WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 16, 1190-1215. Review Article ISSN 2277–7105

# ORODISPERSIBLE TABLETS: AN ACCLAIMED NOVEL INNOVATIVE DRUG DELIVERY SYSTEMS AND EMERGING MARKET PROSPECTS

**K. M. Manjanna and Mounika C. ***

Department of Pharmaceutics, T. V. M. College of Pharmacy, Ballari, Karnataka, India.

Article Received on
02 July 2024,

Revised on 23 July 2024,
Accepted on 13 August 2024

DOI: 10.20959/wjpr202416-33633

***Corresponding Author**
**Mounika C.**
Department of Pharmaceutics, T. V. M. College of Pharmacy, Ballari, Karnataka, India.

## ABSTRACT

In recent scenario, certain novel medicinal products need to the patients for right time for the treatment of therapy either oral or peroral route of administration. Among all route of administration the oral delivery is well known preferred delivery system for systemic administration of therapeutic agents because of accurate dosage, low-cost therapy, self-medication, non-invasive method and ease of administration leading to high level of patient compliance. Orodispersible tablets (ODTs) are the novel dosage form which quickly disintegrates in the mouth (1-3 min) without chewing upon oral administration and without the need of water. ODTs are very credence dosage form to administered peroral route especially in pediatric, geriatric and nomadic patients which is difficult to swallowing in emergency period of treatment. Various scientists have formulated ODTs by following various techniques such as compression, molding, melt granulation, phase-transition process, sublimation, freeze-drying, spray-drying, and effervescent process. Present outline observed in the pharmaceutical technology many number of scientists have explored several poorly water soluble drugs with various superdisintegrates in the form ODTs to improve solubility and bioavailability. The present review has been expressing the details fast and present challenges of ODTs during the formulation, manufacturing techniques and evaluation factors to improving oral bioavailability of lipophillic drugs.

**KEYWORDS:** Disintegration, manufacturing techniques, Orodispersible tablets, Superdisintegrants.

## INTRODUCTION

There are several ways to deliver drugs into the body for the treatment of many diseases and diagnosis purposes, viz oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through skin), pulmonary (through inhalation). Among all these deliveries oral delivery (by swallowing) is well known preferred delivery system for systemic administration of therapeutic agents because of accurate dosage, low-cost therapy, self-medication, non-invasive method and ease of administration leading to high level of patient compliance.[1] Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast dispersing dosage forms, technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes.[2]

In oral drug delivery, many scientific challenges and breakthrough technologies are required to generate novel dosage forms raising drug delivery to higher level. The term oral drug delivery, also referred to as per oral delivery, refers to taking a dosage form by mouth for local action or systemic absorption at any point along the gastrointestinal (GI) tract. The most popular solid oral dosage products such as powders, pills, tablets, capsules are administered for various diseases conditions.[3] Dysphagia, which is also known as difficulty in swallowing, is one of the most common problems associated with tablets and capsules among all age groups. The size, shape, and taste of tablets are commonly cited as a reason for the difficulty in swallowing. Patients who do not have access to water are mainly in need of simple swallowing dosage forms, according to geriatrics, pediatrics, and nomadic patients.[3] To overcome these challenges, new drug delivery systems have been developed for oral administration called Orodispersible tablets (ODTs). When placed in the oral cavity, ODTs quickly melt in saliva without the need of water and disperses quickly before swallowing.

ODTs are also known as mouth dissolving tablets, melt-in-mouth tablets, fast dissolving tablets, rapimelts, porous tablets and quick dissolving tablets.[4] The Unites States Food and Drug Administration (USFDA) have defined ODTs as “A solid dosage form containing

medicinal substance or therapeutic agent which disintegrates usually within a matter of seconds when placed upon the tongue". Generally, the disintegration time for ODTs varies from few seconds to around a minute.

ODTs are a new generation of formulations that combine the advantages of both liquid and conventional tablet forms while simultaneously providing additional benefits over both the traditional dosage forms. They have both the convenience of a tablet form and the convenience of swallowing as provided by a liquid form. These tablets are currently available in the market for treating many disease conditions such as hypertension, migraine, dysphasia, nausea, vomiting, Parkinson's disease, schizophrenia, and pediatric emergency situations.[5] When the fast-disintegrating tablet is orally applied, and the drug substance has to be dissolved so that it can be absorbed. The dissolution process consists of many steps e.g., Wetting, disintegration, and dissolution are all examples. A fast-disintegrating tablet that typically contains several excipients is involved in a complex process that begins when the solvent reaches the solid and penetrates the tablet matrix. Excipients' effects are attributed to the surface properties of the particles and their solid matrix structure.[6] Recently, certain patents are created for the novel techniques such as WOW tab technology, flash tab technique, Zydus and Orosoly for ODTs.[7]

## IDEAL PROPERTIES OF ORODISPERSIBLE TABLETS

ODTs should exhibit specific ideal attributes that differentiate them from traditional conventional dosage forms. Significant desirable characteristics of these dosage forms encompass.[8-10]

i. ODTs are both convenient and effortless as it does not necessitate the utilization of water for oral ingestion. Instead, the medication should rapidly dissolve or disintegrate in the oral cavity within a few seconds.
ii. Enable the incorporation of a large quantity of drugs.
iii. Deliver a delightful sensation when consumed orally.
iv. The compatibility of ODTs should extend to taste masking and other excipients.
v. Produce minimal or no residue in the mouth following oral administration.
vi. Possess an adequate level of strength to endure the challenges posed by the manufacturing process and subsequent handling stages.
vii. Remains unaffected by changes in humidity and temperature, making it insensitive to environmental conditions.

viii. Capable of being conveniently adapted and compatible with standard processing and packaging equipment without incurring substantial expenses.

ix. Obtain a state of portability that is free from any worries about fragility.

## ADVANTAGESOF ODTS

Orodispersible tablets present numerous advantages include[11-15]

i. ODTs are special device for administering medication for patients who face challenges swallowing, such as the elderly, stroke survivors, pediatric, geriatric, and psychiatric patients.

ii. The beneficial mouth feel attribute of ODTs assists in altering the perspective regarding medication as a "bitter pill," especially for pediatric patients

iii. The convenience of administering medication and ensuring accurate dosing is greater when compared to liquid options.

iv. Pregastric absorption can enhance bioavailability, potentially leading to reduced dosages and improved clinical performance by minimizing undesirable effects.

v. The quick dissolution of the drug and subsequent absorption can lead to a rapid onset of action.

vi. Facilitates elevated drug loading.

vii. Swift drug therapy intervention.

viii. Enhancing bioavailability and facilitating rapid absorption through pre-gastric uptake of drugs from the mouth, pharynx, and esophagus as saliva descends.

ix. The dosage form can be administered without the need for water.

## LIMITATIONS OF ODTS[16-17]

i. It is not feasible to implement rapid drug therapy intervention.

ii. At times, there may be a need for increased frequency of medication administration.

iii. Dose dumping could potentially happen.

iv. For adequate stabilization and safety of the ODTs required a specialized pharmaceutical packaging is necessary.

v. Typically, orally disintegrating tablets (ODTs) exhibit insufficient mechanical strength, necessitating careful handling.

vi. Improper formatting may result in an unpleasant taste and/or grittiness lingering in the mouth.

vii. Formulating drugs with relatively larger doses into ODTs poses challenges.

The challenges involved in manufacturing of ODTs are that ODTs should possess enough strength to resist the difficulty of the manufacturing process and post-manufacturing handling. After administration, it should not leave residue in mouth. For administering conveniently, the tablet size should be easy to take and handle as well. Finally ODTs should disintegrates and dissolve in oral cavity without time delay.

