Review Article

MOUTH DISSOLVING TABLETS: AS A POTENTIAL DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT

In the present scenario, there is an ever increasing demand for more patient compliant dosage forms. One of an important innovation in this direction is the development of mouth dissolving tablets that dissolve or disintegrate instantly upon contact with recipient's tongue or buccal mucosa. They have proved to be ideal for geriatric and pediatric population, people suffering from dysphagia, clinical conditions where water intake is not available and for drugs undergoing high first pass metabolism. Mouth dissolving tablets (MDT) are the one which suit the concept of better patient compliance, rapid absorption, rapid onset of action, more efficacy, enough bioavailability to show required pharmacological action and less toxicity. It is found that about 26% of patients experience difficulty to swallow the solid dosage forms like tablets and capsules etc. MDTs show rapid disintegration or dissolution in no time through various mechanisms when placed over the tongue without the need of water and overcome the disadvantages of conventional solid dosage forms. Mouth dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. The aim of this review is to describe the past and the present of mouth dissolving tablet dosage form.

Keywords: Mouth dissolving tablets, Buccal mucosa, First pass metabolism, Patient compliance.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of its manifold advantages it provides to the patients like ease of ingestion, avoidance of pain, versatility, accurate dosing, cost effective and most importantly the patient compliance[1]. Of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. The reason for this preference are that, the tablets and capsules represent unit dosage forms in which one usual dose of the drug has been accurately placed. By comparison, liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions, and elixirs, suffer from the drawbacks of inaccuracy of dosage and inconvenience of transportation and handling[2]. Although tablets and capsules are the most popular solid dosage forms but evident drawback of this dosage forms for some patients, is the difficulty to swallow. This difficulty in swallowing or dysphagia is currently affecting approximately 55% of the general population[3]. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[4]. Such types of tablets are known as mouth dissolving tablets (MDT).

These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form[5]. Mouth dissolving tablets (MDT) are also called as orally disintegrating tablets, orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, immediate release tablets, porous tablets, and rapimelts. United States Food and Drug Administration (FDA) defined MDT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for MDTs generally ranges from several seconds to about a minute. Recently, European Pharmacopoeia has used the term 'Orodispersible tablet' for tablets that disperses readily and within 3 min in mouth before swallowing. Mouth dissolving tablets are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques. Tablets of this type are designed for children and the elderly or for any patient who has difficulty in swallowing tablets[6].

The target populations for these new mouth dissolving/disintegrating dosage forms have generally

been pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea, who are travelling, or who have little or no access to water are also good candidates for mouth dissolving tablets[7]. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain a healthy life. Children may also have difficulty in ingesting because of their underdeveloped muscular and nervous systems. It has been reported that in case of Dysphagia (difficulty in swallowing), which is common among all age groups and in some cases like motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets also become difficult. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy[8]. A survey of 6158 GP patients conducted in Norway indicated that approximately 26% of all patients do not take their prescribed medication as they encountered problems when swallowing conventional tablets. The main complaints often dealt with the size, surface and taste of the tablets. Oral mouth dissolving tablets help overcome some of these problems: the rapid disintegration of the tablet into a solution (containing the drug) enables those who find difficulty in, or experience discomfort when swallowing, to have a more 'patient friendly' experience[9]. Mouth dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance.

Drug Delivery to the Oral Cavity

Drug delivery via oral cavity is promising owing to ease of administration and a rich supply of blood and lymphatic vessels. In addition, this route offers high permeability to drugs and good reproducibility. Drugs absorbed via the buccal mucosa enter the systemic circulation directly through the jugular vein. This ensures a rapid onset of action and avoids first- pass liver metabolism, gastric acid hydrolysis, and intestinal enzymatic degradation[10]. Of the range of pharmaceutical preparations available for administration into the oral cavity, the most popular form is that of a mouth dissolving tablet that releases its drug contents for absorption across the oral mucosa. Various parts of oral cavity are shown in Fig.1.

