flow characteristics. After milling and blending this candy floss matrix with excipients and active substances, it is compressed to FDT. This procedure delivers enhanced mechanical strength and is capable of handling large medication dosages [34,35].

4.6 Sublimation

Volatile chemicals are added to the formulations to create a porous matrix these formulations are then sublimated. Ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride are examples of very volatile substances that can be combined with other excipients to form tablets. Sublimation is then used to remove this volatile substance, leaving behind a very porous matrix. This method has been shown to produce tablets that typically dissolve in 10–20 seconds. It is possible to use solvents such as benzene and cyclohexane as pore-forming agents [36). A schematic representation of the sublimation process is described in Figure 4.

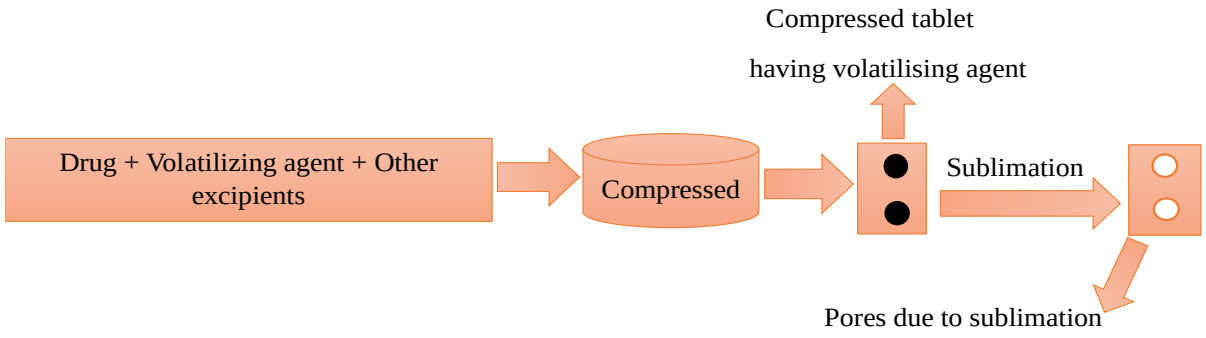

Figure 4: Schematic representation of the sublimation process of orally disintegrating tablets

4.7 Mass-Extrusion

Using a solvent mixture of methanol and water-soluble polyethyleneglycol, the active blend is softened. Then, the softened mass is ejected through a syringe or extruder to create a cylinder of the product that is divided into even segments by a heated blade to produce a tablet. To achieve taste masking, the dried cylinder canal so be used to coat bitter drug particles [37,38].A flowchart for the manufacturing process of mass-extrusion is described in Figure 5.

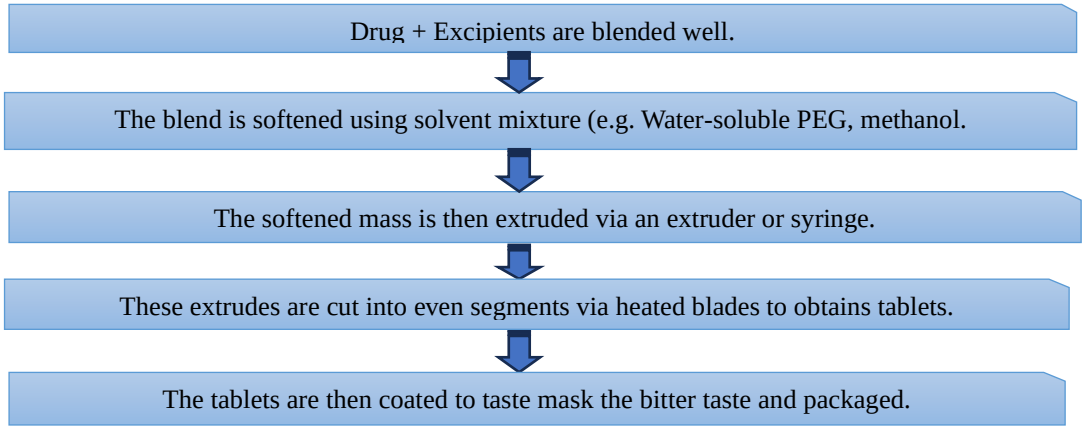

Figure 5: Mass-Extrusion Method

4.8 Three-Dimensional Printing (3DP)

Technology used in rapid prototyping (RP) is three-dimensional printing (3DP). Using liquid binding materials and powder processing, particular layers are built within the prototyping process. Three-dimensional printing (3DP) was used to create a unique fast-dissolving drug delivery device (DDD) containing loose powders. The 3DP system automatically prepared the DDD containing the medication acetaminophen based on computer-aided design models [39]. It was discovered that TAG may be used to produce oral tablets that dissolve quickly and with the right amount of hardness. The large pore size and large total pore volume of the TAG tablets appeared to be the cause of the quick disintegration of the tablets due to water penetration [40].

