Review Article

Orodispersible Tablets: A Novel Approach to Combat Dysphagia

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ABSTRACT

Drug administration via the oral route highly favoured due to its simplicity in taking medication, avoidance of discomfort, adaptability, and most importantly, its ability to promote patient compliance. Scientists have been keen on devising innovative oral delivery of drugs to increase patient acceptance. Over the past decade, there has been a continuous surge in the demand for Orodispersible tablets also known as mouth dissolving tablets (MDTs), leading to the rapid expansion of this sector within the pharmaceutical industry. Mouth dissolving drug delivery systems (MDDDS) have gained significant prominence in the market due to their ability to address past administration challenges. MDTs are specifically formulated to disintegrate and dissolve in saliva, allowing for easy swallowing with no need of water. Hence, MDTs are very much attractive to the patients with dysphagia, individuals who are bedridden, those with psychological conditions, the pediatric and geriatric patients. This stands as a significant advantage over traditional dosage forms. These tablets can be manufactured through several conventional tablets manufacturing techniques, spray drying, moulding, sublimation, also freeze drying. In recent times, various patented technologies have emerged, offering improved performance, heightened patient adherence, and enhanced overall quality. Furthermore, there has been a substantial rise in new chemical entities discovery for novel delivery technology. This review encompasses a comprehensive discussion of formulation aspects, developed technologies, excipients, evaluation tests, and marketed formulations of MDTs, as well as an examination of evaluation parameters encompassing before and after-compression criteria, alongside considerations for the packaging of MDTs.

Keywords: Orodispersible tablets, MDTs, Superdisintegrant, Dysphagia, Fast disintegrating tablets.

INTRODUCTION

Being the most popular route, because of correct dosage, ease of administration, pain prevention, patient acceptance also self-medication, up to 50–60% of all dosage forms are taken orally, which has gained universal acceptance. But swallowing problem is a significant disadvantage of such dosage forms[1]. If water is not available, when motion sickness (kinetosis) occurs, or when they suddenly encounter coughing attacks due to common cold, any allergic reaction, or bronchitis, patients may face trouble in swallowing traditional medication such as tablets[2]. Conventional capsules and tablets are always feels difficult to swallow for people of all ages, but older and dysphagic patients experience it more frequently[3]. Dysphagia is a problem that has been associated to a variety of diseases, including stroke, AIDS, Parkinson's disease, thyroid gland surgery, cerebral palsy along with neck and head radiation therapy[4]. To prevent these issues, pharmaceutical professionals created a drug delivery system which dissolves faster inside the mouth, known as a Mouth Dissolving Tablets. These tablets need not be chewed or dissolved in water; it dissolves with the help of saliva in a few seconds[1].

The synonyms of MDTs are "Fast Dissolving Tablet", "Orodispersible Tablet", "Fast Melting Tablet", "Orally Disintegrating Tablet" etc. The word "orodisperse" is used in the European Pharmacopoeia to describe a tablet which is able to be swallowed whole and immediately dissolves in the mouth before getting ingested[5].

Optimal MDTs should be[6]:

- Capable of rapidly dissolving, dispersing, or disintegrating in the mouth within seconds.
- Provide a satisfying mouth feel.
- Possess an effective taste-masking quality.
- Be more robust and less supple.
- Minimal or no tongue touch residue should remain after dosing.

Following factors must be taken into consideration when developing MDTs[6]:

- Sufficient mechanical strength and quick dissolution within the tablet.
- Don't make your tablet bigger.
- Drugs which are bitter can be effectively masked by flavour.
- Minimal or no tongue touch residue.
- Effective packaging with moisture protection.
- It should feel good in the mouth while taking the dosage.
- Cost-effective formulation.

Following are the few drawbacks of MDTs[6]:

- Medicines with comparatively higher doses are challenging to make into MDTs, such as the antibiotic

ciprofloxacin, which comes in 500 mg tablet form for adults.

- Some people may not be eligible for MDTs if they have Sjogren's disorder or dry mouth caused by decreased secretion of saliva, nor may they be if they are concurrently taking anticholinergic medicine.

Some advantages of MDTs are mentioned below[6]:

- Ease of administration to patients who cannot absorb, like older adults, people having arrows, and bed-rested patients, as well as individuals who are afflicted with mental disease.
- For busy or travelling individuals without easy access to water.
- The mouth-dissolving drug delivery system's pleasant tongue feel contributes to changing people's fundamental perceptions about pharmaceuticals.
- Compared to liquid preparations, ease of administration and precise dosing.
- The advantages of taking liquid medicine instead of a solid formulation.
- The oral cavity and throat have faster absorption of drugs that may facilitate an immediate start of action.

TECHNIQUES FOR FORMULATING MDTs:

MDTs' fast-dissolving and rapid disintegration feature is because of the water's quick entry into the tablet matrix. Consequently, the fundamental criteria for producing MDTs are:

- The tablet matrix's porousness should be as high as possible.
- Useful disintegrating ingredients should be included (e.g.: Crosspovidone, Sodium starch glycolate, Sodium alginate etc).
- The formulation must include excipients which are extremely soluble in water[7].

To date, numerous methods have been invented based on different principles. The formulations differ because of cohesive strength, drug stability, taste, mouthfeel, efficacy of swallowing, disintegration time and oral absorption as well as bioavailability[8].

There are some patented technologies and some non-patented technologies present to manufacture Mouth Dissolving Tablets.

1. Patented Technologies:

1.1. ZydisTechnology[9]: This technique includes the physical entrapment of the drug inside a polymer and saccharide matrix. Alginates, polyvinyl alcohol, polyvinyl pyrrolidine, hydrolyzed dextran, partially hydrolyzed gelatin, dextrin, and these mixes are the most often used polymers. The process entails combining pre-prepared components, which are then dispersed or dissolved prior to being introduced into blister cavities. Subsequently, they are subjected to freezing in a liquid nitrogen environment. To produce porous wafers, the frozen solvent is allowed to sublime. The drug used to prepare the MDT is Loratidine.

Desired Features of Zydis Technology:

- The drug must have chemical stability.
- The drug should be hydrophobic.
- The size of the particles must be less than 50 µm.

