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RESEARCH ARTICLE

SUPERDISINTEGRANTS: AN EFFECTIVE TOOL IN MOUTH DISSOLVING TABLETS

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ABSTRACT

Nearly 35% of general population associated with a number of health-problems like Parkinsonism, mental disability, motion sickness, allergic rhinitis, hypertension and cardiac failure. To overcome such problems, certain innovative drug delivery systems, like Mouth Dissolving Tablets (MDT) have been developed specially for geriatrics and paediatrics patients. Mouth dissolving tablets offers rapid disintegration so as it dissolve very fast in saliva & then easily swallowed without the need of water which is a major benefit over conventional dosage form. The popularity and usefulness of the formulation resulted in development of several mouth dissolving tablet technologies for preparation. In recent past, several manufacturing technologies such as sublimation technique, spray drying technique…etc. are employed to overcome the limitations of conventional tablet dosage forms. Once the mouth dissolving tablets are prepared they are required to be evaluated for various parameters so as to have long term stability and better therapeutic efficacy.

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INTRODUCTION

Amongst the various routes of drug delivery, oral route is the most preferred to the patient and the clinician s alike. The most common way to give medication is orally or by mouth, in which the patient swallows (Ashish *et al*., 2011). A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit dose powders and granules (Kumar *et al*., 2013). From the dosage forms developed for facilitating ease of medication and enhance the patient compliance, mouth dissolving tablet (MDT) is the most widely preferred commercial products (Yadav, 2014). Mouth dissolving tablet is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing (Shukla, 2009). Mouth dissolving drug delivery systems (MDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time offer added advantages over the traditional dosage forms. MDDDS offer the luxury of much more accurate dosing than the primary alternative, oral liquids (Kaushik *et al*., 2004). MDTs are known by various names such as "Fast-melting, Fast –dissolving, Oral disintegrating or Orodisperse." The European Pharmacopoeia defines the term "Orodisperse" as a tablet that can be placed in the mouth where it disperses rapidly before swallowing.

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Recently fast dissolving drug delivery system approved by the united state pharmacopoeia (USP), centre for drug Evaluation and Research (CDER), (Patel, 2014). The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking (Siddiqui, 2010; Fu *et al*., 2004).

Ideal Features of Mouth Dissolving Tablets: (Kumari *et al*., 2014 and Gupta, 2012)

- They should have pleasant mouth feel.
- Quick disintegration and dissolution of the dosage form.
- No need of water to swallow the dosage form.
- Ease of administration to the patient who cannot swallow such as the elderly, pediatric.
- They should allow high drug loading.
- They should be compatible with taste masking and other excipients

Oral Mucosa

Many different routed are employed to produce a systemic pharmacological effect of any drug in which oral route is the most common method from which drug swallowed and directly enters into the systemic circulation through the membrane of small intestine. A drug can be administered via a many different routes to produce a systemic pharmacological effect. The oral route of drug administration is the most important method of administering drugs for systemic effect, in which the absorption of drugs may occur at the various body sites

between the mouth and rectum. Commonly, the higher up a drug is absorbed, the more rapid will be its action. A drug taken orally must withstand large fluctuation in pH as it travels along the gastrointestinal tract, and resist the onslaught of the enzymes that digest food and metabolism by micro flora. It is estimated that 25% of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor resulting in high incidence of non compliance and ineffective therapy (Deshmukh *et al*., 2012). The structure of oral mucosa is shown as Figure 1.

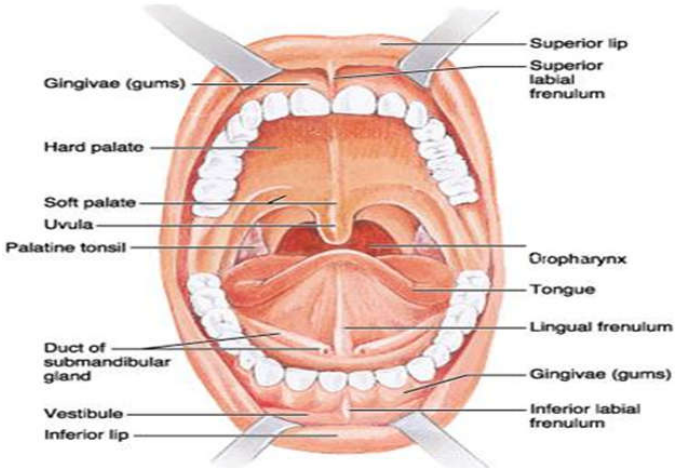
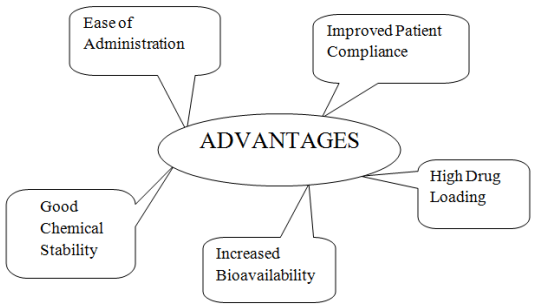


