

A COMPREHENSIVE REVIEW ON MOUTH DISSOLVING TABLETS

ABSTRACT

Oral drug delivery system of Mouth Dissolving Tablets (MDTs) is using a new concept that have been mostly accepted in the pharmaceutical industry in recent days. This system is the most comfortable, safest and inexpensive of drug delivery system, enhancing the patient compliance and extending the patient life. Mouth dissolving formulations using an important ingredient or active agent due to allow release of drug is rapidly after that produce faster dissolution process. The mouth dissolving tablets contain a unique property of tablets like quickly disintegrating or easily dissolving and releasing the active drug within a few minutes and its contact with saliva. In pediatric, geriatric, bed ridden, psychic, dysphagic patients are using the MDTs because of these tablets are easily engulfing or swallowing is most convenient and patient compliance is better to compared than other Delivery systems. The tablets are formulated with an aid of super disintegrant. It's more reliable because of better compliance in patients. There are several technologies used in the MDTs manufacturing process such as patented technology & conventional technology. The important patented technologies are Durasolv technology, Orasolv technology, Zydis technology, Wowtab technology, Flashdose technology, Flashtab technology and Quicksolv technology. The MDTs are improving the demand for rapidly growing areas in the pharmaceutical industry and other fields are also in demand on these formulations. The recent progress of pharmaceutical fields is allowing the improvement of a better route of health care management with avoidance of numerous difficulties are connected to the other Drug Delivery System (DDS).

Keywords: Mouth Dissolving Tablets, Patented technologies, Conventional technologies.

INTRODUCTION

Definition

According to EP



These MDTs should dissolve/disintegrates very

Quickly in mouth without the need of water

According to USFDA ⇒

Defined as solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue [1]

The MDTs have preferred to alternative conventional dosage form such as tablets, capsules and liquid pharmaceutical preparation. All patients may benefit from this oral method of medication administration, which is believed to be the most convenient and the easiest to administer when compared to other ways. The tablets are an extensively suggested the dosage system for regarding to its self-administration, and simplicity of the progress. Pediatric and elderly patients, in particular, have difficulty swallowing or engulfing the pills, and this problem may be increased while travelling due to the lack of or restricted access to water. [2,3]. There are using several synonyms terms are used in the MDTs like Quick dissolving tablets, Fast melt tablets, orally disintegrating agent, Rapid disintegrating tablets, orodisperse tablets, Freeze dried wafers. The advantage of the system is tablets that break up in the mouth. MDTs didn't require for water because of the tablet are quickly break down and disintegrate in saliva and dissolution can occur under the tongue or in buccal cavity. Some of the MDTs are may rapidly break into a small interval and rapidly goes into systemic absorption. Another few tablets contains a DI agent to increase the Disintegration (DI) of tablets. In some of the oral tablets are taken into long time intervals for breakdown of the tablet. MDTs are intended to disintegrate rapidly and dissolve in the mouth less than 60 seconds or short span 20-30 seconds and its produce rapid on action for previous to ingestion, the active pharmaceutical ingredient (API) is designed to be delivered or retained in the gastrointestinal tract [4-6]. Traditional methods of administering medication were a basis for the formation of MDTs. To ensure that the patient receives an appropriate dose of medication in a timely way, and using these disintegrating agents including sweeteners and flavors mask the taste for bitter taste.