1.2. Lyoc[10]: PHARMALYOC holds the patent for this technology. The blister cavities are filled with a prepared oil-in-water emulsion, which is then freeze-dried. Non-homogeneity is prevented by enhancing viscosity with inert filler before allowing sediment to settle out while freeze-drying. Content with high filler makes tablets less porous, which slows down disintegration. The drug used to prepare the MDT is Phloroglucinol Hydrate.

1.3. Quick Solv[11]: The Janssen Pharmaceutical Company holds the patent for the invention. Two solvents are combined to form a matrix, which gets disintegrated rapidly. In this method, Water is used to dissolve the matrix components, and the dispersion or solution is then refrigerated.The water is then extracted from the matrix by applying an excessive amount of alcohol, which causes the matrix to dry. Thus, the resultant product is uniformly porous as well as strong enough to handle. The drugs used to prepare the MDT are Cisapride monohydrate and Risperidone.

1.4. FlashtabTechnology[12]: Ethypharm France holds the patent for this technology. This process involves compressing the excipients into tablets after either dry granulation or wet granulation of the drug and excipients. Excipients used in this technique fall into two different categories. Carboxymethylcellulose and reticulated polyvinyl pyrrolidone are examples of disintegrating agents. Starch, carboxymethylated starch, Carboxy methylcellulose, microcrystalline cellulose etc. are examples of swelling agents. Physical resistance is adequate for these tablets. These tablets disintegrate in less than a minute. The drug used to prepare the MDT is Ibuprofen.

1.5. CeformTechnology[29]: Fuisz holds the patent for this technology. The active drug's microspheres are prepared using this technology. The drug material is put alone or in combination with other pharmaceutical excipients and components in a quickly spinning machine which is constructed very precisely. The centrifugal force propels the dry drug mixture rapidly via hot openings. The heat created by precisely regulated temperature causes the drug blend to liquefy to form a spherical shape, with no effect on the drug's stability. Tablets are created by compressing the resultant microspheres.When drugs and excipients are processed together, a unique microenvironment is created that allows the ingredients

to get absorbed within the microspheres, modifying their characteristics, and enhancing solubility and stability.

1.6. Shearform Technology[29]: Fuisz holds the patent for this technology. "Floss" is a shearform matrix which is prepared by this method. The feedstock which is prepared with sugar carrier is processed using flash heat. Here, sugar is subjected at the same time to both temperature gradient and centrifugal force. This leads to rise in the mass's temperature which in turn creates a flow situation internally that allows moving relatively to the mass for some of the sugar. The rotating head that lets the flowing mass exit by flinging the floss. The floss which is created has a texture of amorphous nature. To create a flow consistency and make it easier to mix, it is further diced using a variety of methods and also recrystallized. The recrystallized matrix, active component, and additional excipients are then mixed, and the mixture is then pressed into tablets.

1.7. Flashdose Technology [29]: Fuisz holds the patent for this technology. To disguise the unpleasant taste of the medicine, this system combines both the Shearform and Ceform technologies. Excipients (sugars of crystalline nature), either single or in combination with drugs, are combined to form a sugar-based matrix known as "Floss" is used. The first commercial product created using this technique was released by Biovail Corporation as a new version of Ibuprofen called Nurofen meltlet, which dissolves in the mouth.

1.8. OrasolvTechnology[13,14]: CIMA Labs has a patent on this invention. To create the MDTs, disintegrating agents of effervescent nature undergo compression at low pressure. The fizzing feeling produces positive organoleptic characteristics by the release of carbon dioxide from tablets. 20–25% of the weight of tablet is the typical concentration of the effervescent mixture used.

Because the tablets are made with a minimal force of compression, they are fragile and soft. This led to the creation of Paksolv, modified packaging designed to prevent tablet breakage during storage and transportation. By using this Paksolv which is a blister package of dome-shaped, Prevention occurs of the vertical movement of the tablet. Paksolv offers packaging that is light, moisture, and child-resistant. The drugs used to manufacture the MDT are Paracetamol and Zolmitriptan.

1.9. Durasolv Technology[15]: CIMA Labs holds the patent for this invention. In this technology, Conventional tableting equipments are used to manufacture the tablets. Mannitol, lactose, sucrose and sorbitol are non-direct compressible fillers that have the advantage of dissolution rapidly while avoiding the granular texture that is typically found in sugar of direct compressibility. The obtained tablets can be packed into blisters or bottles as they are very strong. The drugs used to manufacture the MDT are Hyoscyamine Sulphate and Zolmitriptan.

1.10. WOW tab Technology[16,17]: Yamanouchi Pharma Tech. Inc. patented this tehnology. The name WOW stands for "without water." This methodology makes use of traditional granulation and tableting techniques to create MDTs using saccharides with low such as Lactose, Glucose, Sucrose and high moldability such as Sorbitol, Maltose, Oligosaccharides, and Manitol. Due to lack of desired properties of any one moldability saccharide alone, combination of both saccharides is used to prepare the MDT in this technique. With this approach, combined granulated saccharide as a binder, compressed into tablets, and then treated with moisture. Thus, the resulting tablets showed acceptable hardness and very quick disintegration. The drug used to manufacture the MDT is Famotidine.

1.11. Oraquick[6]: The pharmaceutical company K.V.S. has the patent on this invention. It makes use of the microsphere of taste masking technique known as micromask, which offers an improved tongue feel, high mechanical strength, and rapid product dissolution/disintegration. As part of this procedure, microparticles are created in the shape of a protective matrix for the drug that has the necessary mechanical strength to be compressed. This method is excellent for heat sensetive drugs because of the decreased manufacturing temperatures. For dissolving oraquick it takes a few seconds.

2. Non-Patented Technologies:

2.1. Lyophilization/Freeze-Drying: In this process, produced products are porous in nature. The process in which from a solution the solvent is removed with additives forming structures or a suspension which is frozen is known as Lyophilization. Drugs that have been freeze-dried with additives provide an amorphous, glossy structure that makes the final product extremely lightweight and porous. In contact with the tongue, the tablet disintegrates quickly and dissolves, and the drug is released when the lyophilized unit melts. However, this technique decreased mechanical strength and stability at elevated humidity and temperature[18].