Figure 1. Structure of Oral Mucosa

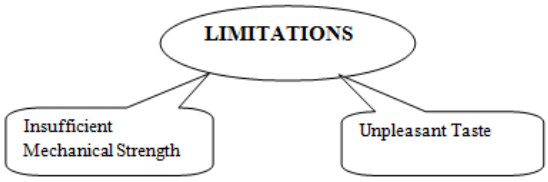
Advantages of oral route: (Deshmukh, 2012)

- It bypasses the GI tract and hepatic portal systems, increase the bioavailability of orally administered drugs which can otherwise undergo hepatic first pass metabolism.
- It improves patient compliance.
- Apart from it the drug is protected from degradation due to pH and GIT enzymes.

Advantages (Khirwadkar and Dashora, 2012; Chotaliya and Chakraborty, 2012)



Limitations (Kumari and Sharma, 2014)



Challenges in formulating mouth dissolving tablets

Palatability: Mostly all drugs are unpalatable. Mouth dissolving tablets contain medicament in taste mask form which upon administration, disintegrates or dissolves in patient[s] oral cavity, thus releasing the active ingredients which come in contact with taste buds hence taste masking of the drugs become critical to patient compliance (Abdurrahman *et al*., 2014).

Mechanical strength and disintegration time

The prime challenge of mouth dissolving tablets is to maintaining the mechanical strength. Many MDTs are fragile and the chances of these fragile tablets will break during packing, transport or handling by the patients. Tablets based on technologies like Zydis need special type of packaging. It is very natural that increasing the mechanical strength will delay the disintegration time. So a good compromise between these two parameters is always essential (Aher, 2015).

Hygroscopicity: Many mouth dissolving dosage forms are hygroscopic in nature. And cannot maintain physical integrity under normal conditions like temperature and humidity. Hence they need protection from humidity which calls for specialized product packaging (Shaikh, 2010).

Size of tablet: The size of tablet is another important challenge in formulation of mouth dissolving tablets. The degree of ease when taking a tablet depends on its size. It has been noticed that the easiest size of tablet to swallow is 7-8 mm and the easiest size to handle was one larger than 8mm. Therefore, the tablet size is both easy to take and easy to handle (Amin, 2006)

Main ingredients used in preparation of Mouth Dissolving Tablets

Drug property: For the ideal mouth dissolving tablet technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of fast dissolving tablets (Sreenivas, 2005).

Taste masking: Taste masking is an essential requirement for mouth dissolving tablets for commercial success. Artificial sweeteners and flavours are used along with other taste masking techniques to improve the efficiency of these techniques (Nayak, 2011).

Superdisintegrants: For the faster disintegration of mouth dissolving tablets, various types of superdisintegrants are commonly used. These are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But they are hygroscopic in nature. So they are not used with moisture sensitive drugs. And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the absorption of water leading to an increase in the volume of granules to promote disintegration (Kumar, 2011).

Types of Superdisintegrants

- Natural
- Synthetic

Natural: Various natural superdisintegrants are used in the formulation of mouth dissolving tablets, due to following reasons.

- Local accessibility
- Eco – friendly
- Bio acceptable
- Renewable source and low price as compared to synthetic products.

and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients. For these types of disintegrates maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. The wicking and swelling process of disintegration is Due to disintegrating particle/particle repulsive forces (Modasiya, 2009).