4.9 Melt granulation

A meltable binder is used in the process of melt granulation technique, which effectively agglomerates pharmaceutical powders. Compared to conventional granulation, this method has the advantage of not requiring the use of organic solvents or water. Compared to wet granulation, this technique takes less time and energy because there is no drying step.This method is helpful for increasing the rate at which medications that are poorly soluble in water, like griseofulvin, dissolve [41].

4.10 Phase transition process

This FDT degradation process involves a phase transition in sugar alcohols containing mannitol (166°C), trehalose (97°C), xylitol (93–95°C) and erythritol (edge point122°C). Two sugar alcohols with high and low melting points are combined into a powder, which is then compressed and heated to a temperature in between to create tablets. Because of their poor fit, the tablets lacked enough hardness before heating. Because the low melting temperature sugar alcohol phase transition creates a connecting surface on the tablet, heating causes the creation of interparticle bonds, which increases the tablet's hardness [42].

4.11 Particle size reduction techniques

Particle size reduction techniques, such as micronization and nanonization, are commonly employed in pharmaceutical formulations to improve the solubility and dissolution rate of poorly water-soluble drugs. These techniques are particularly beneficial for enhancing the bioavailability of drugs, which is crucial for formulating Mouth Dissolving Tablets (ODTs) due to the rapid onset of action required.

Micronization - Micronization is the process of reducing a drug's particle size to micron-scale measurements, usually between 1 and 10 micrometers. This method can be carried out by mechanical procedures including grinding, milling or jetmilling. When a pharmacological material is exposed to aqueous solutions, its surface area rises dramatically and its wettability and dissolving rate improve. This is

achieved by lowering the particle size. For medications that are not very soluble in water, micronization works especially well since it improves the drug's ability to dissolve thus enhancing its bioavailability [43].

Nanonization - Commonly referred to as nanosizing or nanoparticle production, nanonization is the process of further reducing a drug's particle size to nanometer-scale dimensions, usually less than 1 micrometer. Numerous procedures, including high-pressure homogenization, precipitation processes and wet milling, can be used to accomplish this strategy. The process of nanonization greatly expands the drug particles, surface area and surface energy, which improves their solubility and improves their ability to dissolve in aqueous solutions. Improved bioavailability of poorly water-soluble medicines is the result of quicker dissolution kinetics made possible by the greater surface area-to-volume ratio [44].

V. COMPATABILITY STUDIES

Conducting compatibility studies between drug substances and excipients is essential to ensure stability and efficacy. Techniques like differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) can be employed to assess compatibility.

5.1 Differential scanning calorimetry

A potent analytical method for examining the thermal conduct of materials, such as pharmaceuticals and excipients, is differential scanning calorimetry (DSC). With the ability to monitor heat flow into or out of a sample as a function of temperature or time, it can provide important insights into sample interactions, thermal stability, and phase transitions. A controlled temperature program is applied to both the sample and the reference material in a DSC experiment, and the temperature difference between them is determined. The sample and the reference material are treated to identical thermal treatments. A measured heat flow signal is produced by any energy that the sample absorbs or releases as a result of physical or chemical changes.

DSC can identify a arange of thermal occurrences, such as Melting - The process of a solid into a liquid, marked by the absorption of heat and an endothermic peak; Crystallization - The release of heat during the change from a liquid to a solid state, indicated by an exothermic peak; Glass transitions - Often seen in polymers and certain amorphous medications, these are the changes from a stiff amorphous form to a rubbery condition; Breakdown - The sample experiences thermal degradation, which is indicated by the production of break down products and an exothermic peak.
DSC can be used to identify incompatibilities between drug compounds and excipients. These differences in compatibility can show up as new peaks forming, melting or crystallization peaks shifting or variations in the enthalpy of phase transitions when compared to the individual components. These modifications indicate possible interactions between the medication and the excipients, which might have an impact on the pharmaceutical formulation's stability or effectiveness [45].