To obtain the successful response, the suitable amount of active medicament must be absorbed and transported to the site of action at the right time and rate of input can be adjusted to produce the concentrations required to maintain the constant amount of drug in plasma for long period of time is necessary to the patients in many diseases conditions. There are major process are very important in oral absorption of medicaments such as drug solubility, disintegration and dissolution. Thus the manufacturers to be considered physicochemical and biopharmaceutical characteristics of active drug and other added substances in the formulation.

## THE ANATOMY AND PHYSIOLOGICAL CHARACTERISTICS OF THE GI TRACT

The primary functions gastrointestinal tract (GIT) is processes of secretion, digestion and absorption. The GI barrier allows to passing rapidly into systemic circulation of most nutrients and vitamins by passive diffusion but controls entry of higher molecular weight medicaments and toxins. The oral administration of these materials possess into GIT and distributed into different organs or tissues, then followed to absorption and eliminated from the body and must pass through various location of one or more biological membranes/barriers.[18] After oral ingestion the materials are stored in the stomach and mixing with GI-fluid, converted into liquid mass and then passed gradually into the upper small intestine.[5] Thus, the GIT represents a primary barrier for oral absorption of drugs.

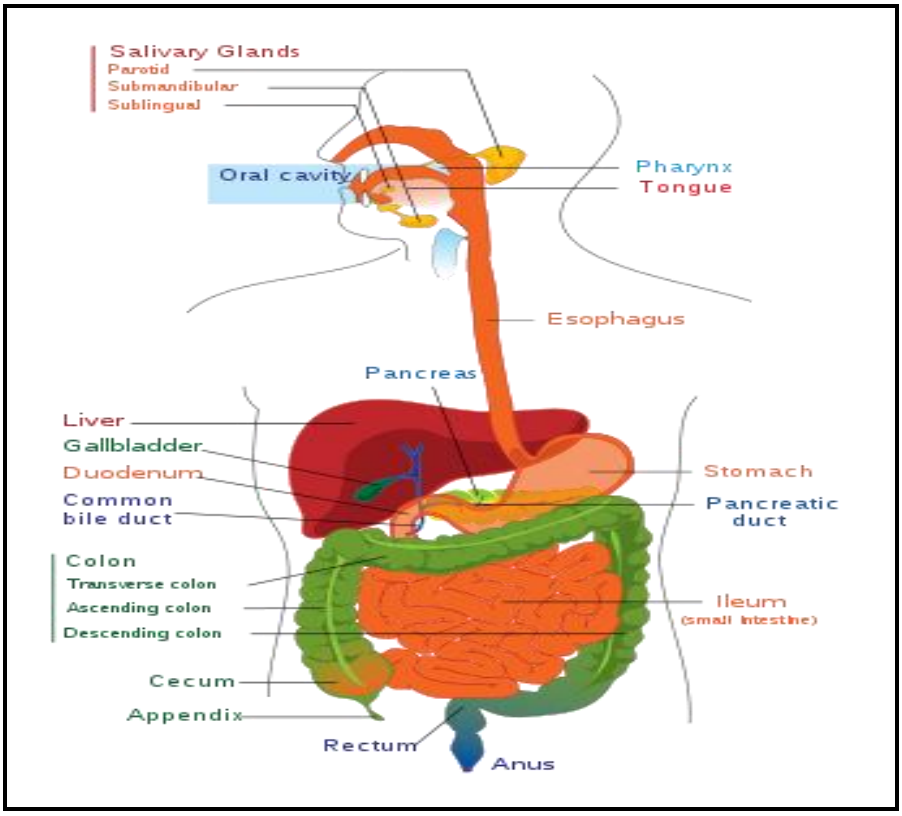


**Figure 1: Schematic representation of the GIT and different sites of drug absorption.**

The gastrointestinal tract consists of three major anatomical regions: the stomach, the small intestine it includes the duodenum, jejunum, ileum, and the large intestine. When the administer drug passed through in various regions of the GI-tract and absorbed at the site of action depending on particular properties of GI-fluid with respect to pH, enzymes, electrolytes, fluidity and surface features.

The stomach is a bag like structure having a smooth mucosa and thus small surface area. Its acidic pH 1-3 due to secretion of hydrochloric acid favors absorption of acidic drugs; if they are soluble in the gastric fluids they remain unionized to large extent in such a pH. After oral ingestion, materials are presented to the stomach, the primary functions of which are storage, mixing, and reducing all components to slurry with the aid of gastric secretions and then emptying these contents in a controlled manner into the upper small intestine.

The small intestine, with its enormous absorptive area of between 200 and 600 $m^2$ is invariably the principal site of drug absorption. In contrast, the perfusion rate of blood to the small intestine is 6 to 10 times that of stomach and the pH range of 5 to 7.5 is most favorable sustained or controlled release dosage forms. The small intestine provides certain significant properties for drug absorption such as high permeability, slow peristaltic movement and long

transit time. The prolonged transit time about 3 to 5 hours through the small intestine is fairly constant and unaffected by food status. If the drug dissolves in the stomach contents, drug solution will then pass in an unimpeded manner to the small intestine for subsequent absorption at the optimal site. Thus, a contribution of all the above factors makes small intestine the best site for absorption of most drugs.[19]

Large intestine having small absorptive area usually plays very little role in the absorption of drugs. In contrast, the stomach being a secretory rather than an absorptive organ and the colon having small absorptive area usually play very little role in absorption of drugs. Nevertheless, particularly in the case of sustained release preparations, the colon may play an important absorptive role for poorly absorbed drugs and sustained release dosage products because of the long residence time. Since transit times through the colon are highly variable ranging from less than 1 hour to more than 60 hours. Absorption from the distal part can be considered negligible since any remaining drug will be embedded in semi-solid fecal matter.

In view of the differences in the local environment such as pH, nature of luminal contents, length and surface area, absorptive capacity of three sections of the GIT, the duration of transit and residence times of a sustained release product in each section, can greatly affects the drug release/absorption from oral drug delivery products. On the other hand, some of the other factors such as drug solubility and dissolution rate, particle size, effective surface area, lipophilicity of the drug, pKa of the drug, polymorphic nature of the drug also influence the drug absorption from oral route.[20]

## MECHANISM OF DISINTEGRATION

Disintegration refers to the mechanical break up of a compressed tablet into small granules upon ingestion and therefore it is characterized by the breakdown of the inter-particulate bonds, which were forged during the compaction of the tablet.[21] Tablet disintegration is a critical step in the drug delivery process as it directly impacts the dissolution and subsequent absorption of medications within the body. When a tablet is ingested, it must disintegrate promptly to release its Active Pharmaceutical Ingredients (APIs) in a form that can be dissolved in the gastrointestinal tract. Effective disintegration ensures rapid and consistent drug release, allowing for optimal bioavailability and therapeutic efficacy.[22]

The disintegration of tablets involves a combination of physical and chemical processes. When a tablet comes into contact with fluids, such as saliva or gastrointestinal fluids,

moisture penetrates the tablet's outer layers, causing it to swell and undergo structural changes.[23] Various mechanisms contribute to disintegration, including capillary action, wicking, and erosion.

**Capillary action**

Capillary action occurs when the liquid is drawn into the tablet through interconnected channels or pores. The liquid fills these channels, causing the tablet to expand and ultimately leading to its disintegration. This mechanism is particularly significant for tablets with porous structures or those containing superdisintegrants, which enhance capillary action and promote rapid disintegration.