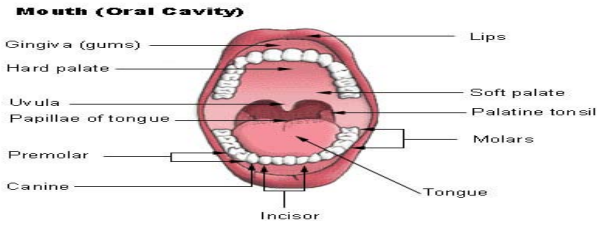

Figure 1: Various parts of mouth (oral cavity)

Blood is richly supplied to the salivary glands and their ducts by branches of the external carotid artery and afterwards, travelling through the many branch arteries and capillaries, returns to the systemic circulation via the jugular veins. The presence of saliva in the mouth is important to drug absorption for two main reasons:

1. Drug permeation across moist (mucous) membranes occurs much more readily than across nonmucous membranes.

2. Drugs are commonly administered to the mouth in the clinical setting in a solid form. The drug must, therefore, first dissolve in saliva before it can be absorbed across the oral mucosa; that is, the drug cannot be absorbed directly from a tablet.

Advantages of Mouth Dissolving Tablets[11]

i) Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. ii) Allows high drug loading. iii) Alternative to liquid dosage form. iv) Formulation is cleared from the esophagus especially in the supine position without lodging or sticking to it when swallowed, thus offering improved safety. v) Cost effective. vi) No risk of choking vii) New business opportunities; line extension, exclusively of product promotion and patent life extension.

Characteristics of Ideal Mouth Dissolving Tablets[12]

i) They should not require water for administration yet dissolve or disintegrate in the mouth within a few seconds. ii) They should have pleasing mouth feel. iii) They should leave minimal or no residue in the mouth after oral administration. iv) They should allow high drug loading. v) They should be compatible with taste masking agents and other excipients. vi) They should exhibit low sensitivity to environmental conditions like humidity and temperature. vii) They should have sufficient mechanical strength to withstand the vigorous of the manufacturing process and post manufacturing handling. viii) They should be adaptable and amenable to existing processing and packaging machinery.

VARIOUS TECHNIQUES FOR MOUTH DISSOLVING TABLETS

The mouth dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to develop mouth dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

1) Freeze drying technology: Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless. Lyophilization is relatively expensive and time consuming

manufacturing process. Other drawback includes fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition[12,13].

2) Tablet moulding technology: Moulded tablets are designed to facilitate fast absorption of drugs through the mucosal lining of mouth by inclusion of water-soluble ingredients. The advantage of this system is that it has a porous structure which enhances dissolution (thereby enhanced bioavailability) and decreased first pass metabolism of certain drugs. As moulding process is employed usually with soluble ingredient (saccharides) which offers improved mouth feel and disintegration of tablets. However, moulded tablets have low mechanical strength, which results in erosion and breakage during handling.

Different moulding techniques can be used to prepare mouth dissolving tablets:

a. Compression moulding: The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

b. Heat moulding: A molten matrix in which drug is dissolved or dispersed can be directly moulded into orodispersable tablets.

c. No vacuum lyophilization: This process involves evaporation of solvent from a drug solution or suspension at a standard pressure[14].

3) Spray drying technology: Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing mouth dissolving tablets. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium[15, 16].

4) Direct compression method: Direct compression is a process by which tablets are compressed directly from mixtures of the drug and excipients, without any preliminary treatment[17]. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. In many cases, the superdisintegrants have a major role in the disintegration and dissolution process of mouth dissolving tablets made by direct compression. The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate. The addition of other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties[18]. The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets due to certain advantages:

a. High doses can be accommodated and final weight of the tablet can exceed that of other methods.

b. Easiest way to manufacture the tablets.

c. Conventional equipment and commonly available excipients are used

d. A limited number of processing steps are involved.

e. Cost-effectiveness.

Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration and high dissolution rates[18,19].

5) Sublimation technology: The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation[20]. Sublimation is a process in which water passes directly from solid state to vapour state without passing through liquid state. This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in 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[21]. Various steps involved in sublimation technique for preparation of MDT are shown in Fig. 2.