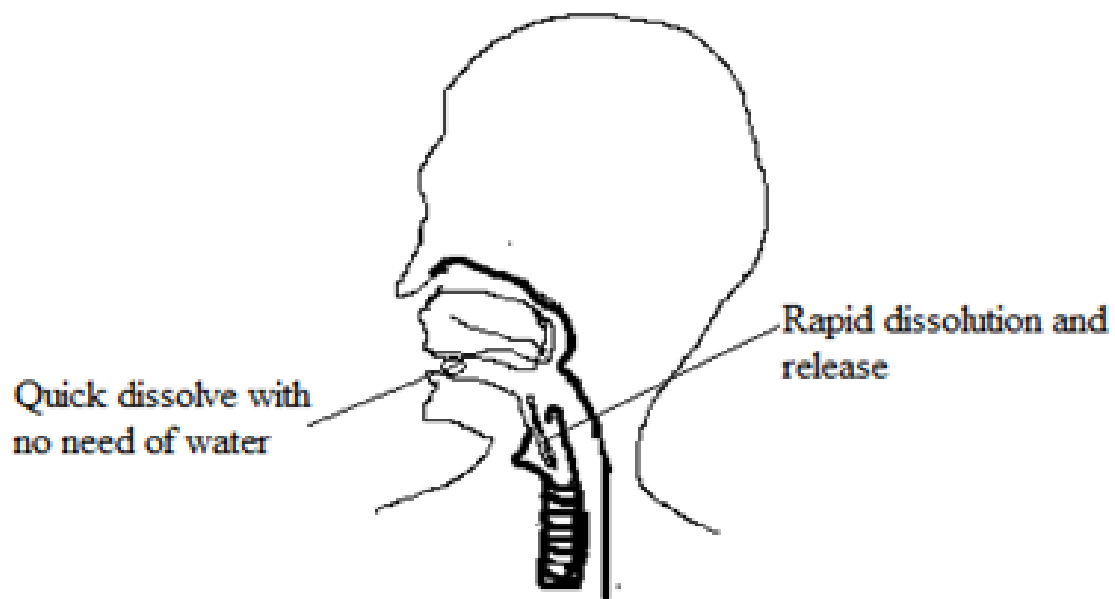


Figure 1: MDTs dissolution and drug release mechanism

Advantages of MDTs [7-10]

- There is no require for water to engulf (or) consume the tablet
- Precise dosing produced as differentiate to liquids.
- Mentally Disabled patients, pediatric patients and elderly patients can be easily administered.
- Decreasing the first pass metabolism & it offers increases the bioavailability at the same time decreases the strength of dose and reduces the side effects.
- MDTs are producing rapid absorption of drug and dissolution rate and it's producing rapid onset of action.
- Improving the drug bioavailability also increases absorption.
- Starting in the mouth, the drug is absorbed into the pharynx, then into the esophagus, and finally into the stomach.

Ideal Properties [11-13]

Medications that meet the following criteria are likely to be appropriate for use in MDTs:

- Medications may permeate into the upper GIT epithelium ($\log P > 2$) if taken orally.
- Drugs that have short half-lives and must be taken regularly.
- The first-pass metabolism of the MDTs produced toxic by-products.

- Multi-drug safe medicines can't use controlled and sustained release pharmaceuticals.
- Quick onset of action will possible on a rapid dissolution and absorption of drug
- Accomplished enough to handle the stress of assembly and post-assembly maintenance.
- As a result, it has a pleasant tongue feel and enables for a high drug loading while exposing low-sensitivity ambient or ecological conditions, such as temperature and humidity.
- As a result, it is both adaptable and prone to present packaging and handling methods.

Restrictions in the usage of MDTs [14-16]

- As a result of the MDTs' abundance in welfares, there was a pre-determined set of restrictions.
- The MDTs Dosage forms usually have insufficient of mechanical strength of the final product hence it needs careful and handling.
- MDTs are dissolves in the sensation of mouth and it is taking a short time interval for DI
- Some of the MDTs had masking or abolishing the bitter taste or roughness in the mouth.
- MDTs Developing is difficulty to extremely high doses for (more than 500mg) and substantial taste masking of bitter tasting activities.
- In addition to these constraints,
 1. Salivation arrangement and worldwide bioavailability may also be a problem.
 2. Due to a decrease in saliva production, the mouth becomes dry.
 3. Plans for tablet.

The super disintegrant's mechanism of action: When a tablet breaks down, there are four main processes at work.

Swelling

The mechanism of action for tablet disintegration is often used for swelling action. High porosity shows the lack of DI in tablets due to insufficient of desirable swelling force. Another side of tablets having low porosity of the swelling force is applied on the tablet [17,18]. When the tablet comes into contact with water, the starch and other disintegrating agents cause it to dissolve. Example: Sodium starch glycolate, Plantago Ovata.