**Wicking**

Wicking involves the migration of fluid into the tablet *via* capillary action, where the liquid is drawn into the tablet's matrix structure, leading to swelling and the subsequent disintegration. Wicking is especially relevant for tablets with hydrophilic matrices or those incorporating disintegrating agents that facilitate fluid penetration and disintegration.

**Erosion**

Erosion refers to the dissolution of tablet components upon exposure to fluids. When the tablet's surface erodes, it exposes the underlying layers, allowing fluid penetration and further disintegration. Erosion-driven disintegration is commonly observed in immediate-release tablets with fast-dissolving excipients or in effervescent formulations that generate carbon dioxide upon contact with water.[24]

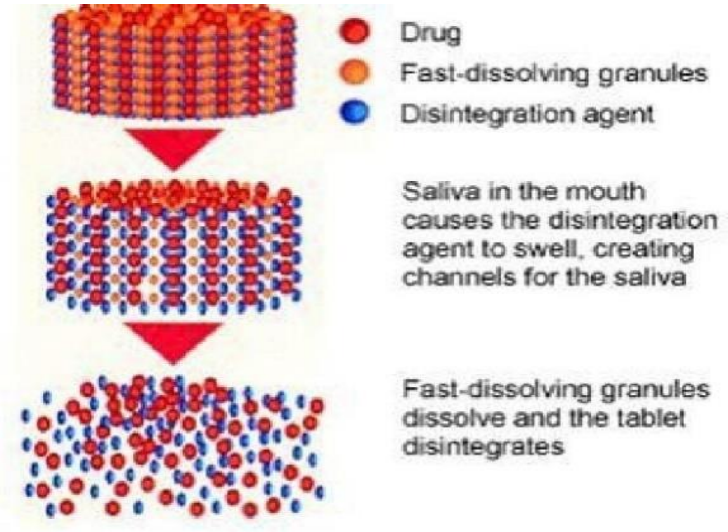


**Figure 2: Concept of Disintegration.**

**Factors influencing tablet disintegration**

Several factors can impact the disintegration of tablets, affecting drug release and bioavailability. These factors include formulation characteristics, such as excipients, superdisintegrants, and binders, as well as manufacturing processes like compression force, tablet hardness, and coating thickness. Additionally, environmental conditions like pH, temperature, and the presence of enzymes can influence tablet disintegration rates.

**Formulation characteristics**

The choice of excipients, superdisintegrants, and binders can significantly impact tablet disintegration. Excipients with high water-sorption capacities, such as microcrystalline cellulose, enhance capillary action and promote disintegration. Superdisintegrants like croscarmellose sodium or crospovidone aid in rapid disintegration by swelling or generating gas upon contact with fluids. Binders, on the other hand, ensure tablet integrity during manufacturing but can impede disintegration if used in excessive amounts.

**Manufacturing processes**

The compression force and tablet hardness during manufacturing affect tablet porosity and, consequently, disintegration. Higher compression forces and hardness can lead to denser tablets with reduced porosity, hindering disintegration. Similarly, thicker coatings can create barriers that delay fluid penetration and prolong disintegration.

**Environmental conditions**

Environmental factors such as pH, temperature, and the presence of enzymes in the gastrointestinal tract can impact tablet disintegration rates. PH-sensitive coatings can be designed to disintegrate in specific regions of the gastrointestinal tract where the pH varies. Temperature-sensitive formulations can respond to body heat, triggering disintegration. Enzymes present in the digestive system can also break down certain tablet components, promoting disintegration.

**Drug selection criteria for ODTs:** There are several factors that should be considered while selecting an appropriate drug candidate in formulation of orally disintegrating tablets. For example, the drug should have the ability to permeate the oral mucosa with good solubility in water and saliva. Dose of the drug should be lower in ODTs (preferably less than 50 mg). It should be partially non-ionized at oral cavity pH. It should possess the ability to diffuse into the epithelium of the upper GIT. Drugs which need frequent dosing, have short half-life and

possess bitter taste are unsuitable for formulation as ODTs. ODTs are also unsuitable in case of controlled/sustained release dosage form formulation.

## APPROACHES TO FROMULATE ODTS

The different technologies employed in the production of orodispersible tables include:-

**I. Conventional technologies**

- Freeze drying or Lyophilization
- Spray drying
- Sublimation
- Direct compression
- Tablet molding
- Cotton candy process
- Mass extrusion
- Nanonization

**II. Patented technologies**

- Zydis technology
- Orasolv technology
- Durasolv technology
- Wowtab technology
- Flashdose technology
- Novel hole technology

## CONVENTIONAL TECHNOLOGIES

### Freeze drying/ Lyophilization[25-26]

This pharmaceutical procedure facilitates the drying of heat-sensitive drugs and biological materials at low temperatures through the application of vacuum to remove water via sublimation. In the lyophilization procedure, the active pharmaceutical ingredient (API) is either dissolved or dispersed within an aqueous solution containing a water-soluble excipient, such as gelatin, mannitol, starch, or hydrophilic gum. This resulting mixture is then poured onto the blister film. The filled blisters undergo a cryogenic freezing stage, which is specifically tailored to regulate the final size of ice crystals. Subsequently, these frozen units are transferred to large-scale freeze dryers for the sublimation process, during which the remaining moisture is extracted from the tablets. Finally, the freeze-dried open blisters are

sealed using a heat-sealing process to ensure stability and safeguard the product against fluctuating environmental conditions.

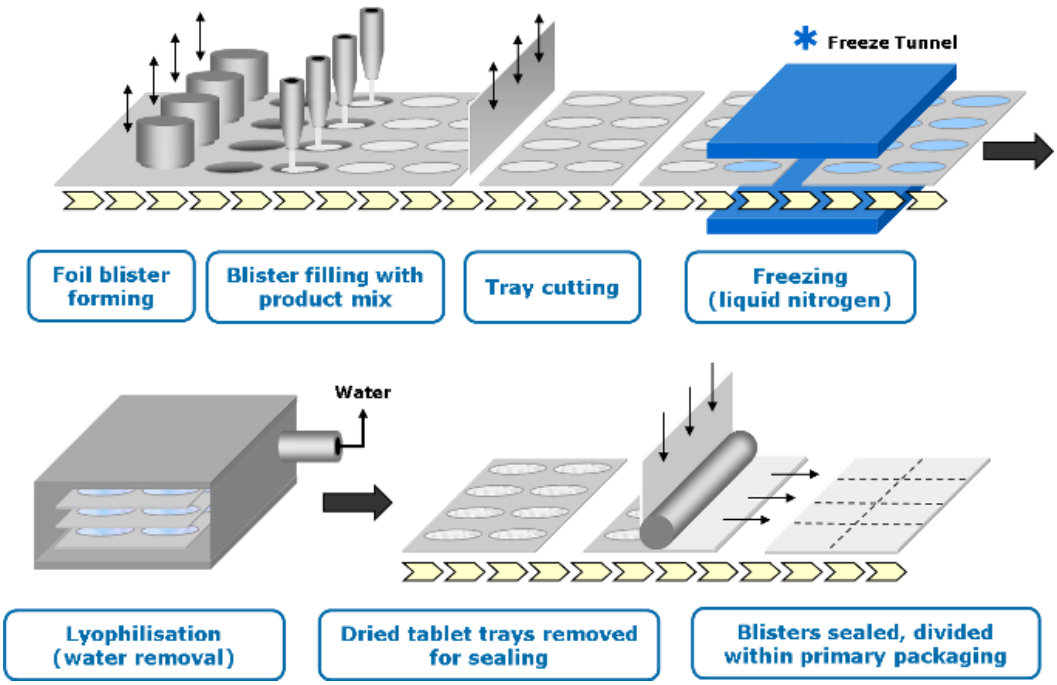


**Figure 3: Schematic diagram of lyophilization technique.**

The primary benefit of lyophilization lies in mitigating the negative impact of heat on pharmaceutical products, as active pharmaceutical ingredients (APIs) are not subjected to high temperatures. An optimal candidate for formulating orally disintegrating tablets.