Excipients such polymers (to provide the tablets strength and stiffness, such as dextrin, gelatin and alginates); polysaccharides (to improve palatability, crystallinity and hardness of the matrix, such as sorbitol and mannitol); anti-collapse excipients (to stop the shrinking of the product in its packaging throughout production or storage, such as glycine); flocculating agents (to ensure uniform drug particle dispersion, such as gum acacia); preservatives (to protect microbiological development, like methyl parabens); penetration enhancer (to increase permeation of transmucosal like Sodium Lauryl Sulphate); pH modifier (for stability like citric acid); Water is added for the creation of pores, while flavours and sweeteners help patients to comply with treatment are commonly used in MDTs produced by the lyophilization method[8].

Advantages: The primary benefit of utilising this method is that the tablets made using it have a very short time to disintegrate and have excellent mouthfeel because of the quick melting action[8].

Disadvantages: Despite being a very common procedure, lyophilization has significant drawbacks, including costly and longprocess. Additionally, the resultant product is brittle in nature and insufficiently stable, making standard packaging inappropriate[8].

2.2. Tablet Moulding: Typically, water-soluble substances are found in moulded tablets, resulting in complete and rapid dissolution. The various processes for moulding tablets are as follows:

2.2.1. Compression Moulding[19]: In This technique the powder combinations are wetted with hydro-alcoholic solvent and pressed into a wetted mass with the help of mould plates. Tablet triturates are prepared by removing the solvent by air drying. The compactness of the prepared tablets are less in comparison to compressed one, and they dissolve more quickly due to their porous structure.

2.2.2. Heat-Moulding[20]: This process involves creating a liquefied substance that contains the evenly distributed drug. For preparing the tablet, agar solution is used as a binding agent here; blister packing is used for moulding. Initially a suspension consisting of sugar, agar and drug is prepared. After that, the resulting mixture is poured to the blister packaging, where it is then dried under vacuum at a temperature of about 30°C.

2.2.3. Moulding by Vacuum Evaporation without Lyophilization[21]: Here, at first the API and other additives should be mixed, and then the mixture is poured in a matrix of required extent, form a solidified matrix by freezing and at last at a temperature, vacuum drying is done between its equilibrium freezing temperature and its collapse temperature. As a result, a matrix which is partially collapsed is created. The difference between this process and the technique of lyophilization is that the previous involves the controlled evaporation from a solid of free solvent which is unbound via the liquid phase to a gas. The later approach involves sublimation. Opposite to lyophilization, vacuum drying assists in densifying the matrix, which raises the product's mechanical strength.

Advantages[8]: Disintegration is done quickly of the moulded tablet and with better taste as the dispersion mould is made of sugars which are water-soluble. These qualities are improved when components that have undergone physical modification during the moulding process are used or porous structures tablets are created. Tablets made using the technique of moulding are simpler to adjust to an industrial scale than those made using the lyophilization process.

Disadvantages[8]: The moulded tablets may erode and break during handling because of their weak mechanical strength. Although hardening can make tablets stronger, it would lengthen the time of disintegration.

2.3. Direct Compression (DC): Due to the few processing stages, low production costs, and ability to handle high doses, this method makes it simple to formulate MDTs. The final weight of a tablet can simply be more than that of another technique of manufacture[6]. The effects of the disintegrant, water-soluble excipients and effervescing agents can be used alone or in combination to determine how easily directly compressed tablets dissolve. The hardness and size of the tablet have a big impact on how well it disintegrates. The disintegration properties can be enhanced by moderate or smaller size of tablet, minimum physical resistance and low hardness. Selecting an appropriate and ideal concentration of disintegrant is essential for ensuring rapid disintegration as well as rapid dissolving rates[16,22]. In order to further improve dissolution or disintegration capabilities, water soluble excipients or effervescent agents may be used. Due to the formulation's combination of swelling and water absorption, super disintegrants offer fast disintegration[23].

2.4. Spray-Drying[6]: In this technique the organic solvent evaporated resulting porous tiny particles. Here croscarmellose sodium or sodium starch glycolate are choice of superdisintegrant, mannitol as diluent, and both hydrolysed and non-hydrolysed gelatin is used as the supporting matrix. By adding alkali or acidic compounds like acidic acid and sodium bicarbonate respectively, dissolution and disintegration were accelerated even further. The porous powder produced by this formulation method has a disintegration time of 20 seconds or less.

2.5. Cotton Candy Process[6]: It is so called as it has a unique mechanism of spinning to prepare a crystalline structure that looks like a floss and which is similar to cotton candy. In order to form a matrix containing polysaccharides or saccharides, flash melting as well as spinning are done simultaneously under the cotton candy method. Partial crystallization of the matrix leads to enhance its fluidity. After milling and blending this candy floss matrix with the active ingredients and additives, it prepares MDTs by compressing them.

2.6. Sublimation[8,24]: High porosity MDTs have been created using sublimation. Conventional tablets sometimes fail to dissolve quickly despite having highly water-soluble components due of their poor porosity. During the tableting process, the volatile components can increase the porosity through sublimation. The volatile components and other excipients are compressed into tablets before being subjected to a sublimation process; as a result a porous matrix is formed. For this, inert solid substances with high volatility, such as urea, urethene, naphthalene, hexamethylene tetramine, benzoic acid, camphor, and ammonium bicarbonate, have been

utilised. For creating the porosity in the matrix, solvents like cyclohexane and benzene were also proposed. Created MDTs utilizing camphor, a volatile substance derived from compacted tablets composed of a camphor-mannitol blend. Camphor was made into tablets, and then they were evaporated for 30 minutes at 80°C in a vacuum.

2.7. Mass-Extrusion: With this innovation, the active mixture is made soft using a water-soluble mixture of carbinol and PEG, and the relaxed mass is ejected through an extruder to urge a hollow, rounded extrude that is then cut into even pieces using a warmed edge to prepare tablets. In order to disguise the flavour of bitter pharmaceutical granules, this procedure can also be utilised[8].

2.8. Nanonization: A recently created technique termed as Nanomelt, decreases drug particle size into nanoscale by using a revolutionary wet-milling method[25]. Adsorption on specific stabilizers on the surface ensures that the drug nanocrystals are protected from clumping together, allowing for their seamless incorporation into MDTs. Poorly water-soluble drugs get great benefit by this method. The rapid dissolution/disintegration of nanoparticles leads to enhanced absorption, consequently improving bioavailability and allowing for dosage reduction, as well as the technology's cost-effective manufacturing procedure, are additional benefits[8].