Porosity and capillary action (Wicking)

The capillary action is the initial stage towards disintegration. Particles with weaker intermolecular interactions are separated from the tablet by submerging it in an appropriate aqueous media, which removes the air from the tablet and breaks it into smaller pieces [19]. There are a number of requirements that the tablets must meet, like as Drugs and excipients in tablets are hydrophilic, therefore their water absorption is determined by their hydrophilicity and the water-soluble network that is formed around the drug particle in the tablet. Example: Crosspovidone & Crosscarmellose.

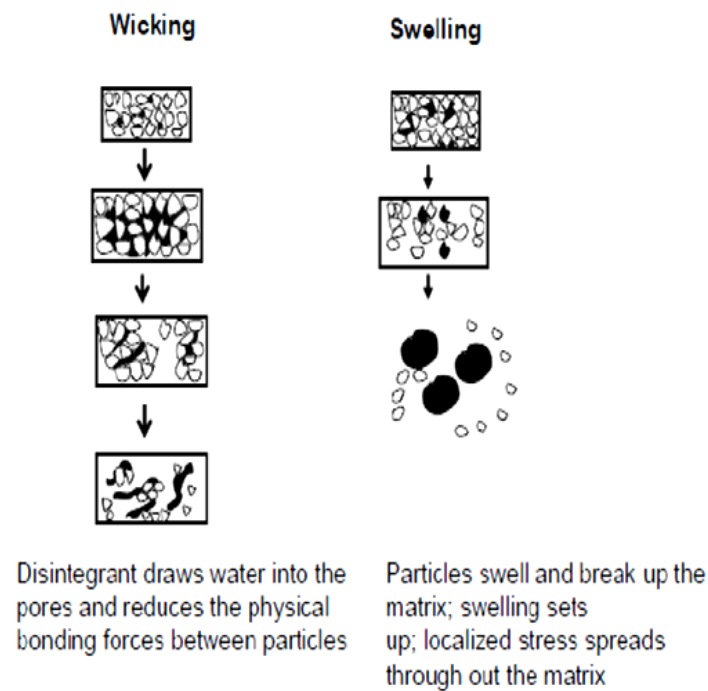


Figure 2: Wicking and swelling mechanism of tablets.

Due to disintegrating particle/particle repulsive forces

The Guyot-Hermann theory is important one of particle/particles repulsive forces and Another disintegrant experiment mechanism to elaborate the swelling of tablets are produced to 'non-swellable' disintegration [20,21]. The disintegration process relies heavily on particles having electric repulsion forces (between the particles) and water.

Due to deformation

The fragmented particles are deformed by tablet compression and subsequently return to their original configuration. During the tablet compression hereafter, the particles come in communicate or contact with water fluid or aqueous media [22]. Sometimes, increasing the size of the particles induces the breakage of the tablet and the starch is used as a disintegrant and increasing swelling capacity of starch. During compression, the granules were

temporarily deformed [23]. The mechanism of starch was recently start and this mechanism only studied.

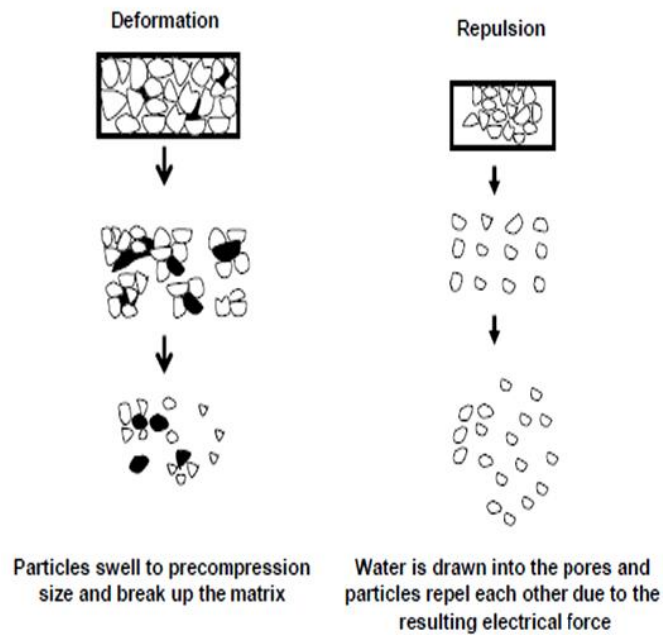


Figure 3: Deformation and repulsion of tablet ddisintegration

Newer manufacturing technologies used now a days for MDT's [24-27]