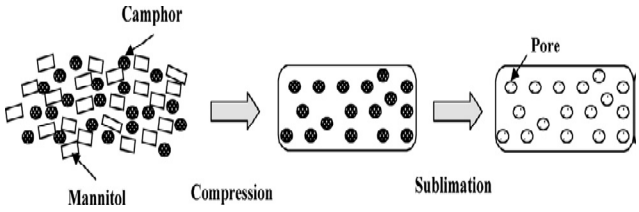

Figure 2: Schematic view of the preparation of a porous tablet using sublimation of camphor

6) Mass-extrusion technology: This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste[22].

7) Melt granulation technology: Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time

consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin[23]. This approach to prepare MDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate, PEG-6-stearate)[24].

8) Phase transition process: MDTs were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min(as shown in Fig.3) After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol[25].

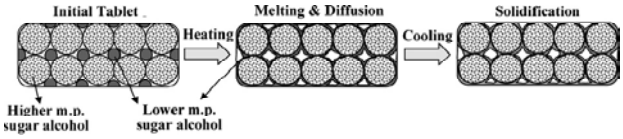

Figure 3: Schematic illustration of a mouth dissolving tablet prepared by the phase transition method using a higher melting sugar alcohol and a lower melting sugar alcohol.

9) Cotton Candy Process: The cotton candy process is also known as the "candy floss" process and forms the basis of the technologies such as Flash Dose (Fuisz Technology). An MDT is formed using a candyfloss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candyfloss can then be milled and blended with active ingredients and other excipients and subsequently compressed into ODT. However the high processing temperature limits the use of this technology to thermostable compounds only[26].

DIFFERENT PATENTED TECHNOLOGIES

1) Zydis Technology: Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. Tablet is prepared by lyophilization of the drug in a matrix of water soluble carrier (eg. Gelatin). The tablet dissolves in the mouth within seconds after placement on the tongue[27]. More than twenty products are currently available using Zydis technology. In the U.S., they include: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis.

Advantages

i) The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. ii) The Zydis formulation is self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. iii) The combination of lyophilization and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch.

Disadvantages

i) Process is expensive and time consuming. ii) Zydis tablets are light weight and fragile, thus unsuitable for conventional blister packaging. iii) The Zydis formulation has poor stability at higher temperatures and humidities. If there is any pinhole or minor damage to the package, the patient may find the lyophilized product has collapsed due to absorption of moisture[28].

2) Orasolv Technology: OraSolv is Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. Orasolv technology is an oral dosage form that combines taste-masked drug ingredients with an effervescent excipient system and requires conventional manufacturing process and equipment. The OraSolv technology is utilized in more than eight marketed products: four Triaminic Softchew formulations, Tempra FirsTabs, and Remeron SolTab.

Advantages

i) Orasolv dosage forms have been developed containing >1000mg of active load and are capable of combining multiple active ingredients in a tablet. ii) Low degree of compaction used in orasolv avoids the fracture of the particle coating being used for taste-masking. Lyophilization and high degree of compaction (used in other techniques) may disrupt such a taste-masking approach.

Disadvantages

i) The tablets are very soft and friable. ii) The Orasolv tablets take 15-60 seconds to dissolve in the mouth, which is longer than fast melting oral dosage forms[29].

3) Durasolv Technology: DuraSolv is Cima's second-generation mouth-dissolving/disintegrating. In this technology active ingredient is mixed into a matrix containing non-direct compression filler, a relatively high lubricant content and a wicking agent and then compressed into tablets. Durasolv is an appropriate technology for products requiring low amounts of active ingredients. DuraSolv is currently available in more than four products.

Advantages

i) DuraSolv has much higher mechanical strength than Orasolv, due to the use of higher compaction pressures during tableting. The DuraSolv product is thus produced in a faster and more cost-effective manner. ii) DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials.

Disadvantages

i) The technology is not compatible with larger doses of active ingredients, because the formulation is subjected

to high compaction pressure. The structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound[30].

4) Wowtab Technology: The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients, which display high aqueous solubility and sweetness and hence, imparts taste masking and a pleasing mouth feel[31]. Mizumoto. *et al.,* have classified sugar-based excipients into two types based on their mouldability and dissolution rate[32].

Type I Saccharides: lactose and mannitol exhibit low mouldability and a high dissolution rate.

Type II Saccharides: maltose and maltitol exhibit high mouldability and low dissolution rate.