2.9. Melt Granulation: The hydrophilic PEG-6-stearate is used as waxy binder to prepare the MDTs. It has HLB value of 9 (which indicates balanced hydrophilic-lipophilic profile) and melting point 33-37^{0}C. Not only it functions as a binder but also strengthens the hardness of the tablets, but it aids in tablet disintegration by swiftly melting and rapidly solubilizing without leaving any residue in mouth. The molten form of super polystate is used to create granules in the formulation of MDTs[26].

2.10. Fast Dissolving Films: Here the drug and other ingredients are dissolved in organic solvent and a hydrophilic polymer which forms a film (Hydroxypropyl methylcellulose, carboxy methylcellulose, sodium alginate etc.) is mixed and the solvent is allowed to evaporate for the formation of the film. When using pungent drugs, coated microparticles or resin adsorbate of the drug may be added to the film[27]. After administering in the mouth, the drug is released as a suspension or solution in which the film readily dissolves. This system's advantages include rapid delivery of drugs, disintegration in 5 seconds, and flavoured after taste[8].

2.11. Three-dimensional Printing (3DP): It is a type of rapid prototyping (RP) technology. With the use of liquid binding materials and powder processing, prototypes are built up from specified layers. Drug delivery device (DDD) which contained loose particles is fast dissolving, which is created by the three-dimensional printing (3DP) method. The 3DP system automatically prepared the DDD carrying the drug acetaminophen using computer-aided design models[28].

EXCIPIENTS USED TO PREPARE MDTS[7,30,31]:

1. **Super-disintegrants:** Pregelatinized Starch, Modified Corn Starch, Sodium Starch Glycollate, Crospovidone, Calcium Carboxymethylcellulose and Microcrystalline Cellulose. SSG has better flowability than CCS. The fibrous substance crospovidone has excellent compactability.
2. **Flavoring Agents:** Peppermint flavor, flavored oil and oil like anise, clove, thyme oil, peppermint, bay, eucalyptus, citrus, vanilla, bitter almonds, and fruit essences.
3. **Fillers:** Pregelatinized starch, Sorbitol, aluminium hydroxide, Mannitol, magnesium carbonate, calcium carbonate, magnesium trisilicate, calcium phosphate, and xylitol are all directly compressible spray-dried ingredients.
4. **Surfactants:** Sodium dodecyl sulfate, Tweens, SLS, Spans, Polyoxyethylene stearate etc are the examples of surfactants used in MDTs.
5. **Binding Agents:** PVA, HPMC, PVP etc are the examples of Binding agents used in MDTs.
6. **Lubricants:** Zinc state, Stearic acid, calcium state, talc, Magnesium stearate, Magnesium laurysulfate, liquid paraffin etc are the examples of lubricants used to prepare MDTs.
7. **Coloring Agent:** Amaranth, Sunset yellow etc. are the examples of coloring agents used to prepare MDTs.

PRE-FORMULATION STUDIES OF MDTs[7,32,33]:

The term "pre-formulation study" refers to pharmaceutical and analytical research done prior to and in support of formulation development activities of the drug substance's dosage form. Pharmaceutical excipients with drug combination are added to the dosage form which provides information that is necessary to define about drug substances nature. Therefore, on the drug sample that was collected, the following pre-formulation investigations were carried out:

1. **Angle of Repose (θ):** It indicates friction forces of the setting powder. Between the horizontal plane and powder pile surface a greatest angle is formed which is characterized by the angle of repose. A funnel at a specific height was set up on the stand, and through which the flow of powder mixture was allowed. The height and radius of the created hill of powder were then measured to determine the angle of repose.

   $$\tan\theta = h / r$$

   $$\text{Or, } \theta = \tan^{-1}(h / r)$$

   Where, θ = Angle of Repose; h = PileHeight; r = HeapRadius (Powder occupied plane surface).

Following is the table of flow properties based on the Angle of Repose:

Sl. No.	Angle of Repose (°)	Type of Flow
i.	25 to 30	Excellent
ii.	31 to 35	Good
iii.	36 to 40	Fair
iv.	41 to 45	Passable
v.	46 to 55	Poor
vi.	56 to 65	Very Poor
vii.	> 66	Very very Poor

2. **Bulk Density (ρ_b):** It is the mass (M) to bulk volume (V_b) ratio. For measuring it, a person should pour the pre-sieved powder mix into a graduated cylinder and take the weight. The measured volume is known as Bulk Volume. The unit used to express the bulk density is g/ml. To calculate the Bulk Density a person needs to put the above-mentioned measurements into the equation:

$$\rho_b = M / V_b$$

Where, M = Powder Mass, V_b= Powder Bulk Volume

3. **Tapped Density (ρ_t):** It is the mass (M) to tapped volume (V_t) ratio. For measuring the tapped density, a person should pour the pre-sieved powder mix into a graduated cylinder and place it on a mechanical tapping apparatus. After placing the measuring cylinder on the apparatus, start the tapping apparatus and let it run until no changes in the volume noticed. The unit used to express the tapped density is g/ml. The calculation of tapped density is done by the equation:

$$\rho_t = M/V_t$$

Where, M = Powder Mass, V_t = Powder Tapped Volume.

4. **Carr's Index:** By this a person comes to know about the flowability of powder. The formula for calculating it is:

%Compressibility = [(Tapped Density - Bulk Density) / Tapped Density] × 100

Following is the table of relation between %Compressibility and flowability:

Sl. No.	%Compressibility	Flowability
i.	< 10	Excellent
ii.	11 to 15	Good
iii.	16 to 20	Fair Passable
iv.	21 to 25	Passable
v.	26 to 31	Poor
vi.	32 to 37	Very Poor
vii.	> 38	Very Very Poor

5. **Hausner Ratio:** Measurement of the flow property of the drug-excipients mixed powder. The formula for calculating Hausner Ratio is:

Hausner Ratio = Tapped Density / Bulk Density.