1. Freeze drying/Lyophilization
2. Molding
3. Sublimation
4. Spray Drying
5. Direct Compression
6. Mass Extrusion
7. Nanonization
8. Cotton Candy Process

1. Freeze drying/Lyophilization process

The basic principle in freeze-drying is the sublimation process; these are shifted from a solid directly into a vapor state. Just like evaporation, sublimation process occurs then a molecule increases the energy to break the molecules around it on MDTs. Which sublimation of water occurs after the product has been frozen [28]. The formulations having an amorphous structure to bulking agents in a drug are produced to increase the dissolution characteristics. Some of the crystal forming materials or mannitol provide rigidity to amorphous form. The formation of eutectic mixtures is one of the most serious problems associated with water-soluble drugs and its collapse on sublimation process factors like depression and creation of

glassy solid on freezing and freezing point. The ideal drug properties for a good aqueous stability of suspension having water insolubility with fine molecule size. When drug substances are freeze-dried/Lyophilized at room temperature, they avoid the harmful consequences of heated processing. This approach is not widely used because of the high cost of equipment and processing. The disadvantage of this process is the final dosage forms are insufficient of battle are important for the standard blister packaging

2. Molding [29]

Tablets manufacturing process in Molding technique easier method for industry Molding process are classified into 2 types:

1. Solvent method
2. Heat method

Solvent method:

Moistening powder (blend) + hydro-alcoholic solvent = molded plates are compressed at low pressures the moist mass is created and the solvent is removed with the use of air drying. When tablets are formed, they have a porous structure and are less compact than compressed tablets.

Heat method:

Most suspensions are prepared by heat Molding method. Solidified and dried at 30°C under vacuum, the agar is ready to use. after the drug + agar + sugar (lactose or mannitol) suspension is poured into blister walls. The primary concern of mechanical strength and using binding agents for molded tablets and taste masking drug particles are used in the MDTs.

3. Sublimation [30]:

With the assistance of inactive volatile compounds, sublimation is facilitated (camphor, naphthalene, urea, and urethane) and other excipients are blending into form tablets. sublimation is removal of volatile substances and produce pores in tablet structure. Pore forming agents (benzene, cyclohexane solvent) are additionally used. MDTs dissolve and contact into saliva. The MDTs have good mechanical strength and highly porous structure is developed by this method.

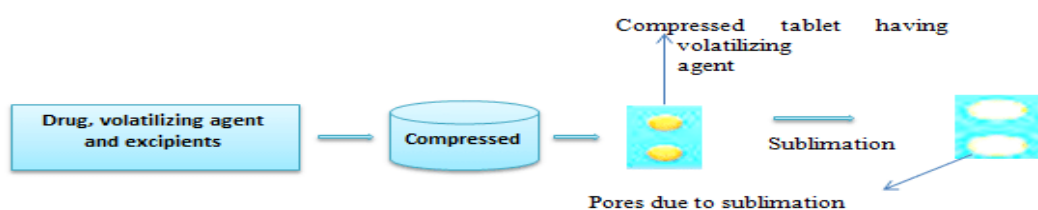


Figure 4: Step Involved in Sublimation Process

4. Spray Drying

MDTs are formulated by spray drying technology. The MDTs contains supporting material or agents (hydrolyzed gelatin and non-hydrolyzed gelatin) + bulking agent (mannitol) + disintegrant as a (Crosscarmellose or sodium starch glycolate) + [adding acid (citric acid) or alkali (sodium bicarbonate) are enhancing the DI and dissolution] the above the suspension form were compressed into tablets and DI time of tablets is < 20 seconds in aqueous medium.

5. Direct compression [31]:

The easiest and most cost-effective way to make tablet capsules is to use this procedure. MDTs also prepared by this method and it's increased the availability of the excipients is divided into two types:

Super disintegrants: Hydrophilic or Water-soluble excipients & effervescent agents increase the DI. The addition or extra of super disintegrants are affected the rate of DI.