Table 1. Mechanism of Action of Natural Superdisintegrants

Natural Polymer	Marketed product	Concentration	Mechanism of Action
Gum Karaya	Amlodipine	4%w/w	Rapid disintegrating property
Fenugreek seed Mucilage	Metformin Hydrochloride	4%w/w	Better disintegrating property
Soy Polysaccharides	Lornoxicam	8%w/w	Better disintegrating property
Mango peel pectin	Aceclofenac	0.1-4%w/w	Higher swelling index
Mangifera indica Gum	Paracetamol	6%w/w	Binder and Emulsifier
Lapidium sativum	Nimesulide	10%w/w	Binding property
Guar gum	Glipizide	1%w/w	Thickening agent
Hibiscus rosa sinensis mucilage	Aceclofenac	6%w/w	Suspending agent

Table 2. Mechanism of Action of Synthetic superdisintegrants

Example (Synthetic)	Superdisintegrants	Mechanism of action	Special comments
Crosslinked cellulose	crosscarmellose® Ac-Di -Sol® Primmelose®	Swells 4-8 folds in < 10 Seconds. Swelling and wicking both	Swelling is in two dimensions. -Direct compression or granulation -Starch free
Crosslinked PVP	Crosspovidone	Swells 7-12 folds in 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Crosslinked starch	Sodium starch Glycolate	Swells 7-12 folds in 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Cross linked alginic acid	Alginic acid NF	Rapid swelling in aqueous Medium wicking action.	Promote disintegration in both dry or wet granulation

Synthetic: Synthetic superdisintegrants are also widely used in the formulation of mouth dissolving tablets like crospovidone, carmellose, sodium starch glycolate, ion exchange resins (indion 414).

Advantages of synthetic superdisintegrants are….

- Effective in low concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly. (Singh *et al*., 2015; Gupta *et al*., 2013)

Mechanism of action of Super- disintegrant

Swelling: Swelling is the main mechanism of superdisintegrants. Tablet with high porosity show poor disintegration due to lack of adequate swelling force. Sufficient swelling force is exerted in the tablet with low porosity. Disintegration again slows down (Malke, 2009). The Mechanism of action of swelling superdisintegrants is shown as Figure 2.

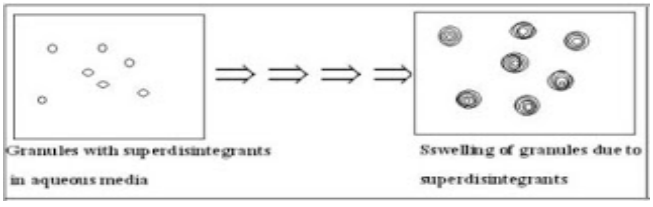


Figure 2. Swelling Mechanism of Super- disintegrants

By capillary action (wicking): When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet

The Mechanism of action of Wicking superdisintegrants is shown as Figure 3.

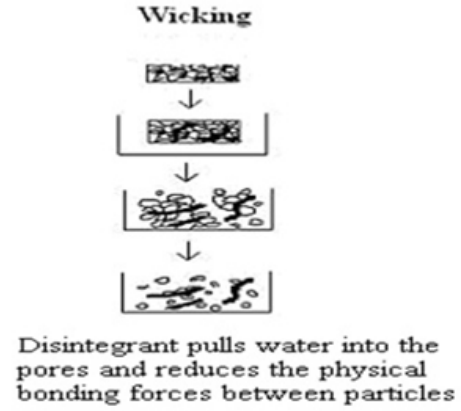


Figure 3. Wicking Mechanism of Super- Disintegrants

Due to deformation: During tablets compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablets (Gandhi, 2012). The Mechanism of action of deformation superdisintegrants is shown as Figure 4.

Heat of wetting: When disintegrants with exothermic properties get wetted, localized stress is created due to capillary

air expansion, which aids in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents (Yadav, 2014).

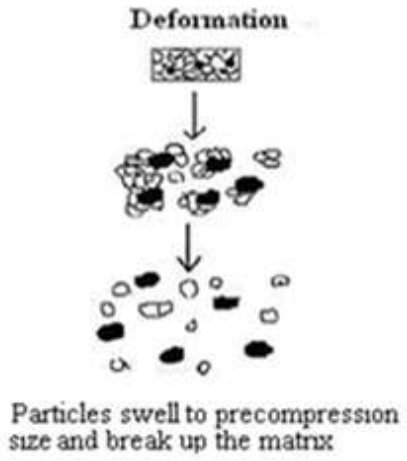


Figure 4. Deformation Mechanism of Super Disintegrants

By enzymatic reaction: These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous Increase in the volume of granules to promote disintegration (Bushra *et al*., 2008). The Mechanism of action of Superdisintegrants is shown as Figure 5.