Following is the table of relation between Hausner Ratio and Flowability:

Sl. No.	Hausner Ratio	Flowability
i.	1.00 to 1.11	Excellent
ii.	1.12 to 1.18	Good
iii.	1.19 to 1.25	Fair Passable
iv.	1.26 to 1.34	Passable
v.	1.35 to 1.45	Poor
vi.	1.46 to 1.59	Very Poor
vii.	> 1.60	Very Very Poor

6. **Porosity (€)**[34]: Experimentation can confirm the expectations that porosity is an excellent indicator of how liquids will penetrate the tablet matrix. In a study on the development of tablet formulations, tablet volume and total weight were used to calculate the porosity values. The equation helps to calculate the porosity is :

$$\% (€) = [(1 - (W/V\rho)) \times 100]$$

Where, W = Tablet weight, V = Tablet volume, ρ = Powder True density

EVALUATION STUDIES FOR MDTs:

After preparing tablets some tests should be done to understand the activity of the tablet. These tests or studies are known as Evaluation studies.

1. **Overall Appearance:** The overall appearance of a tablet is the outlook of the tablet which helps in customer acceptance. It includes the Shape, Size, Odour, Colour, Surface texture etc. of the tablets[35].

2. **Thickness of Tablet:** It is one of the very important evaluation studies as by this study a person can presume whether the amount of the filler was sufficient or not during the tablet preparation. Generally, ten random tablets are taken to measure the thickness and their average is calculated. Vernier Calipers can be used to measure the thickness of a tablet. The unit used to express the thickness of a tablet is mm[36].

3. **Measurement of tensile strength of tablets:** It is nothing but to determine how hard the tablet is. It can be measured by applying the required force to break down the same. Monsanto Hardness Tester is used to measure tablet hardness. The unit used to determine the Tensile Strength is Kg/cm^2. It can be calculated by the following formula:

$$T = 2F / \pi dt$$

Where, F = Crushing load, d = diameter, t = thickness[37].

In spite of being a widely accepted method, this method is not used for the tablets made by lyophilization technique[38]. This test is generally done for tablets which are made by direct compression method or by moulding method. The tensile strength should be less for Mouth Dissolving Tablets to ensure less disintegration time.

4. **Weight Variation:** After taking random 20 tablets, individually their weights are taken on the weighing balance machine and the average weight is determined. By this method, uniformity of drug content can be predicted.

5. **Friability:** According to Pharmacopoeia a friability test should be done for 4 minutes at 25 rpm (100 rotations). The maximum acceptance limit for weight loss is 1% of its original weight. After tumbling, if any tablet gets cracked, chipped or broken, the whole sample gets disqualified from the test[41]. The test is not performed for tablets made with the Lyophilization technique or Flashdose Technique. But for tablets made with the direct compression method and moulding method, this test is most recommended. The purpose of this test is to make sure the tablet has sufficient mechanical strength to endure shipping-related abrasion[38]. The percentage of Friability can be determined by this equation[7]:

$$\% \text{ Friability} = \{(W_1 - W_2) / W_1\} \times 100$$

Where, W_1 = Initial weight, W_2 = Final weight

6. **Moisture Uptake Study:** A lot of hydrophilic additives with least amount of hardness is contained in MDTs, which collectively increases their sensitivity to moisture absorption. Special care must be taken when storing and packaging these forms of dosage to safeguard their structural integrity and surface texture. Therefore, it is strongly recommended to perform moisture uptake study for MDTs. Ten tablets can be used for the test, along with calcium chloride, and they can be kept in a desiccator for a day at room temperature. After weighing keep it in room temperature for two weeks at 75% relative humidity. The weight gain percentage is calculated after reweighing the tablets. A product needs a dedicated dehumidified room for manufacture and packaging if its tendency to absorb moisture is high. For packaging, it is best to utilize materials with a high degree of moisture resistance. It is strongly advised to use an appropriate amount of adsorbent in HDPE bottle pack with the least amount of head space possible to ensure the longevity of the product throughout its shelf life[22,38].

7. **Tablet Porosity Measurement:** Tablet porosity is measured by using mercury penetration porosimeter. It is an assessment in the formulation by the degree of water which leads to fast disintegration. Phenomenon of capillary rise where more pressure is needed to form a liquid of non-wetting nature is based on by this instrument to climb up a narrow capillary[38]. In this test, the surface tension is 0.486 N/m between the tablet and mercury and the contact angle between the two is maintained at 140°. This method is effective for measuring pores between 0.06 µm to 3.60 µm[39] by the following equation:

$$\Delta P = -(2\gamma/r)cos\theta$$

Where, γ = Surface tension, r = Perpendicular radius, θ = angle between capillary walls and liquid. This equation is known as the Washburn equation[40].

If the calculation is not possible by the above-mentioned equation due to the variation of the pore size, the below mentioned equation can be used:

$$\varepsilon = 1 - m/(\rho t V)$$

Where, ρt = True density, m = Tablet weight, and V = Tablet volume[37].

8. **Wetting Time and Water Absorption Ratio:** A double folded tissue paper is placed in a petri dish containing 6 ml water. A pre-weighed tablet is placed on that and note the time for complete wetting which is the wetting time. Then, after weighing that wetted tablet, the ratio of water absorption is calculated by using this formula:

$$R = \{(W_a - W_b) / W_b\} \times 100$$

Where, W_b = Tablet weight before water absorption, Wa = Tablet weight after water absorption[39].

9. **Disintegration Test:** It is performed to determine whether the product (Here MDT) is disintegrating within the time which is prescribed after placing it in a medium of liquid or not. The tests should be done with 6 tablets with the help of the apparatus specified in Indian Pharmacopoeia. As the liquid media distilled water should be used at 37±2°C temperature[41]. After fulfilling all the criteria, the disintegration time should be noted in seconds using a stopwatch. The maximum time should be 180 seconds for disintegrating a mouth-dissolving tablet[38].

10. **Dissolution Test:** To evaluate MDT in vitro, the common technique of dissolution can be used. Preliminary in-vitro investigations can be used to better simulate in vivo environments by using the dissolving conditions for the reference mentioned drugs that are accessible in USP. To understand their *in-vivo* effectiveness and pharmacological equivalence, multimedia dissolving tests in different pH levels of a variety of buffer solutions, such as pH 1.2, 4.5 and 6.8 buffers should be conducted, with a speed of 50 rpm, USP apparatus 2 (paddle type) and an acceptable dissolving media volume for maintaining sink condition. When employing USP prescription conditions, MDTs often dissolve relatively quickly, and in these circumstances, the dosage forms act nearly similarly. Therefore, reduced paddle speeds can be used to develop profiles and improve

discriminating between different batches created during the developing stage. There is a chance that a pile will form at the dissolution vessel in the bottom part in the case of tablets that are close to or heavier than one gram and consist of reasonably dense insoluble particles. Increasing the paddle speed to 75 rpm can fix this problem[42].