**Table 1: Orally disintegrating tablets available in Indian market.**

| Brand name | Active ingredients | Company |
|---|---|---|
| Domray MD | Domperidone | Ray Remedies |
| Velrid MD | Domperidone | Shreyam Health Care |
| Vomidon MD | Domperidone | Olcare Lab |
| Zotacet MD | Cetirizine Hcl | Zota Pharma |
| OlanexInstab | Olanzepine | Ranbaxy |
| Manza RDT | Olanzepine | Mano Pharma (Orchid) |
| Romilast | Montelukast | Ranbaxy |
| Torrox MT | Rofecoxib | Torrent |
| Ziflam | Rofecoxib | Kopran |
| Doloroff | Rofecoxib | Indoco |
| Rofaday MT | Rofecoxib | Lupin |
| Dolib MD | Rofecoxib | Panacea |
| Orthoref MD | Rofecoxib | Biochem |
| Rbcox-25 MD | Rofecoxib | Shalman Pharma |
| Roffec MD | Rofecoxib | Excare Lab |
| Roftab MD | Rofecoxib | Olcare Lab |

| | | |
|---|---|---|
| Zofex-25 MD | Rofecoxib | Zota Pharma |
| Valus | Valdecoxib | Glenmark |
| Nency MD | Nimesulide | Zenon Health Care |
| Nexus MD | Nimesulide | Lexus |
| Nimex MD | Nimesulide | Mexon Health Care |
| Nimez-MD | Nimesulide | Zota Pharma |
| Nisure-MD | Nimesulide | Suzen Pharma |
| Nimulid-MD | Nimesulide | Panacea |
| Olnim-MD | Nimesulide | Olcare Lab |
| Sulbid-Md | Nimesulide | Alpic remedies |
| Topmide | Nimesulide | Antigen Health Care |
| Nimpain MD | Nimesulide | Prompt Cure Pharma |
| Mosid MT | Mosapride | Torrent |

(ODTs) via lyophilization is a tasteless, water-insoluble drug with a particle size ideally smaller than 50 micrometers. Particle size is a crucial factor, as larger particles may lead to sedimentation issues during the manufacturing process. Water-insoluble medications are typically favored due to the risk of incomplete freezing or structural collapse associated with water-soluble drugs at low eutectic freezing temperatures. Drugs with low solubility exhibit weaker bonding with the solvent, making them more amenable to conversion into freeze-dried forms. Additionally, formulations containing weakly soluble drugs tend to be less palatable and don't necessitate taste masking. Water-soluble drugs may be transformed into less soluble forms using ion-exchange resin, converted into their base form, or undergo polymorphic changes to facilitate lyophilization.

**Spray drying**[27-28]

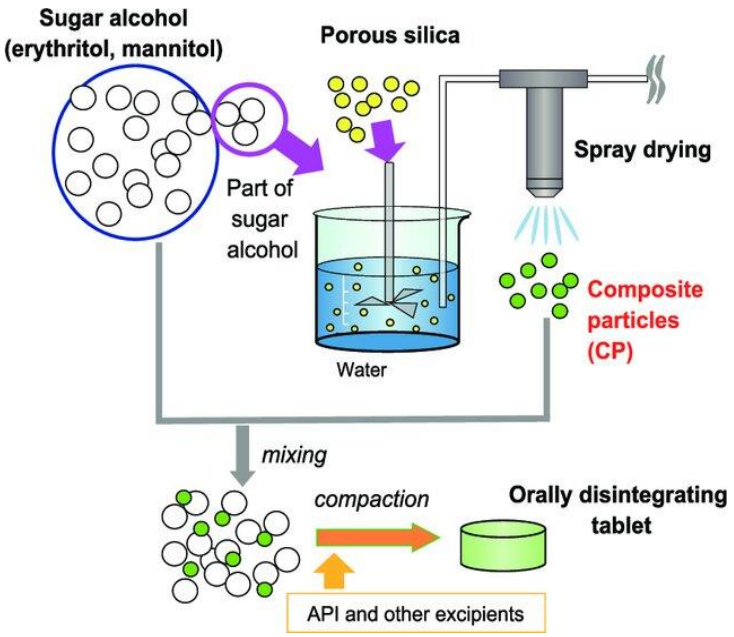


**Figure 4: Schematic diagram of spay drying technique.**

Spray dryers find extensive application in pharmaceuticals and biochemical processes due to their efficiency. They offer a rapid and cost-effective means of eliminating solvents while generating finely porous powders. Through spray drying, one can achieve powders with high porosity and fine texture, facilitating rapid dissolution. This method revolves around creating a particulate support matrix by spray drying an aqueous mixture comprising the support matrix and additional components, resulting in finely porous powders. Following this, the spray-dried powder is combined with active ingredients and compacted to form tablets. The rapid dissolving tablet, produced using the spray drying method, disintegrates within 20 seconds.

**Table 2: Orally disintegrating tablets available in International market.**

| Brand name | Active ingredient | Company |
|---|---|---|
| Zomig 2MT and Rpimelt | Zolmitriptan | Astra Zeneca |
| Alavert | Loratadine | Wyeth Consumer Healthcare |
| Cibalginadue FAST | Ibuprofen | Novartis Consumer Health |
| Hyoscyamine Sulfate ODT | Hyoscyamine sulfate | ETHEX Corporation |
| NuLev | Hyoscyamine sulfate | Schwarz Pharma |
| Nurofen FlashTab | Ibuprofen | Boots Healthcare |
| Kemstro | Baclofen | Schwarz Pharma |
| Fluoxetine ODT | Fluoxetine | Bioavail |
| Benadryl Fastmelt | Diphenhydramine | Pfizer |
| Zolpidem ODT | Zolpidem tartrate | Bioavail |
| Nasea OD | Ramosetoron | Yamanouchi |
| RaliviaFlashDose | Tramadol HCL | Bioavail |
| Gaster D | Famotidine | Yamanouchi |
| Excedrin Quick Tabs | Acetaminophen | Bristol-Myers Squibb |
| Claritin RediTabs | Loratadine | Sching Corporation |
| Remeron SolTab | Mirtazepine | Organon Inc. |
| Feldene Melt | Piroxicam | Pfizer |
| TempraQuicklet-Tempra Firs Tabs | Acetaminophen | Bristol-Myers Squibb |
| Maxalt-MLT | Rizatriptan benzoate | Merck |
| PropulsidQuicksolv | Cisapride monohydrate | Janssen |
| Pepcid ODT | Famotidine | Merck |
| Imodium Instant melts | Loperamide HCL | Janssen |
| Zyprexa | Olanzapine | Eli Lilly |
| Childrens Dimetapp ND | Loratadine | Wyeth Consumer Healthcare |
| Zofran ODT | Ondansetron | Glaxo Smith Kline |
| Klonopin Wafers | Clonaxepam | Roche |
| Risperidal M-Tab | Ripseridone | Janssen |
| Zelapar | Selegiline | Élan/Amarin |

| | | |
|---|---|---|
| | | Corporation |
| Zubrin (pet drug) | Tepoxaline | Schering Corporation |
| Aricept ODT | Donepzil HCL | Eisai and Pfizer |
| Fazalco | Clonzapine | Alamo Pharmaceuticals |
| Permax | Pergolide | Amarin Corporation |
| Febrectol | Paracetamol | Prographarm |
| Benadryl Fast melt | Diphenhydramine and psuedoephedrine | Warner Lambert |