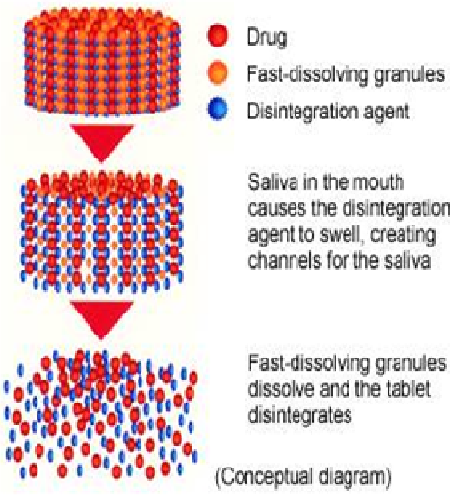


Figure 5. Mechanism of Superdisintegrants

Approaches for preparation of MDTs: (More, 2013; Ray; Chowdary *et al*., 2013 and Momin, *et al*., 2015)

Various approaches are used for preparation of mouth dissolving tablets. They are….

- Freeze drying or lyophilization
- Sublimation
- Direct compression
- Spray drying
- Moulding
- Mass extrusion

Freeze drying or lyophilization:

It is one of the first techniques for preparing FDT, in which sublimation of water takes place from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation.

Steps for Freeze drying process

- Material is frozen to bring it below the eutectic point.
- Primary drying to reduce the moisture around 4% w/w of dry product.
- Secondary drying to reduce the bound moisture up to required final volume.

Due to lyophilization, bulking agent and sometimes drug acquire glossy amorphous structure and thus dissolution is enhanced. The tablets prepared by freeze drying or lyophilisation are very porous in nature and disintegrate or dissolve rapidly when it comes in contact with saliva.

Sublimation

This process involves addition of some inert volatile substances like urea, urethane, camphor etc to other excipients and compression of blend into tablet. Removal of volatile material by sublimation creates pores in the tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Fast dissolving tablets with highly porous structure and good mechanical strength have been developed by this method. The Technique of Sublimation is shown as Figure 6.

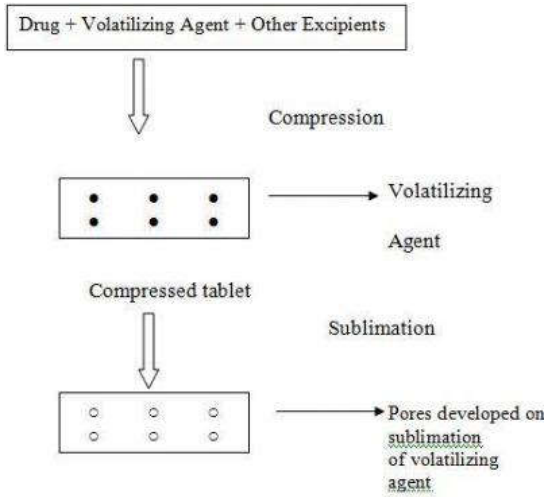


Figure 6. Sublimation process

Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. The disintegration and solubilization of directly compressed tablets

depends on single or combined action of disintegrants, water soluble excipients and effervescent agents' used. Breakage of tablet edges during handling and tablet crack during the opening of blister alveolus, all result from insufficient physical resistance. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can promote improved dissolution or disintegration properties. But the main problem of using effervescent excipients is that they are highly hygroscopic in nature. The steps involved in direct compression technique are shown as Figure 7.

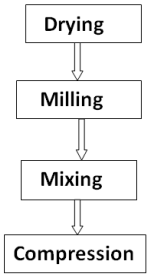


Figure 7. Steps involved in Direct Compression Technique

Spray drying

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution. The spray drying technique is shown as Figure 8.