11. ***In-vitro* dispersion Time:** Tablets containing solid dispersion formulations are evaluated using an *in-vitro* dispersion study. Solid dispersion technique improved the solubility and dissolution rates of hydrophobic drugs[43]. For this test three tablets from each batch are taken and individually dropped into 50 ml Sorenson's buffer pH 6.8 and measurement of *in-vitro* dispersion time is done[38].

12. **Stability Study:** The ICH recommendations for accelerated studies specify that the tablets which fast dissolves is kept in specific conditions for a certain duration of time after being packaged, i.e. at 37±1°C, 40±1° and 50±1°C, with a RH of 75%±5%. Then the removal of tablets and their physicochemical properties (like hardness, friability, visual flaws disintegration, and so on) and content of drug were examined after 15 days. First order equation is employed to determine the degradation kinetics. The shelf life at 25°C is calculated using accelerated stability data displayed with the Arrhenius equation[44].

REASONS FOR SHIFTING FROM CONVENTIONAL (SWALLOWABLE) TABLETS TO NOVEL MDTs[1,45]:

In comparison to traditional (swallowable) tablets, mouth-dissolving tablets are an innovative way of drug delivery. There are some factors, which lead the formulation scientists to develop Mouth Dissolving Tablets. The factors are as follows:

1) **Patient Related Factors:**

   a) Both Pediatric patients without permanent teeth and geriatric patients with complete tooth loss finds it difficult to swallow or chew conventional solid swallowable tablets.

   b) Conventional dosage forms have the risk of choking or suffocating while taking the solid dosage form. To prevent this phenomenon, MDTs play a huge role.

   c) Older patients can face tablet swallowing problem. To prevent this, MDTs are very useful.

   d) A child with allergies may demand to take some different form of medication than regular antihistamine syrup.

   e) A patient with schizophrenic syndrome may use MDTs for proper drug intake.

   f) Breast cancer patient must undergo several radiation therapies. The patient also needs to swallow H2 blocker daily, but the patient might be too nauseous while taking H2 blocker. To prevent this, MDTs can be used.

2) **Effectiveness Factors:**

   a) MDT improved bioavailability as well as onset of action. They are capable of being absorbed through the pharynx, buccally, and gastrically as it disintegrates inside the mouth.

   b) Drugs with high levels of hazardous metabolites produced by first-pass metabolism might have their safety profiles improved.

   c) If a sizable portion of the medicine is lost via metabolism in liver, the drug dose can be lowered since pre-gastric absorption of drugs avoid the first-pass metabolism.

3) **Manufacturing and Marketing Factors:**

   a) Pharmaceutical companies must create novel drug delivery methods and apply them to product developments if they are to thrive.

   b) Pharmaceutical companies frequently innovate and enhance the formulation for a particular drug component when the patent period is over.

   c) A new form of dosage enables a company to increase its market dominance, differentiate their product, and so on.

   d) When marketers provide a special, easy to consume dosage form which meets the patient's needs who are underserved, their company reputation and corporate image are improved.

CHALLENGES IN FORMULATING MDTs[46]:

- **Disintegration Time and Mechanical Strength:** MDTs are designed to achieve disintegration times that are typically less than sixty seconds. A major issue when doing this is maintaining strong mechanical strength. Most MDTs are fragile, so there is a good probability that a few of these fragile tablets will shatter while being packed, transported, or handled by patients. Special packaging is required for tablets built with some patented technology like Zydis. It makes perfect sense that improving mechanical strength will decrease the disintegration process. So, it's always important to find a decent balance between both of these variables.
- **Hygroscopicity:** Some Mouth dissolving tablets are hygroscopic, which means that they cannot maintain their structural stability under normal circumstances of moisture and temperature. For this it should be packed in well closed container.
- **Taste Masking:** Several drugs have an unpleasant taste. A tablet with bitter taste of drug, will provide a negative impact on patient acceptance when it disintegrates / dissolves in the mouth of a patient.

So, efficient taste masking of unpleasant drugs is required in order to mask the bitter taste.

- **Mouth Feel:** MDTs shouldn't produce larger particles after degradation into the mouth. After being swallowed, MDTs must leave little or no trace in the mouth. Additionally, the inclusion of flavors as well as cooling substances improves the tongue feel.
- **Size of Tablet:** According to reports, tablets that are 7-8 mm in size are the simplest to consume by mouth, while those that are bigger by about 8 mm are the simplest to handle. As a result, it is challenging to create tablets which are both convenient to use and convenient to swallow.
- **Amount of Drug:** The maximum amount of drugs which can be included in a single dose restricts the applicability of MDT technology for MDTs. The amount of drug used during lyophilized formulations must be below 400 mg in insoluble drugs as well as below 60 mg in soluble drugs. This characteristic presents a challenge when creating oral film and wafer that dissolve quickly.
- **Cost:** When it comes to the price of the finished product, the methods employed for MDT preparation need to be affordable. The cost is significantly increased by techniques including Orasolv and Zydis which require special equipment and unique packaging.