**Sublimation method**[29-30]

The essential factor enabling swift disintegration of mouth dissolving tablets lies in the existence of a porous structure within the tablet matrix. Conventional compressed tablets containing highly water-soluble components often struggle to dissolve quickly due to their low matrix porosity. Therefore, in order to create a porous matrix, volatile ingredients are incorporated which are subsequently subjected to a sublimation process. Incorporating highly volatile ingredients such as ammonium bicarbonate, ammonium carbonate, benzoic acid, menthol, camphor, naphthalene, urea, urethane, or phthalic anhydride into a tablet along with other excipients allows for compression. Subsequently, the volatile material is eliminated through sublimation, resulting in a highly porous matrix. Tablets produced through this method typically disintegrate within 10-20 seconds and demonstrate adequate mechanical durability. Pore-forming agents such as benzene and cyclohexane can serve as solvents in the process.

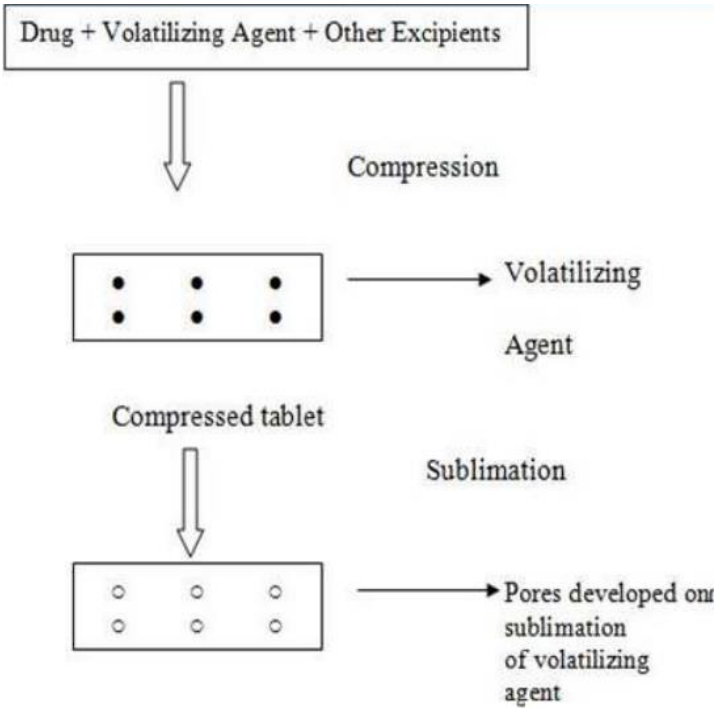


**Figure 5: Schematic representation of the Sublimation method.**

**Direct compression**[31-32]

The direct compression method stands out for its simplicity, offering benefits such as reduced manufacturing expenses, compatibility with standard equipment, readily accessible excipients, and fewer procedural stages. Through direct compression, it becomes feasible to accommodate high doses and potentially surpass the final tablet weight compared to alternative methods. Superdisintegrants, water-soluble excipients, and effervescent agents are integral components in tablet formulations, influencing the disintegration characteristics of the tablet. The disintegration process of fast-dissolving tablets crafted via the direct compression method predominantly hinges on the choice of superdisintegrants employed. Direct compression is widely regarded as the preferred method for manufacturing tablets containing thermolabile and moisture-sensitive drugs. The advancement in excipient availability, particularly notable in superdisintegrants and sugar-based excipients, now allows for the application of this technique in the preparation of Fast Dissolving Tablets (FDTs).

**(a) Superdisintegrants**

In numerous orally disintegrating tablet technologies utilizing direct compression, the inclusion of superdisintegrants primarily impacts the disintegration rate, thus influencing dissolution. The optimization of tablet disintegration time can be achieved by increasing the concentration of disintegrants. Below a critical concentration, the tablet's disintegration time decreases inversely with the concentration of disintegrants. Conversely, above this critical concentration level, the disintegration time remains relatively constant or may even increase**.**

Microcrystalline cellulose, cross-linked carboxymethyl cellulose sodium, cross-linked polyvinyl pyrrolidone, and partially substituted hydroxypropyl cellulose, despite being water-insoluble, exhibit water absorption and swelling through capillary action. These characteristics render them an effective disintegrants in the formulation of fast dissolving tablets.

Fast tablet disintegration can also be attained through the inclusion of effervescent disintegrating agents, which produce carbon dioxide. This process also contributes to partially masking the unpleasant taste of the drug. However, a significant drawback of effervescent excipients is their tendency to absorb moisture, necessitating strict control of humidity during manufacturing and protection of the final product. These factors influence the overall cost of the product.

**(b) Sugar-based excipients**

Here's another method for manufacturing Fast Dissolving Tablets (FDT) through direct compression. Utilizing sugar-based excipients, particularly bulking agents such as: dextrose, fructose, isomalt, lactilol, maltitol, sorbitol, starch hydrolysate, poly dextrose and xylitol, which possess high aqueous solubility and sweetness, thereby providing taste-masking properties and a delightful mouth feel.

**Table 3: Drugs explored for orally disintegrating tablets.**

| Category | Drug | Category | Drug |
|---|---|---|---|
| NSAIDS | Ketoprofen | Anti depressants | Mitraxepine |
| | Piroxicam | | Fluoxetine |
| | Paracetomol | | |
| | Rofecoxib | Antiparkinsonism | Selegiline |
| | Nimesulide | | |
| | Ibuprofen | Antimigrane | Sumatriptan |
| | Tepoxaline (Canine NSAID) | | Rizatriptan benzoate |
| Anti ulcer | Famotidine | | Zolmitriptan |
| | Lansoprazole | | |
| Anti histaminics | Loratadine | Antiemetics | RamosetoronHcl |
| | Diphenhydramine | | Ondansetron |
| | Meclizine | Miscellaneous | Baclofen |
| Hypnotic and sedatives | Zolpidem | | Hydrochlorthiazide |
| | Clonazepam | | Ethenzamide |
| | Atenolol | | TramodolHcl |
| Antipsychotics | Olanzepine | | Propyphenazone |
| | Risperidone | | Spiranolactone |
| | Pirenzepine | | Phioroglucinol |
| | | | Sildenafil |

**Tablet molding**[33-34]

This technology employs water-soluble components to facilitate rapid disintegration and dissolution of tablets. The powder mixture is moistened with a hydro alcoholic solvent and subsequently molded into tablets using compression pressure lower than that of conventional tablet compression methods. The solvent is then eliminated through air-drying. Two frequently encountered challenges are inadequate mechanical strength and ineffective taste masking properties. The inclusion of binding agents like sucrose, acacia, or polyvinylpyrrolidone can enhance the mechanical integrity of the tablet.

The molding process can be categorized into two methods:

(a) The solvent method

(b) The heat method.

**(a) Solvent method:** In the solvent method, the powder blend is moistened with a hydro alcoholic solvent. Subsequently, it is compressed at low pressures in molded plates to create a wetted mass, a process known as compression molding. The solvent is then removed by air-drying. Tablets produced using this approach is less dense compared to compressed tablets and exhibit a porous structure, which accelerates dissolution.