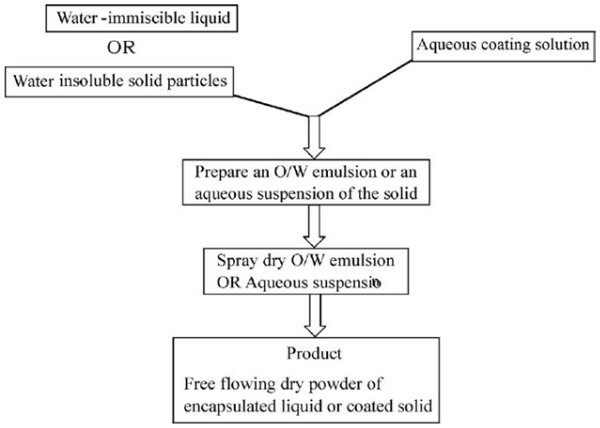


Figure 8. Spray drying process

Mass extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product which is finally cut into even segments with the help of heated blades to get tablets.

Moulding

Moulding process is of two type's i.e. solvent method and heat method. Solvent method involves damping the powder blend using an alcoholic solvent and later on compressing at low pressure in molded plates to form a wet mass (compression moulding).The solvent is then removed by air-drying. The tablets prepared by this technique are less compact than compressed tablets and posses a porous structure that accelerates the dissolution. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30ºC under vacuum. The mechanical strength of molded tablets is to be notified and hence binding agents are mixed to give strength. Taste masking is an additional trouble in this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cotton seed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization method, tablets formed by the molding technique are easier to upgrade for industrial manufacture. The steps involved in Moulding technique are shown as Figure 9.

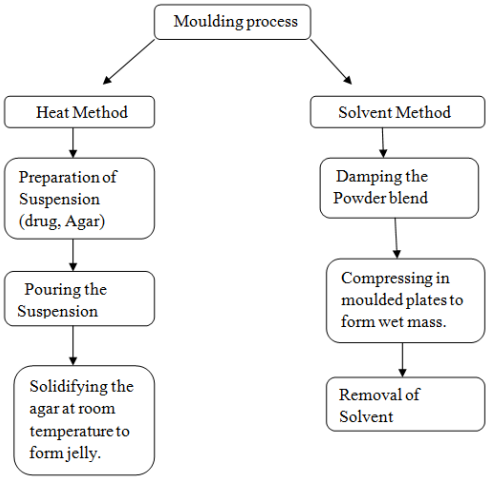


Figure 9. Steps involved in Moulding process

The List of Patented Technologies for mouth dissolving tablets is shown as Table 3.

Drug Candidates for Mouth dissolving Tablets (Kaur, 2011):

- Anti bacterial agents: ciprofloxacin, Tetracycline, sulphadiazine, penicillin
- Antidepressants: Trimipramine Maleate, Amoxapine, Trazodone HCL.
- Anthelmintics: Albendazole, Mebendazole, Dichlorophen.
- Antidiabetics: Glipizide, Tolbutamide, Tolazamide.
- Antihypertensive: Nifedipine, Amlodipine, Carvedilol.
- Analgesics: Diclofenac sodium, Ibuprofen, Ketoprofen.
- Antihistamines: Cetrizine, Loratadine, Triprolidine.

- Diuretics: Furosemide, spironolactone, Acetazolamide.
- Antiprotozoal agents: Metronidazole, Tinidazole, Omidazole.
- Gastro-intestinal agents: Cimetidine, RanitidineHCL, Omeprazole.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet Thickness: Tablet thickness is an important characteristic in reproducing appearance and also in couting by using filling equipment.

Table 3. List of Patented technologies for MDTs: (Gupta *et al*., 2014)

Patented technology	Basic of technology	Developing company	Brand names
Zydis	Lyophilization	RP.Scherer Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
Quicksolv	Lyophilization	Jansen Pharmaceutical	Cisapride monohydrate(Propulsid Quicksolv), Risperidone(Risperdal M-tab)
Flashtab	Lyophilization	Ethypharm	Ibuprofen (Nurofen Flashtab)
Lyoc	Multiparticulate Compressed tablets	Farmlyoc	Phloroglucinol Hydrate (Spasfon Lyoc)
Orasolv	Compressed tablets	Cima Labs Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan(Zolmig Repimelt)
Durasolv	Molding	Cima Labs Inc.	Hyoscyamine Sulfate(NuLev), Zolmitriptan (ZMT)
Ziplets	Molding	Eurand	Ibuprofen (Cibalgina Due Fast)
Oraquick	Micromask taste Masking	KV Pharm. Co., Inc.	Hyoscyamine Sulfate ODT
AdvaTab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetrizine, AdvaTabParacetamol