5.2 Fourier-Transform Infra-Red spectroscopy

Fourier transformation identifies and characterizes functional groups and molecular structures in a sample, Infrared Spectroscopy (FTIR) is a potent analytical method that is frequently utilized in pharmaceutical research and development. It works by measuring the absorption of infrared radiation in the sample. FTIR spectroscopy is very helpful in evaluating possible interactions that can happen when mixing medicinal ingredients and excipients in compatibility tests. The spectra of each medicinal ingredient and excipient are initially acquired independently while doing compatibility investigations with FTIR spectroscopy. The spectra of the drug-excipient blend or physical mixture, are then compared to those of each component separately. The presence of additional peaks or shifts in absorption peaks in the mixture's FTIR spectra could be signs of chemical interactions between the drug and excipients. The stability, effectiveness or safety of the finished pharmaceutical formulation may be impacted by compatibility problems that can be revealed by these detected spectrum alterations. Incompatibility investigations, FTIR spectroscopy is frequently used to identify interactions between the medicine and excipients, such as hydrogen bonding,ion-dipole interactions or co-valent bonding [46].

VI. PATENTED TECHNOLOGIES

Utilizing patented technologies can provide ready-made solutions for ODT formulation and manufacturing, potentially simplifying the process and reducing development time.

6.1 Zydis technology

Zydis is an exclusive oral solid dosage form that dissolves quickly on the tongue in less than three seconds and can be taken without the need for water. To create a product that dissolves quickly, the drug is physically trapped in a water-soluble matrix and then freeze-dried. Excipients such as polymers (such as gelatine, alginates and dextrin) give tablets strength and rigidity, polysaccharides (such as mannitol and sorbitol) give the matrix crystallinity and hardness and improve palatability, collapse protectants (such as glycine) to stop the product from shrinking in its packaging during manufacturing or storage and flocculating agents (such as xanthan) are typically present in the matrix to ensure uniform dispersion of drug particles water to ensure the formation of porous units flavors and sweeteners to improve patient compliance, preservatives (like parabens) to prevent microbial growth, permeation enhancers (like sodium lauryl sulphate) to improve transmucosal permeability and pH adjusters (like citric acid) to optimize chemical stability. Based on Zydis technology, there are currently thirteen products available. The Zydis products that are available in the United States are Zyprexa Zydis, Pepcid RPD, Maxalt-MLT, Feldene Melt, Dimetapp Quick Dissolve and Claritin Reditab. Zydis formulations for loperamide, enalapril, lorazepam and oxazepam are also offered on the global market [47].

6.2 Orasolv technology

This innovation was created by CIMA laboratories. In essence, the system produces tablets with taste-masked active ingredients and an effervescent disintegrating agent that quickly dissolves and releases the taste-masked active ingredient when it comes into contact with saliva. To reduce the amount of time that tablets take to dissolve in the mouth, they are made by direct compression at very low compression force. The resulting soft and friable tablets come in a specially designed pick-and-place package. There are two ways in which the Orasolv formulation masks taste: Orasolv's coating of the drug powder and effervescence are two ways to mask the taste of an unpleasant drug, in addition to sweeteners and flavors [48].

6.3 Dura Solv technology

CIMA's second-generation fast dissolving tablet formulation is called Durasolv. Durasolv, which is made similarly to Orasolv, has a lot more mechanical strength than Orasolv because it uses more compaction that is created during tableting. As a result, the durasolv product is made more quickly and affordably. Due to high compaction pressures during formulation, one drawback of durasolv is that higher doses of active ingredients are incompatible with the technology. Right now, Durasolv comes in two products: Zorlip and Nulev [49].

6.4 Wow Tab technology

Yamanouchi Pharmaceutical Co. has a patent on Wowtab technology. The WOW in Wowtab indicates that the tablet should be administered "WithOut Water". To create fast-dissolving tablets using traditional granulation and tableting techniques, it is composed of a combination of low-moldability saccharides such as lactose, mannitol, glucose, sucrose and xylitol and high-moldability saccharides such as maltose, sorbitol and oligosaccharides.

6.5 Flash tab technology

The Flash tab technology is patented by Prographarm Laboratories. With the use of this technology, a tablet that dissolves quickly and contains microcrystals as the active ingredient is prepared. All of the traditional tabletting techniques, including microencapsulation, coacervation, extrusion-spheronization and basic pan coating techniques were used in the preparation of drug micro granules. These tablets disintegrate in less than a minute [50].