**(b) Heat method:** The heat molding process entails creating a suspension comprising a drug, agar, and sugar (such as mannitol or lactose), then pouring this suspension into the wells of blister packaging. The agar solidifies at room temperature to form a jelly, which is subsequently dried under vacuum at 30°C. Ensuring adequate mechanical strength in molded tablets is a significant consideration. Incorporating binding agents is essential to enhance the tablets' mechanical integrity.

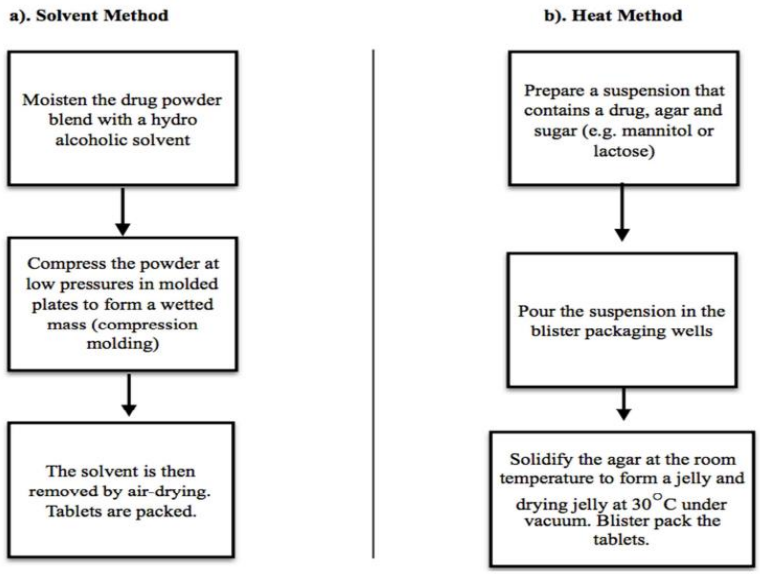


**Figure 6: Procedure of tablet molding.**

Taste masking presents an additional challenge in this technology. The taste-masked drug particles were formulated by spray congealing a molten blend consisting of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol, and an active ingredient, transforming them into a lactose-based tablet triturate form. In contrast to the lyophilization method, tablets manufactured via the molding technique offer greater ease of scalability for industrial production.

**Cotton candy process**[35-36]

This method is aptly named for its utilization of a unique turning system to generate a floss-like crystalline structure, resembling cotton candy. The cotton candy process involves organizing a matrix of polysaccharides or saccharides through the synchronized actions of flash melting and spinning. The resulting network structure is predominantly recrystallized to improve flow properties and compressibility. This candy floss network is subsequently combined with drugs and excipients before being packed into rapidly dissolving tablets.

**Mass extrusion**[37]

This technique entails first softening the active blend by employing a solvent mixture containing water-soluble polyethylene glycol, along with methanol. The softened mass is then extruded through an extruder or syringe to obtain a cylindrical product, which is subsequently divided into uniform segments using a heated blade to form tablets. Additionally, the dried cylinder can be utilized to coat granules of bitter-tasting drugs, effectively masking their unpleasant taste.

**Nanonization**[38]

A newly developed Nanomelt technology involves reducing the particle size of the drug to nanoscale through proprietary wet-milling techniques. The resulting nanocrystals of the drug are prevented from agglomeration by surface adsorption onto specific stabilizers, which are then integrated into Fast Dissolving Tablets (FDTs). This method is particularly advantageous for poorly water-soluble drugs. Additional benefits of this technology include rapid disintegration and dissolution of nanoparticles, leading to enhanced absorption and increased bioavailability, potentially allowing for dose reduction. Moreover, it offers cost-effective manufacturing processes, conventional packaging options due to exceptional durability, and accommodates a wide range of doses, up to 200 mg of drug per unit

**Table 4: Patented technologies to formulate ODTS.**

| Sl. No. | Patented Technologies | Inventers |
|---|---|---|
| 1 | Zydis technology | Zydis |
| 2 | Takeda technology | Takeda (Osaka, Japan) |
| 3 | Novartis technology | Novartis Consumer Health (Basel, Switzerland) |
| 4 | Nippon Shinyaku technology | Nippon Shinyaku (Kyoto, Japan) |
| 5 | Flashtab technology | Ethypharm (Paris, France) |
| 6 | Wowtab technology | Yamanouchi (Tokyo, Japan) |
| 7 | Daiichi technology | Dalichi (Tokyo, Japan) |

| | | |
|---|---|---|
| 8 | Orasolv technology | Cima Labs (Eden Prairie, MN) |
| 9 | Ziplets technology | Eurand (Pessano con Bornago, Italy) |
| 10 | Lyoc technology | Pharmalyoc |
| 11 | Nanocrystal technology | Elan, King of Prussia |

**Table 5: Various recent patents in ODT field.**

| Title | Patient Number | Publication Year |
|---|---|---|
| Fast disintegrating tablet | EP1058538B2 | 2012 |
| Disintegrating particle | EP2465539A1 | 2012 |
| Fast dissolving solid | EP2493457A1 | 2012 |
| Rapidly disintegrating tablet | US20120028949 | 2012 |
| Quick dissolve compositions and tablets based thereon | US20120082729 | 2012 |
| Orodispersible tablets | US20120077888 | 2012 |
| Taste-masked orally disintegrating tablets of memantine hydrochloride | EP2583669A1 | 2013 |
| Orally disintegrating tablet | EP2591774A1 | 2013 |
| Mozavaptan formulations | EP2609909A1 | 2013 |
| Coated effervescent tablet | EP2595609A1 | 2013 |
| Orally disintegrating composition comprising mirtazapine | T0418/09 | 2013 |
| Fast release solid oral compositions of entecavir | W02013072937A2 | 2013 |

**Patented methods**

**1. Zydis Technology[39-40]**

The Zydis formulation represents a distinctive freeze-dried tablet, where the drug is either physically trapped or dissolved within a fast-dissolving carrier matrix. Upon placement in the mouth, Zydis units promptly disintegrate without the need for water, offering effortless swallowing. The Zydis matrix comprises various materials tailored to fulfill multiple objectives. Polymers like gelatin, dextran, or alginates are added to confer strength and durability during handling, resulting in a glossy amorphous structure. Saccharides such as mannitol or sorbitol are included to achieve crystallinity, elegance, and hardness. Water is utilized in the manufacturing process to produce porous units for rapid disintegration, while various gums prevent sedimentation of dispersed drug particles. Collapse protectants like glycine prevent Zydis units from shrinking during freeze-drying or extended storage. If required, suspending agents and pH adjusting agents can be employed. Additionally, preservatives may be included to hinder microbial growth. Zydis products are packaged in blister packs to shield the formulation from environmental moisture. An additional moisture-proof foil punch is frequently necessary due to the high sensitivity of this dosage form to moisture.

**Drawbacks**

- A maximum of 400 mg per tablet or less can be incorporated for a water-insoluble drug, whereas for a water-soluble drug, the incorporation is limited to 60 mg per tablet or less.
- The dosage form exhibits fragility and inadequate stability when stored under challenging conditions.

**2. Orasolv Technology[41]**

This marks CIMA Lab's initial foray into mouth-dissolving formulations. The technology entails taste masking of the active drug, along with the incorporation of an effervescent disintegrating agent. Tablets are prepared using conventional blenders and tablet equipment. A lower compaction force is employed during manufacturing to yield soft and rapidly disintegrating tablets. However, a limitation of this technology is the formation of soft and delicate tablets, necessitating packaging in specially designed pick-and-place package systems.