Sugar based excipients: The main function of the sugar-based excipients is highly aqueous solubility, taste masking property, preferred pleasing mouth sensation and sweetness produced. Mostly these excipients are used in tablets to increases the bulk property eg: [mannitol, Maltitol, lactilol, maltose, fructose, xylitol] The sugar-based excipients classification based on its dissolution rate and mouldability.

Type 1 Saccharides [mannitol and lactose]

- Low mouldability
- High dissolution rate

Type 2 Saccharides [maltitol and maltose]

- High mouldability
- Less dissolution rates.

6. Mass extrusion

This process is a blend (or) grind with solvent mixture as (PEG & CH₃OH) water soluble properties. The softened (or) smooth mass is excreted through the syringe or extruder in a cylindrical shape; To make the tablets, soft mass extrude is cut into even pieces with a heated blade. Bitter drug granules are sometimes coated in order to mask the taste.

7. Nanonization

Nanomelt, or nanoization, is a new technique that has just been invented. When a wet-milling method is used to reduce the size of drug particles to nano size, the term "nanonization" is used. Most of the time, these technologies are used in water-soluble medications with doses

of up to 200 mg. Stabilization of the drug's nano crystals against agglomeration by adhering them to specific stabilizers, which are then combined into MDTs.

8. Cotton candy process

Thermolabile drugs are safely included in the preparation and highly porous products are containing rapid solubilization of sugar content present in saliva so that produce the very pleasurable mouth feel.

The formulations process is divided into two ways:

Floss blend:

The floss blend is formulated by blending or mixing in 80% of sucrose + 1% of surfactant.

Surfactants

- Maintaining- floss fibers structural integrity
- Acting- as crystallization enhancer
- Helping- retaining the dispersed drug and rectifying the emigration of the mixture

Floss processing:

The mechanism is similar to the cotton candy formation and it's containing two elements one is a spinning head & another one is heating elements. Two procedures included flash flow and flash heat processes create matrix from the carrier ingredients. After the amorphous-shaped floss is produced when centrifugal force is applied to the flossing action.

Evaluation test for MDTs [32]

Tablets that disintegrate in the mouth are evaluated based on a variety of parameters, such as how quickly they dissolve and weight variation test, hardness, friability test, drug content etc. While MDTs' success for drug delivery is dependent on these traditional end objectives, certain particular restrictions are critical. Disintegration time, wetting time, dissolution study, and moisture retention are the limitations or boundaries of this investigation.

Weight variation test

Using an electronic weighing scale, 20 tablets of each formulation were weighed, and the test was performed in accordance with the IP.

Table 1: Weight Variation Limit for Tablet as stated in IP 2018

S.no	Average weight of the tablet	% Deviation
1.	80mg or less	+/- 10
2.	More than 80mg but less than 250mg	+/- 7.5
3.	250mg or more	+/- 5.0

Hardness test

Crushing a tablet with radial compression requires a certain amount of force. On the day of compression, the tablet's crushing strength was measured using a Monsanto hardness tester. The three findings are then averaged and summarized.

Friability test

Each batch was tested using the Roche Friabilator, which measures friability. Rotating at 25rpm in 100 revolutions for 4 minutes, ten tablets are inserted in the friabilator and rotated. To determine the percentage of weight reduction, the tablets were weighed again. It is more important to consider surface abrasion as an indicator of friability, and a lower friability number indicates a stronger tablet. The formula gives the friability (F).

$$F = (\text{Initial weight} - \text{Final weight} / \text{Initial weight}) \times 100$$

Assay

20 tablets from a batch were accurately weighed, and powdered drug equivalent to 100 mg was stirred in a 100 ml amber colored volumetric flask with 100 ml of 0.1N hydrochloric acid, and 10 ml was pipette out and then diluted to 100 ml. Pipette out 10 ml of standard solution and dilute to 100 ml in ml once more.