6.6 Pharma burst technology

SPI Pharma is in the process of patenting pharmaburst technology. Tablets made using this technology can be packaged in blister packs and bottles and have sufficient potency. This method produces tablets that dissolve in 30 to 40 seconds. First, a dry mixture of medication, flavoring and lubricant is combined, and then the mixture is compressed into tablets [50].

6.7 Ora quick technology

Patents related to this technology are held by K.V.S. Pharmaceuticals. This technology uses a patented taste masking technique to produce fast-acting or mouth-dispersing tablets. This technology makes use of micro-masks or taste-masking microspheres, which offer better mouth-feel than taste-masking alternatives, strong mechanical properties and quick product dissolution.

6.8 Flash dose technology

Fuisz is the patent holder for this innovation. Biovail Corporation's first commercial product is a new version of ibuprofen called Nurofenmeltlet, which is prepared using flash dose technology and is meant to dissolve in the mouth like tablets. The "floss" in" flashdose" tablets is a self-binding shear form matrix. WOW or "WithoutWater," prepares shear form matrices. To create a powerful tablet that melts quickly, a combination of low and high-moldability saccharides is used in this process. Lactose, glucose and mannitol are examples of low-moldability saccharides that are combined with the active ingredient and maltose and oligosaccharides are examples of high-moldability saccharides that are granulated [51].

6.9 Shear form technologies

The technique is based on the preparation of floss, also referred to as"Shear form Matrix", which is made by flash heating feedstock that contains a sugar carrier. During this process, the sugar is simultaneously exposed to a temperature gradient and centrifugal force, which raises the mass temperature and creates an internal flow condition that allows some of the sugar to move in relation to the mass. Because the resulting floss is amorphous, it must be further chopped and recrystallized using a variety of methods to give it a form flow properties. This makes their crystallized matrix easier to blend with other tablet excipients and an active ingredient. A tablet is formed by compressing the resultant mixture [52].

6.10 Ceform technology

Microspheres with an active ingredient are created using ceform technology. Placing a dry powder containing mostly pure drug material or a unique combination of drug material plus other pharmaceutical compounds, along with excipients, into a precisely engineered and quickly spinning machine is the fundamental step in the manufacturing process of ceform microspheres. The dry drug blend is thrown through tiny, heated apertures at a high speed by the centrifugal force of the ceform machine's rotating head. After that, the microspheres are compressed or blended into the oral delivery dosage format of choice. The capacity to process the drug and excipient at the same time creates a special micro-environment where materials can be added to the microsphere to change the properties of the drug material [51,52].

6.11 Ziplet technology

Italy's Passano con Barnago holds the patent for this technology. Using this method, water-insoluble ingredients are combined with one or more potent disintegrants to create ODT that has a reduced compression force, optimal disintegration time and increased mechanical strength [53].

6.12 Frosta technology

Akina implemented this technology and this Frosta technology produces solid tablets with high porosity by compressing plastic granules under low pressure using a basic principle. Porous plastic materials combined with a water penetration enhancer in this process and then it is granulated with a binder. Nearly any drug can be produced using this technology, including ones that are sold and ones that prolong the innovator's patent. Clinical research demonstrates the ODTs' ability to increase patient compliance, offer a quick start of action, as well as boost bioavailability. It won't be long before the majority of oral formulations are made in ODT forms, given the numerous advantages of ODTs.

6.13 Nanocrystals technology

Elans' proprietary nanocrystalline technology can produce and enhance composite activity and end-product properties for rapid tablet melting. The melting rate rises when the particle size is reduced because it increases the surface area. With the use of nanocrystalline technology, this can be effectively predicted. Nanocrystalline particles are produced by grinding the drug using a patented wet milling technique. They are easily small drug particles, usually with a diameter of less than 1000 nanometers (nm). Orally administered nanoparticles offer pharmacokinetic benefits to nanocrystal fast-dissolving technology [54].

6.14 Lyo (Pharmalyoc)

After making an oil-water emulsion, it was put straight into the blister cavities and allowed to lyophilize. It is possible to avoid homogeneity during lyophilization by increasing the viscosity after sedimentation by adding inert filler. Because of the high filler content, the tablet's porosity is decreased, which lowers light refraction [55].