**3. Durasolv Technology[42-43]**

Durasolv represents CIMA's second-generation fast-dissolving tablet formulation, following a production process akin to Orasolv. Tablets produced using this technology comprise a drug, filler, and lubricant. They are manufactured using conventional tabletting equipment and exhibit excellent rigidity. Furthermore, these tablets can be conveniently packaged using conventional systems such as blisters. Durasolv technology is particularly suitable for products necessitating low quantities of active ingredients.

However, Durasolv boasts significantly greater mechanical strength compared to its predecessor, primarily attributed to the application of higher compaction forces during tabletting. This advancement allows for faster and more cost-effective production of Durasolv. Nonetheless, one drawback of this technology is its incompatibility with larger doses of active ingredients, as the formulation is subjected to high pressures during compaction. Currently, Durasolv is offered in two products: Nulev and Zorlip.

**4. Wowtab Technology[44]**

The Wowtab mouth-dissolving/disintegrating tablet formulation has been available on the Japanese market for several years. The term "WOW" in Wowtab indicates that the tablet is intended to be administered "With Out Water.". This technology utilizes a blend of low and high moldability saccharides to produce rapidly dissolving tablets via traditional granulation

and tableting methods. As outlined in the patent, saccharides are categorized into two groups: high and low moldability. Low moldability saccharides yield tablets with hardness ranging from 0-2 kg when 150 mg of the saccharide is compressed under a pressure of 10-15 kg/cm2 using an 8 mm diameter die. Commonly utilized low moldability saccharides include glucose, lactose, mannitol, xylitol, and sucrose. Conversely, high moldability saccharides result in tablets with hardness exceeding 2 kg under the same conditions. Examples of high moldability saccharides encompass sorbitol, maltose, maltitol, and oligosaccharides**.** Because of its notable hardness, the Wowtab formulation exhibits greater stability in environmental conditions compared to Zydis or OraSolv formulations. It is adaptable for packaging in both conventional bottles and blister packs. Wowtab products dissolve rapidly in 15 seconds or less.

### 5. Lyoc[45]

The Lyoc technology is proprietary to the Cephalon Corporation. CIMA, a subsidiary of Cephalon, oversees the Lyoc research and development endeavors. Lyoc was the pioneering freeze-drying-based technology introduced for orally disintegrating tablets (ODTs). The process entails preparing a homogeneous liquid solution or suspension of the drug along with fillers, thickening agents, surfactants, non-volatile flavoring agents, and sweeteners. This liquid mixture is then dispensed into blister cavities and undergoes freeze-drying.

### 6. Flash Dose Technology[46-47]

Fuisz Technologies offers three oral drug delivery systems focused on rapid dissolution. The initial two generations, Soft Chew and EZ Chew tablets, necessitate some chewing. However, these innovations laid the foundation for Fuisz's latest advancement, Flash Dose. The Flash Dose technology employs a distinctive spinning mechanism to create a floss-like crystalline structure reminiscent of cotton candy. This crystalline sugar can then integrate the active drug and be compacted into a tablet. The matrix is created by processing saccharides or polysaccharides into an amorphous floss through the simultaneous action of flash melting and centrifugal force. Subsequently, it undergoes partial recrystallization (or curing) to yield a compound with desirable flowability and compressibility for tabletting purposes. Flashdose tablets, whether comprising powder or coated miniparticles, disperse rapidly, can accommodate high active doses, and exhibit satisfactory mechanical strength.

However, it's worth noting that the elevated temperature necessary for melting the matrix may restrict the applicability of the Shearform matrix with heat-sensitive drugs. This process,

patented by Fuisz and termed Shearform, results in a final product with an exceptionally high surface area for dissolution. Once placed on the tongue, the tablet disperses and dissolves rapidly. Interestingly, altering temperature and other production conditions can significantly modify the product's characteristics.

### 7. Flashtab Technology[48]

Prographarmlaboratories holds a patent for the Flashtab technology, which entails the creation of rapidly disintegrating tablets containing an active ingredient in the form of microcrystals. These drug microgranules can be prepared using conventional techniques such as coacervation, extrusion-spheronization, simple pan coating methods, and microencapsulation. The microcrystals or microgranules of the active ingredient are then added to a granulated mixture of excipients prepared through wet or dry granulation. Subsequently, they are compressed into tablets using conventional tabletting technology. Tablets produced using this process is reported to possess good mechanical strength and disintegrate in less than one minute.

### 8. Oraquick Technology[49]

The Oraquick formulation was developed utilizing patented taste masking technologies like FlavourTech and MicroMask. In the MicroMask approach, taste masking is achieved by incorporating the drug into matrix microspheres. KV Pharmaceutical asserts that MicroMask offers superior taste masking compared to FlavourTech. In the Oraquick technique, tablets are prepared by dissolving sugars (such as sucrose, mannitol, sorbitol, xylose, dextrose, fructose, or mannose) and proteins (albumin or gelatin) in a suitable solvent like water, ethanol, isopropyl alcohol, or ethanol-water mixture. This matrix solution is then spray-dried to produce highly porous granules, with the porosity of the resulting granules depending on the amount of solvent used in the process. These granules are subsequently mixed with the drug and other tablet ingredients or excipients and compressed at low compression pressure. The compressed tablets undergo a sintering step, where they are treated in an oven at around 50 to 100 °C for a few minutes to a few hours, or subjected to 90 °C for 10 minutes. This sintering process imparts significant mechanical strength to the tablets without compromising the taste masking.

### 9. Pharmaburst Technology[50]

Pharmaburst technology, patented by SPI Pharma in New Castle, employs coprocessed excipients for the creation of MDTs (Mouth Dissolving Tablets) that dissolve within a time

frame of 30-40 seconds. This methodology encompasses the dry blending of the drug, flavoring agents, and lubricants, succeeded by compression into tablets. The resulting tablets exhibit adequate strength, facilitating their packaging in both blister packs and bottles.

## REFERENCES


1. Nayak AK, Manna K. Current developments in orally disintegrating tablet technology. Journal of Pharmaceutical Education and Research, Jun. 1, 2011; 2(1): 21.
2. Rajan K. Verma and Sanjay Garg, "Current Status of Drug Delivery Technologies and Future Directions," Pharmaceutical Technology On-Line, 2001; 25(2): 1–14.
3. Thapliyal S, Bhatt G, Kandpal G. Orodispersible Tablets: A Review. World J. Pharm. Res., May 2, 2018; 7(13): 146-62.
4. Roshan K, Keerthy HS. Orodispersible Tablets: A Compendious Review. Asian Journal of Pharmaceutical Research and Development, Jun. 15, 2021; 9(3): 66-75.
5. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets: A novel drug delivery system. Pharma times, Jun. 2003; 35(1): 7-9.
6. Chowdary KP, Aishwarya KV. Recent research on fast dissolving tablets–A review. Journal of Global Trends in Pharmaceutical Sciences, 2013; 4(1): 940-54.
7. Baghel P, Roy A, Chandrakar S, Bahadur S. Fast dissolving drug delivery systems: a brief review. Research Journal of Pharmacy and Technology, 2013; 6(6): 597-602.
8. Sano S, Iwao Y, Kimura S, Itai S. Preparation and evaluation of swelling induced-orally disintegrating tablets by microwave irradiation. International journal of pharmaceutics, Sep. 15, 2011; 416(1): 252-9.
9. Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, Sharma R, Gupta N. Orally disintegrating tablets: formulation, preparation techniques and evaluation. Journal of Applied Pharmaceutical Science, Jun. 30, 2011: 35-45.
10. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth dissolving tablets I: An overview of formulation technology. Scientia Pharmaceutica, Jun. 2009; 77(2): 309-26.
11. Pahwa R, Piplani M, Sharma PC, Kaushik D, Nanda S. Orally disintegrating tablets-Friendly to pediatrics and geriatrics. Archives of applied science research, 2010; 2(2): 35-48.
12. Ghosh T, Ghosh A, Prasad D. A review on new generation orodispersible tablets and its future prospective. International journal of pharmacy and pharmaceutical sciences, Jan. 2011; 3(1): 1-7.