Table 4. Mouth dissolving tablet products available in Market: (Saurabh *et al*., 2012)

BRAND NAME	ACTIVE INGREDIENT	APPLICATION	COMPANY
Clarittin RediTabs	Loratadine	Antihistamine	Scherig corporation
Feldene Melt	Piroxicam	NSAIDs	Pfizer
Maxalt –MLT	Rizatritpan benzoate	Migrane	Merck
Pepeid ODT	Femotidene	Anti-ulcer	Merck
Zyperxa	Olazepine	Psychotropic	Eli Lilly
Zofran ODT	Olandansetron	Antiemetic	Galaxo Smith kline
Resperdal M-Tab	Resperidone	Schizophrenia	Janssen
Zubrin (Pet drug)	Tepoxelin	Canine NSAIDs	Scherig corporation
Zelapar	Selegiline	Parkinsons disease	Elanl Amarin corporation
Klonopin wafer	Clonazepam	Sedation	Roche
Abilify Discmelt	Aripiprazole	Antipsychotics	Otsuka America/Bristol-Myers Squibb
Allegra ODT	Fexofenadine	Antihistamine	Sanofi Aventis
Aricept ODT	Donepezil	Acetylcholinesterase inhibitors.	Eisai Co.
Alavert Quick Dissolving Tablets	Loratadine	Antihistamine	Wyeth
Benadryl Fastmelt	Diphenhydramine and Pseudoephedrine	Antihistamine	Warner Lambert, NY, USA
Romilast	Montelukast	Antiasthmatic	Ranbaxy lab.Ltd.New Delhi
Zomig –ZMT	Zolmitriptan	Serotonin	Astra Zeneca.
Rybix ODT	Tramadol	Opioid	Victory Pharma.
Domary MD	Domperidone	Anti emetic	Ray Ramedies

Evaluation parameters of Mouth dissolving Tablets (Bharti *et al*., 2012; Mishra *et al*., 2014; Abdul Sayeed *et al*., 2011 and Indian Pharmacopoeia, 1996):

- General appearance
- Size and shape
- Tablet thickness
- Weight variation
- Hardness
- Friability
- Wetting time
- Water absorption ratio
- In vitro dispersion time
- In vitro dissolution test

General appearance

The general appearance of tablets its visual identity and overall elegance is essential for consumer acceptance and tablet$_s$ size, shape, colour, presence or absence of odour, taste and surface texture of any identifying marking.

Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets are taken and their thickness is recorded by using micrometer.

Weight Variation: 20 tablets were selected randomly from the lot and are weighed individually and check for weight variation. Weight variation specification as per I.P

Hardness: Hardness of the tablet is defined as a force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends upon its hardness. Hardness of tablet of each formulation is determined by using Monsanto Hardness Tester.

Friability: Friability of the tablet determined by using Roche Friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablet is placed in the friabilator and are subjected to the 100 revolutions.

$$F = W_{initial} - W_{final} / W_{initial}$$

Wetting Time: Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose a tablet is placed on a piece of tissue paper folded twice and kept into a small petri dish containing 6ml of water, and the time of complete wetting is measured.

Water absorption ratio: A piece of tissue paper folded twice in place in a small petri dish containing 6ml of water. A tablet was put on the paper and the time required for the complete wetting is measured. The wetted tablet is then weighed. Water absorption ratio is determined by using following equation

R=10(wa/wb)

Where w_a is weight of tablet before water absorption and wb, is weight of tablet after water absorption

In vitro dispersion time: In vitro dispersion time can be measured by dropping a tablet in a beaker containing 50ml of sorenson[s] beffer PH 6.8. Three tablets of each formulation are randomly selected and in vitro dispersion time is performed.

In vitro dissolution Test: The development of dissolution methods for MDTs is comparable to the approach taken for conventional tablets and is practically identical. Dissolution condition for drugs which are listed in pharmacopoeia monograph is a good place to start with scouting runs for a bioequivalent MDT. Other media such as 0.1M HCL and buffer (4.5 and 6.8) should be evaluated for MDT much in the same way as their ordinary tablet counterparts. It has been USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used.

Conclusion: The popularity of MDTs has increased tremendously over the last decade because of better patient acceptance and compliance and may offer improved biopharmaceutical properties, For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules improved efficacy, and better safety compared with conventional oral dosage forms.

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