VII. EVALUATION OF ORALLY DISSOLVING TABLET

Precompression and post-compression study

In Table 3 and Table 4, the precompression [17, 30, 33, 56] and post-compression parameters [30,33,56] of orally disintegrating tablet with necessary methods to evaluate and the compliance details are described

Table 3: Precompression parameters of orally disintegrating tablet

Parameters	Methods	Compliance
Angle of repose(Ɵ)	Funnel method - A precisely weighed granules/powder mixture is poured into a funnel. The diameter of the powder cone is measured and the angle of repose is calculated by using the following formula: Ɵ = Tan-1 h/r	Angle of repose / Flow property <20 Excellent 20-30 Good 30-40 Passable >34 Very poor
Bulk density	A weighed quantity of blend is poured into a graduated cylinder, and the volume and weight are measured to determine the apparent bulk density. Bulk density = Weight of Powder / Volume of Powder	Determine optimal fill volume in dosing disc. High bulk density indicates good compressibility.
Tapped density	A weighed quantity of blend is poured into a graduated cylinder and allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. Tapping continued until no further change in volume. Tapped Density = Weight of Powder / Volume of Tapped Powder	Tapped density measures how closely packed the particles are within a sample. Higher tapped density indicates greater compactness.
Compressibility Index (%)	The compressibility of the blends is determined by the compressibility index. Compressibility Index (%) = [(TD-BD) X 100 / TD]	% C.Index / flow / % C.Index / flow 5-12 Excel 23-35 Poor 12-16 Good 33-38 Poor+ 18-21 Fair to Passable > 40 poor++
Hausner's Ratio	A similar index to indicate the flow properties can be defined as Hausner's ratio. The formula is, Hausner's Ratio = Tapped Density x 100/ Bulk Density	H ratio / Flow / H ratio / Flow 1.00-1.11 Excel 1.35-1.45 Poor 1.12-1.18 Good 1.46-1.59 Poor+ 1.19-1.25 Fair >1.60 Poor++ 1.26-1.34 Passable

Table 4: Post-compression parameters of orally disintegrating tablet

Parameter	Methods	Compliance
General appearance	Visually Inspect under daylight for defects in tablet size, shape, color, taste, texture, odor and consistency, as well as the legibility of any identifying information.	No defects with consumer acceptability and overall "elegance".
Size and Shape	The size and shape of the tablet are dimensionally described, monitored and controlled. Tablets with appropriate size and shape to comply with the specification limit.	Easier for patients to swallow, enhancing medication adherence and patient comfort.
Thickness	Measured by digital vernier caliper / Automated device	To keep the necessary hardness

Hardness (Crushing Strength)	The test has been performed by the standard procedure. By placing each tablet transversely between the two plungers of the tablet hardness tester and exerting pressure until the tablet completely splits into two parts.	Sufficient mechanical integrity and strength of tablets to withstand handling after manufacturing and during it's stability studies.
Friability	Friability of tablets tested by Roche friability tester. Before being put in the friabilator, the tablets were weighed. Tablets are turned up to 100 times or four minutes at a speed of 25 rpm. After that, the tablets are removed, cleaned and reweighed. % Friability = (initial weight- final weight) x 100 (initial weight)	The mechanical strength of tablets tested According to USP 24. Limit: % friability value should be <1.
Wetting time	10 cm dia circular tissue papers are arranged in a 10 cm diameter Petri dish. To the Petri dish, 10 ml of water was added, along with the water-soluble pigment eosin. The tissue paper is gently positioned over a tablet.	"Wetting time" is the amount of time it takes for water to reach its upper surface, a short time leads to fast disintegration.
Water absorption ratio	A piece of tissue paper folded twice is put on a small petri dish having 6 ml of water. The tablet is located on the tissue paper and allowed to be completely wet and is then weighted. The water absorption ratio, R is determined by: R = 100 × Tablet Wt. after water absorption – Tablet Wt. before water absorption / Tablet Wt. after water absorption.	Tablets with higher water absorption ratios have a greater capacity to absorb water, which can facilitate disintegration and drug release.
Dispersion Time	It was measured by dropping a tablet in a beaker containing 10 ml of phosphate buffer pH 6.8 at 37±0.5°C. 6 tablets from each formulation were randomly selected and the time required for complete dispersion time was measured.	Tablets with shorter dispersion times dissolve or disperse quickly in the medium.
Disintegra-tion test	The test was carried out on 6 tablets using a tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus.	Ensure disintegration time meets specifications and fast disintegration leads to a quick onset of action.
Weight variation	The weight of 20 randomly chosen tablets is determined using analytical balance then the mean weight is calculated.	Average weight (mg) / Limit of Max. Difference 130 or less — 10 % less than 324 — 7.5 % More to 324 — 5 %
Drug content	Required number of tablets from each formulation to be powdered to make a test solution and then using a standard solution, analysis was performed using UV / HPLC	If the API is less than 25 mg, the content-uniformity test is used. Otherwise, the weight variation test is applicable.
Dissolution	The in vitro drug release was determined by estimating the dissolution profile using a USP 2 paddle device. Paddle was rotated at 50 rpm and phosphate buffer (pH 6.8) 900 ml was used as the dissolution medium.	Compliance to meet as per specification. Batch-to-batch uniformity and batch release.
Moisture uptake	Required numbers of tablets are weighed initially and put in a desiccator exposed to 75% RH at room temperature for 7/15 days. Increase in weight to be recorded.	Used to evaluate the stability of the formulations against moisture attack.
Stability studies	The ICH recommendations for accelerated and real-time stability conditions are below. 40±2°C/75%RH for six months; 25±2°C/60±5%RH for 12 months/shelf life. During stability visual flaws, hardness, friability, moisture uptake/loss disintegration and dissolution were examined.	Evaluate product integrity over time and decide its shelf life/expiry.