SUITABLE DRUG CANDIDATES FOR MDTs[1,46]:

- **Anti-diabetics:** Tolazamide, Tolbutamide, Glipizide, Gliclazide, , Glibenclamide.
- **Anti-Depressants:** Mianserin HCL, Maprotiline HCL, Trazodone HCL, Amoxapine.
- **Sedatives, Hypnotics, Neuroleptic and Anxiolytic:** Alprazolam, Bentazepam, Brotizoiam, Barbitone, Amyiobarbitone, Butobarbitone, Bromazepam, Bromperidol, Carbromal, Chlormethiazole, Chlordiazepoxide.
- **Anti-Migraine Agents:** Pizotifen Maleate, Ergotamine Tartrate, Sumatriptan Succinate, Dihydroergotamine Mesylate, Methysergide Maleate.
- **Anti-Epileptics:** Ethotoin, Carbamazepine, Methoin, Beclamide, Oxcarbazepine, Methsuximide, Clonazepam, Methylphenobarbitone.
- **Anti-Hypertensive Agents:** Reserpine, Amlodipine, Nifedipine, Darodipine, Nicardipine, Benidipine.
- **Anti-Gout Agents:** Probenecid, Allopurinol, Sulphinpyrazone.
- **Anti-Parkinsonian Agents:** Lysuride Maleate, Bromocriptine Mesylate.
- **Anti-inflammatory Agents and Analgesics:** Etodolac, Aloxiprin, Fenbufen, Azapropazone, Fenoprofen Calcium, Auranofin, Diflunisal, Benorylate.
- **Anti-Bacterial Agents:** Ethionamide, Ciprofloxacin HCL, Imipenem, Doxycycline, Benethamine Penicillin, Nalidixic acid, Cinoxacin, Erythromycin, Nitrofurantoin, Rifampicin, Clarithromycin, Cloxacillin.
- **Anti-Malarials:** Pyrimethamine, Chloroquine, Mefloquine salt, Chlorproguanil salt, Proguanil salt, Halofantrine HCL, Amodiaquine.
- **Anti Protozoal Agents:**Metronidazole, Ornidazole,Benznidazole, Nimorazole, Tinidazole, Clioquinol, Nitrofurazone, Furzolidone, Diiodohydroxyquinoline, Dinitolmide, Diloxanide Furoate, Decoquinate.
- **Anti-Fungal Agents:** Fluconazole, Clotrimazole, Econazole Nitrate, Butoconazole nitrate, Amphotericin.
- **Anthelmintics:** Albendazole, Thiabendazole, Oxfendazole, Mebendazole, Cambendazole, Bephenium Hydroxynaphthoate, Pyrantel Embonate, Ivermectin, Oxamniquine, Praziquantel, Dichlorophen.
- **Anti-Arrhythmic Agents:** Flecainide Acetate, Amiodarone, Quinidine Sulphate, Amiodarone.
- **Immunosuppressants and Anti-Neoplastic Agents:** Cyclosporin, Azathioprine, Etoposide, Aminogluethimide, Dacarbazine, Chlorambucil, Amsacrine, Estramustine, Busulphan.
- **Anti-Coagulants:** Phenindione, Nicoumalone, Dipyridamole, Dicoumarol.

DRUG RELEASE MECHANISM FROM MDTs[47,48]:

Tablet disintegration occurs through five main mechanisms, which are listed below:

1. **Swelling:** Some disintegrating substances, like starch, are thought to transmit the dissolving action by swelling. When water comes in contact with a tablet, swelling occurs, defeating the adhesiveness of the other ingredients, leading the tablet to break e.g. Sodium Starch Glycolate.

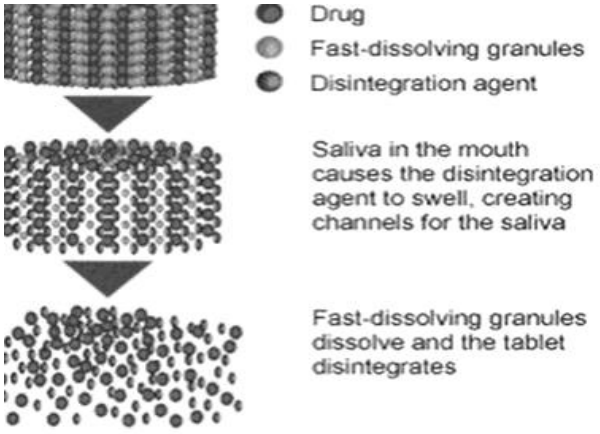

Figure 1: Disintegration through swelling mechanism[47].

2. **Porosity and Capillary Action (Wicking)**: It is hypothesized that efficient disintegrating agents that

have no swelling, convey their disintegrating activity via wicking.The porosity of tablets creates channels through which liquid can enter the tablets. The poor cohesion and the compressibility of the disintegrating particles itself act to increase porosity while establishing these entryways within the tablet. By capillary action, the liquid is pulled up or "wicked" into those paths where it breaks the interparticulate linkages that hold the tablet together. E.g.: Crosscarmillose, Crospovidone.

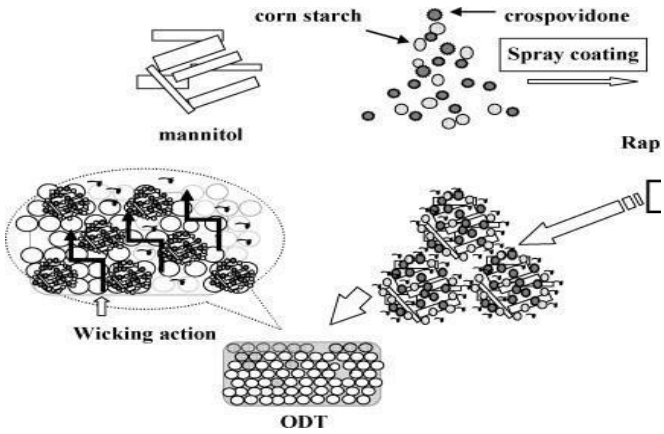

Figure 2: Disintegration through wicking action[47].

3. **Deformation:** Granules of starch are commonly believed to have an "elastic" character, which implies that once pressure is applied, the granules will distort but will immediately return to their former shape. These granules, however, are thought to have been irreversibly altered by the forces of compression used in tabletting as well as are described as "energy-rich," with that energy released when the granules come into contact with water. To put it another way, starch granules that have been exposed to pressure are more likely to deform than starch granules that have not, hence the ability of starch to swell tends to be greater in "energy-rich" starch granules.

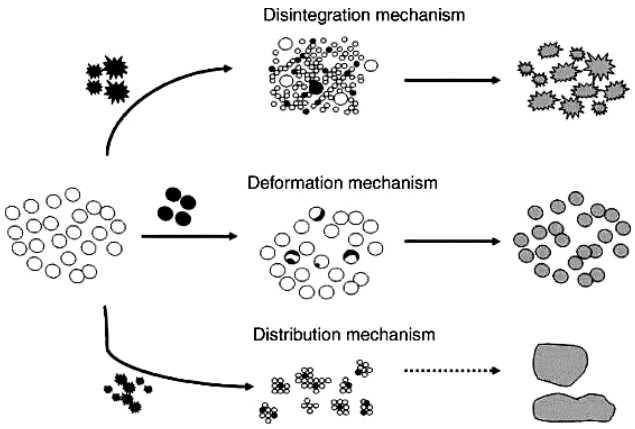

Figure 3: Disintegration through deformation mechanism[47].