Stimulated Wetting time

MDTs' wetting time is directly related to the site of contact. Tablet disintegration properties should be examined; a shorter wetting time suggests faster tablet breakdown. A tablet is placed on a piece of tissue paper folded twice and kept in a little Petri dish (ID = 10 cm) for this purpose. Consequently, it has a substantial impact on the manufacturing of MDTs. A 10 cm wide Petri dish was used to test the wetting time of a water-soluble dye. A Petri plate with

a 10 cm width was filled with 10 ml of distilled water containing eosin, a colourant that dissolves in water. The time it took for water to come into touch with the top surface of the tablet was recorded in the Petri dish. Wetting time is the term for this period.

Disintegration test

MDTs may be broken in less than a minute, and now is the best time to do it and it is intended or expected DI times are between 5 and 30 seconds, the patient might feel it. It is difficult to estimate short disintegration times using the standard disintegration test procedures often used for these MDTs.

Dissolution Test

“For oral dissolving medications, a dissolution test is crucial, if not critical. To examine the *in-vitro* dissolution of MDTs at 50 pm, the tablet dissolution test apparatus (USP XXII type) is employed. The dissolving solution is pH 6.8 phosphate buffer, and the temperature should be 37 0.5°C. Test samples are collected at various time intervals or frequencies and analyzed using the appropriate analytical procedure”.

Moisture uptake studies

Keep in mind that the various excipients utilized in MDTs to measure moisture absorption are hygroscopic in nature. Ten tablets are chosen and stored in a desiccator containing calcium chloride at 37°C for 24 hours. After roughly 14 days, the tablets are weighed and opened at room temperature with a relative humidity of 75%. For three days, the bottom of the desiccators is maintained at a relative humidity of 75% for NaCl. To test the effect of moisture absorption on various excipients, one tablet is preserved as a control (without super disintegrant). Weight changes in the pills are meticulously weighed and documented.

Table 2. Patented technologies for Mouth Dissolving Tablets [33]

S.no	Patented technology	Method	Handling/storage of dosage form	Drug release/bioavailability	Active moiety	Company
1.	DURASOLV TECHNOLOGY (CIMA, LABS,INC)	Direct compression method. Effervescent DI is used. Lightly compressed and individual taste masking butits containing a better mechanical strength	Packaged in a foil or bottles or blisters.	DI-depending upon the tablet size. DI time:5-45 sec	zolmitri ptan	Cima Labs, Inc., 10000 Valley Hill Road, Eden Prairies,

				No changes in drug bioavailability		MN, USA
2.	ORASOLV TECHNOLOGY (CIMA, LABS, INC.)	Effervescent DI used materials are lightly compressed. Direct compression method. Individual taste masking used	There is no required for a specially designed pick and place packed system for a soft and fragile tablet	DI- depending upon the tablet size. DI time: 5-45 sec There is no significant change in drug bioavailability	Paracetamol	Cima Labs, Inc., 10000 Valley Hill Road, Eden Prairies, MN, USA
3.	ZYDIS TECHNOLOGY (R.P.SCHERER, INC.)	Lyophilization method or unique freeze drier is to formulated tablets. MDTs with the active drug in a water-soluble matrix, and transformed into the blister pockets and its remove the water	Fragility and poor stability during storage under the stressful conditions, this dosage form are packed into blister package and moisture proof foil is the secondary pack for this dosage form. its very moisture sensitive.	DI time:2-10 sec These may allow for a pre-gastric absorption. These absorption leads to increase the bioavailability	Loratidine	R. P. Scherer, Frankland Road, Swindon, UK
4.	WOWTAB TECHNOLOGY (YAMANOUCHI PHARMACEUTICALS, INC.)	Direct compression method is used for the molded tablets. Proprietary taste masking is used.	Avoid subjection to moisture or humidity (RH). Blister packs and bottles are used in packaging of this dosage form.	DI- depending upon the tablet size. DI time: 15 sec or less. There is no significant change in drug bioavailability	Famotidine	Yamanouchi Pharmaceuticals, 1050 Arastradero Road, Palo Alto, CA, USA
5.	FLASHDOSE (FUISZ TECHNOLOGIES, LTD.)	Direct compression method is used. Individual spinning mechanism producing a floss-like crystalline from as cotton candy process	Avoid subjection to moisture or humidity (RH). Its requiring a specialized packaging of this dosage form.	DI time: within 1 minute. It enhances the bioavailability.	Ibuprofen	Prographarm, Chateaufort-en-Thymeriaia, France