VIII. MARKET POTENTIAL OF ORALLY DISSOLVING TABLETS FORMULATIONS

In Table 5 some example formulations manufactured using ODT platform technology and well established in the world market for their specific therapeutic applications.

Table 5: Orally disintegrating tablet formulations in the market

Brand Name	Active drug	Indication	Manufacturer	Technology
Abilify®	Aripiprazole	Anti-psychotic	Otsuka America Pharmaceutical, Inc.	Zydis®
Claritin® RediTabs®	Loratadine	Anti-histaminic	Bayern Schering Corporation	
Zofran® ODT	Ondansetron HCL	Anti-emetic	GlaxoSmithKline	
Loperamide® Lyoc®	Loperamide chlorhydrate	Anti-diarrheal	Teva	Lyoc®
Paralyoc®	Paracetamol	Analgesic, anti-pyretic	Teva	
Remeron®SolTab	Mirtazapine	Anti-depressant	Organon Inc.	Orasolv®
Zomig® Rapimelt	Zolmitriptan	Migraine	AstraZeneca	
Niravam™	Alprazolam	Anxiety	Schwarz Pharma	Durasolv®
NuLev®	Hyoscyamine sulfate	Antispasmodic	Schwarz Pharma	
Benadryl® Fastmelt	Diphenhydramine Citrate	Anti-histaminic	Pfizer	WowTab®
Gaster® D	Famotidine	Anti-ulcer	Yamanouchi	
Nasea® OD	Ramosetron HCL	Anti-emetic	Yamanouchi	
Dolflash®	Acetaminophen	Analgesic, anti-pyretic	Sanofi-Aventis	Flashtab®
Nurofen® Flashtab	Ibuprofen	Analgesic, anti-pyretic	Boots Healthcare	
OxynormOro®	Oxycodone chlorhydrate	Cancer-related pain	Mundipharma	

IX. CONCLUSION

Prior knowledge and understanding of challenges encountered at various stages of orally dissolving/disintegrating tablet development concerning critical quality attributes is mandatory for successful dosage form development and drug delivery. Pharmaceutical companies and research institutions are continuously working to overcome these challenges for optimizing ODT formulations using specialized approaches/techniques in therapeutic areas including psychiatry, emergency medicine, geriatrics and pediatrics, where ODTs have experienced massive growth and acceptance. The approach of orally dissolving tablets is a helpful tool for extending the life of an existing product, by obtaining a patent for the same drug molecule and hence majority of pharma businesses are being forced to adopt it. In addition, ongoing research and development in this area are necessary to fulfill the changing demands of patients and healthcare professionals, address new issues and enhance ODT formulations. This review proves that high potential for developing quality dosage forms that improve patient outcomes and satisfaction through the optimization of ODT formulations and it's production methods. In conclusion, scientific understanding and addressing the challenges contiguous to ODTs is a key to the efficient delivery of many existing and new drug molecules of different therapeutic categories in the coming days. Varied strategies are important due to the complexity of these challenges and this review is one of a roadmap to plan the development activities for continual improvement in formulation research.

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