4. **Due to Particle Repulsive Forces / Disintegrating Particle[50]:** The swelling of tablets made with "non-swellable" disintegrants can be explained by a different disintegration mechanism. Guyot-Hermann's idea of particle repulsion depends upon the findings that the tablet disintegration also caused by the non-swelling particles. For disintegration, water is essential, the reason behind it is the electric repulsive interactions among particles. According to research, wicking comes next to repulsion. The majority of disintegrants are thought to operate through many mechanisms. Instead, It is probably the result of how these crucial processes interact with one another.

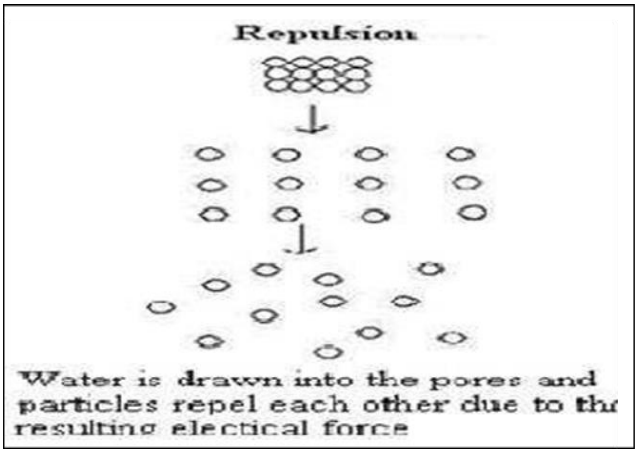

Figure 4: Disintegration through particles repulsion[48].

5. **Enzymatic Reaction[54]:** The human body's own enzymes serve as disintegrants as well. Enzymes like these improve the binding effect of the binders and aid in breakdown. The tablet cracks because of swelling and the granules disintegrate more quickly because of rapid water absorption.

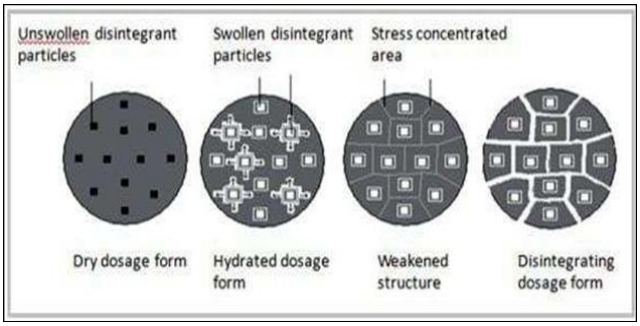

Figure 5: Disintegration through enzymatic action[48].

PACKAGING OF MDTs[6]:

One of the critical steps in the manufacture of MDTs is packaging. There are various technologies which produce products which in some of the parameters may vary such as higher extent mechanical strength. By the lyophilization process the products which are produced, which uses a number of technologies, including Zydis, Quicksolv, Lyoc, and Nanocrystal which in nature is porous, are moisture-sensitive, have a physical resistance which is low and may disintegrate with higher levels of relative humidity in environments. The aforementioned factors necessitate specific packaging for the produced goods. In most cases, to box Zydis units, peelable backing foil is used.

Paksolv is a specialized packing unit used for Orasolv tablets. It comprises a blister of dome- shaped that prohibits movement of the tablet vertically inside the cavity and guards against tablet breakage during storage and shipping. Some MDTs created using the WOW Tab, Durasolv, Ziplets and Oraquick technologies have enough durability to survive shock during handling and transport; hence they are typically packaged in blisters which is pushable or bottles.

FUTURE PERSPECTIVEs[38]:

Despite the wide range of commercial medicines available, there are still numerous areas where MDT formulations might be strengthened. Despite today's highly developed MDT technology, it can still be difficult to formulate hydrophobic drugs, particularly when the dosage is high. Incorporating greater quantities of hydrophobic medications without compromising their ability to dissolve quickly is now possible thanks to a novel technique. Scientists should now eventually work on creating MDTs with controlled release characteristics. It would be a significant advancement in the MDT technique if one MDT could deliver medications having short half-lives lasting 12–24 hours. The development of efficient taste-masking qualities will lead to the invention of novel innovations in the future. Drugs with bitter tastes are frequently coated, however, this raises the overall finished formulation volume. Therefore, with ongoing advancements, one can anticipate the development of more unique techniques for MDTs in the days ahead. It is anticipated that in the near future, these fast-dissolving tablets would likely replace a significant portion of conventional products due to their exceptional advantages.

CONCLUSION

With their increased compliance of patient, bioavailability, convenience and rapid onset of action, MDTs have the possibility to surpass conventional dosage forms. Over the decade, this has attracted the interest of numerous manufacturers. The acceptance of MDTs among individuals has also grown significantly. By creating a tablet which is porous matrix or by incorporating effervescent excipients as well as superdisintegrant, helps to accomplish the primary purpose of MDT formulation is faster disintegration, dissolving, or melting inside the oral cavity. MDTs can enhance compliance of patient is demonstrated by the clinical studies and boost bioavailability. It also offers improved efficacy compared to conventional products. As an illustration, in comparison to traditional capsules and tablets, they offer greater drug bioavailability, improved absorption profiles with fewer amounts of Active Pharmaceutical Ingredients. Given their lack of mechanical strength, this dosage form needs to be treated with care. The way MDTs are packaged is also crucial. Patients who experience oral dryness should avoid being prescribed MDTs as a minimum amount of saliva is required for their disintegration. Both pediatric patients without permanent teeth and geriatric individuals with complete tooth loss can benefit greatly from this dosage type. Numerous studies have been done in the past to examine MDTs, and it has been found that many of them exhibit strong discriminatory power. Therefore, it is anticipated that this delivery mechanism will soon be given more value than traditional ones.

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