13. Jain D, Amul M. A review-formulation & development of orodispersible tablet. IJPE., May 2014; 4: 21-38.
14. Bidkar S, Kakade M, Mantry S, Mahajan KC, Meher A, Bidkar J, Dama G. A Novel Approach For Drug Delivery System In Orodispersible Tablet. Journal of Pharmaceutical Negative Results, Jan. 1, 2023; 484-502.
15. Manivannan R. Oral disintegrating tablets: A future compaction. Drug Invention Today, Nov 1, 2009; 1(1): 61-5.
16. Shaikh S, Khirsagar RV, Quazi A. Fast disintegrating tablets: an overview of formulation and technology. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(3): 9-15.
17. Brahmankar D.M and Sunil B. Jaiswal, Bio-pharmaceutics and pharmacokinetics A-Treatise, First edition, Vallabh Prakashan, New Delhi, 1995; 51-55.
18. Leon Shargel, Andrew Yu, Susanna, Wu-Pong, Applied bio-pharmaceutics and pharmacokinetics, 5th edition, Kindle publications, New York, 1996; 138.
19. Schanker L.S., Mechanism of drug absorption and distribution, Annuual Review of pharmacology, 1961; 1: 29-45.
20. Rouge N., Buri P., Doelker E, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm., 1996; 136: 117-139.
21. Gupta DK, Maurya A, Varshney MM. Orodispersible tablets: An overview of formulation and technology. World journal of pharmacy and pharmaceutical sciences, Aug. 13, 2020; 9(10): 1406-18.
22. Ramu S, Kumar YA, Rao DS, Ramakrishna G. Formulation and evaluation of Valsartan oral dispersible tablets by direct compression method. American Journal of Advanced Drug Delivery, 2014; 2(6): 719-33.
23. Masih A, Kumar A, Singh S, Tiwari AK. Fast dissolving tablets: a review. Int J Curr Pharm Res., 2017; 9(2): 8-18.
24. Ratnaparkhi MP, Mohanta GP, Upadhyay L. Review on: Fast dissolving tablet. Journal of pharmacy research, Jan. 2009; 2(1): 5-12.
25. Badgujar B, Mundada A. The technologies used for developing orally disintegrating tablets: A review. Acta pharmaceutica, Jun. 1, 2011; 61(2): 117-39.
26. Chaturvedi AK, Verma A. Fast disintegrating tablet technology: newly prospects. International Journal of Pharmaceutical Sciences and Research, Dec. 1, 2011; 2(12): 3046.

27. Khan AB, Tripuraneni A. Fast dissolving tablets–a novel approach in drug delivery. Rguhs J Pharm Sci., 2014; 1: 7-16.
28. Sharma I, Sharma V. A comprehensive review on fast dissolving tablet technology. Journal of applied pharmaceutical science, Jul. 30, 2011: 50-8.
29. Singh S, Virmani T, Virmani R, Kumar P, Mahlawat G. Fast dissolving drug delivery systems: formulation, preparation techniques and evaluation. Univ J Pharm Res., 2018; 3(4): 60-9.
30. RADA SK, Kumari A. Fast dissolving tablets: waterless patient compliance dosage forms. Journal of drug delivery and therapeutics, Jan. 15, 2019; 9(1): 303-17.
31. Prateek S, Ramdayal G, Kumar SU, Ashwani C, Ashwini G, Mansi S. Fast dissolving tablets: a new venture in drug delivery. American Journal of PharmTech Research, Jul. 2012; 2(4): 252-79.
32. RoshanRai R, Chirra P, Thanda V. Fast dissolving tablets: A novel approch to drug delivery–A Review. International journal of preclinical and pharmaceutical research, 2012; 3(1): 23-32.
33. Khanna K, Xavier G, Joshi SK, Patel A, Khanna S, Goel B. Fast dissolving tablets-A novel approach. International Journal of Pharmaceutical Research & Allied Sciences, Jan. 1, 2016; 5(2): 311-22.
34. Gholve S, Kaware A, Thonte S, Kaudewar D, Bhusnure O. Orodispersible tablets: a systematic review. World J Pharm Res., Jan. 21, 2018; 7(6): 152-65.
35. Yadav G, Kapoor A, Bhargava S. Fast dissolving tablets recent advantages: A review. International journal of pharmaceutical sciences and research, Mar. 1, 2012; 3(3): 728.
36. Momin MM, Dev A. Fast dissolving tablets: a novel approach. Indian Journal of Pharmaceutical and Biological Research, Jan. 1, 2015; 3(1): 18.
37. Chauhan K, Solanki R, Sharma S. A review on fast dissolving tablet. Int J Appl Pharm., 2018; 10(6): 1-7.
38. Ratnaparkhi MP, Mohanta GP, Upadhyay L. Review on: Fast dissolving tablet. Journal of pharmacy research, Jan. 2009; 2(1): 5-12.
39. Beri C, Sacher I. Development of fast disintegration tablets as oral drug delivery system-A review. Indian J. Pharm., Sep. 2013; 1: 3.
40. Gupta AK, Mittal A, Jha KK. Fast dissolving tablet-A review. The pharma innovation, Mar. 1, 2012; 1(1): 1-8.

41. Patil PB, More VN, Tour NS. Recent trends in orodispersible tablets–An overview of formulation technology and future prospects. International Journal of Pharma Sciences and Research, 2015; 6(7): 1056-66.
42. Phadatare SA, Yadav VD, Jadhav PD, Navale SD. A REVIEW ON ORO-DISPERSIBLE TABLETS AND PATENTED TECHNOLOGY.
43. Sharma I, Sharma V. A comprehensive review on fast dissolving tablet technology. Journal of applied pharmaceutical science, Jul. 2011 30: 50-8.
44. Sah SK, Badola A. MOUTH DISSOLVING TABLET: A BETTER APPROACH TO DRUG DELIVERY.
45. Patil HK, Patil GM, Jain VH, Tadvi SA, Pawar SP. A review on mouth dissolving tablet. Journal of Applied Pharmaceutical Research, Apr. 29, 2017; 5(2): 09-15.
46. Kumar S, Sachdera M, Bajpai M. Formulation and evalution of mouth dissolving tablets. Journal of Pharmaceutical Science and Technology, 2010; 2(4): 202.
47. Pandey P, Dahiya M. Oral disintegrating tablets: a review. International Journal of Pharma Research & Review, Jan. 2016; 5(1): 50-62.
48. Chandan S, Varun D, Ashish G, Dabeer A, Ayaj A. Orally disintegrating tablets: A review. International Journal of pharmacy and life sciences, 2010; 1(5): 250-6.
49. Arora P, Sethi VA. Orodispersible tablets: A comprehensive review. Int J Res Dev Pharm Life Sci., Feb. 2013; 2(2): 270-84.
50. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies. Taste-Masking Clin Stud., 2004; 21(6): 44.