6.	FLASHTAB (PROGRAPHAM GROUP)	Compressed dosage form and its drug a microcrystals structure as cotton candy process	These are requiring only conventional tableting technology	Dissolves within 1 minute. It enhances the bioavailability	Tramadol hydrochloride	Fuisz Technologies, 14555 Avion At Lakeside, Chantilly, VA, USA
7.	QUICK – DIS TECHNOLOGY	Lyophilization or freeze-dried method is used	It provides in various packaging configurations, unit-dose pouches to multiple-dose blister package	DI Time:5-10 seconds & 30seconds. It enhances the bioavailability	Film none	Lavipharm laboratories Inc.
8.	QUICKSOLV TECHNOLOGY	Lyophilization or freeze-dried method is used. These are patented for taste masking technology	It protects the drug powder in microencapsulated particles is more pliable	These are dissolves within 1 minute.	Risperidone	Janssen Pharmaceutica, 1125 Trenton-Harbourton Road, Titusville, NJ, USA

Table 3. Drugs are incorporated in the mouth dissolving tablets

S.no	Categories	Drugs
1.	Anti-malarial	Chloroquine, Mefloquine, Pyrimethamine
2.	corticosteroids	Betamethasone, Prednisone, Hydrocortisone, Beclomethasone
3.	Anti-hypertensives	Amoldipine, Prazosin hcl, Nifedipine, Minoxidil
4.	Anti-diabetics	Glipizide, Tolbutamide, Chlorpropamide, Tolazamide
5.	Anti-bacterial agents	Tetracycline, Erythromycin, Doxycyclin, Ciprofloxacin
6.	Anti-histamines	Cetirizine, Loratadine, Triprolidine, Cinnarizine
7.	Anti-protozoal agents	Tinidazole, Omidazole, Metronidazole, Benzidazole

8.	Diuretics	Acetazolamide, Furosemide, Spirinolactone, Amiloride
9.	Anti-fungal agents	Ketoconazole, Griseofelvin, Nystatin, Fluconazole, Amphotericin
10.	Anti-thyroid agents	Carbimazole, propylthiouracil
11.	Analgesics and Anti-inflammatory agents	Ibuprofen, Ketoprofen, Indomethacin, Mefenamic acid, Naproxen, Piroxicam
12.	Anti-gout agents	Allopurinol, Probenecid, Sulphinpyrazone
13.	Anti-parkinsonism agents	Bromocriptine mesylate, Lysuride maleate
14.	Nutritional agents	Vitamin A, Vitamin C, Vitamin K, Beta-carotene, Vitamin E
15.	Local- anaesthetics	Lidocaine
16.	Anxiolytic, sedatives, hypnotics, and neuroleptics	Meprobamate, Lorazepam, Alprazolam, Chlordiazepoxide
17.	Opioid analgesics	Morphine, Methadone, Pentazocine, Nalbuphine
18.	Stimulants	Amphetamine, Dexamphetamine, Pemoline, Fenfluramine
19.	Sex hormones	Testosterone, Oestradiol, Norgestrel, Methyltestosterone, Progesterone
20.	Oral-vaccines	Polio, Tetanus, Hepatitis, Dengue fever, Rubella, Rabies, Diphtheria

CONCLUSION

Mouth dissolving tablets give a wide range of advantages. Improved absorption, patient compliance, and effectiveness are all benefits as compared to other oral dosage forms. When developing a new tablet, it's essential to take all of these things into consideration. Initially, prescription ODT products were designed to alleviate dysphagia in pediatric, geriatric, and psychiatric patients. To ensure patient compliance in the later phases of patient-oriented dosage forms. Faster onset, enhanced bioavailability, less side effects, and improved security are all advantages that modern advances in manufacturing provide tablets. As new pharmaceutical excipients continue to be developed, MDTs should anticipate to see even more revolutionary advances in the near future.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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