The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate[32, 33].

The Wowtab product dissolves quickly in 15 seconds or less.

Advantages

i) Sufficient hardness to maintain the physical characteristics of the dosage form during production until it comes in contact with moisture such as saliva in mouth. ii) More stable to the environment than Zydis or Orasolv product due to its significant hardness. iii) Suitable for both conventional bottle and blister packaging. iv) The taste-masking technology utilised in Wowtab offers a superior mouthfeel due to the patented smoothmelt action. v) High dissolution rate and high mouldability due to two types of saccharides used.

Disadvantages

It cannot be used in patients of diabetes and other sugar related problems[34].

5) Flashdose Technology: Flashdose utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as Ceform and serves as an alternative method of taste masking[35].

6) Flash Tab Technology: It is a rapid method to produce the disintegrable multiparticulate tablet. The ingredient mixture is suitable for imparting a faster disintegration rate in the mouth (< 60 seconds), due to the presence of active substance in the form of coated microcrystals or uncoated microgranules. Coated multiparticles of active ingredients have the advantage of taste masking. These may be prepared by using conventional techniques like coacervation, microencapsulation, and extrusion-spheronisation.

Advantages

i) Conventional tableting techniques are used. ii) The produced tablets have high mechanical strength. iii) Taste- masking is effectively done by coating the microcrystals[36].

7) Quicksolv Technology: This technology is patented by Janssen Pharmaceuticals. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling[37].

8) Lyoc Technology: Lyoc technology is patented by pharmalyoc. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Nonhomogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered[38].

9) Ziplets Technology: Recently Eurand (Pessano con Bornago, Italy) developed the Ziplets technology, which can be used with water insoluble compounds as both bulk actives and as coated microparticles (the latter containing soluble and/or insoluble drugs). In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in a much longer disintegration time. As the soluble components dissolve on the tablets outer layer, the rate of the water diffusion into the tablet core decreases because of the formation of concentrated viscous solutions[39].

10) Oraquick Technology: The Oraquick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives[40].

Various patented technologies with their company name and the list of active ingredients manufactured by them are listed here under in Table 1.

Table 1: List of various Patented technologies with their Company and Product Name

S. No.	Patented Technology	Basis of Technology	Technology developed by Company	Active Ingredient (Brand Names)
1	Zydis	Lyophilization	R.P.Scherer, Inc	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve).
2	Orasolv	Direct compression	Cima Labs, Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt).
3	Durasolv	Direct compression	Cima Labs, Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)
4	Wowtab	Direct compression	Yamanouchi Pharma Tech. Inc.	Famotidine (Gaster D)
5	Flashdose	Cotton Candy Process	Fuisz Technology. Ltd.	Tramadol HCl (Relivia Flash dose)
6	Flashtab	Direct compression	Ethypharm	Ibuprofen (Nurofen FlashTab)
7	Quicksolv	Lyophilization	Janssen pharmaceutics	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal MTab)
8	Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate(Spasfon Lyoc)
9	Ziplets	Direct compression	Eurand International	Ibuprofen (Cibalgina DueFast)
10	Oraquick	Micromask taste masking	KV Pharm.Co.,Inc.	Hyoscyamine Sulfate ODT
11	Advatab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetrizine, AdvaTab Paracetamol

Reported Advances in Mouth Dissolving Tablet Dosage Forms:

Table 2: Recently used drugs along with super disintegrant added and method adopted for preparation of mouth dissolving tablet dosage form.

S.NO	DRUGS	SUPERDISINTEGRANT	METHODS	REFERENCES
1	Granisetron Hydrochloride	Kolliodon CL, Explotab, Camphor, Citric Acid, Ammonium Bicarbonate, Sodium Bicarbonate,	Direct Compression, Sublimation Method, Effervescent Method.	43
2	Oxcarbazepine	Polyplasdone XL10 Primojel, Ac-Di-Sol	Direct Compression	44
3	Aceclofenac	CP, CCS, SSG	Direct compression	45
4	Felodipine	CP, SSG	Direct Compression	46
5	Losartan Potassium	Polyplasdone XL 10, CCS, Explotab	Direct Compression	47
6	Carbamazepine	CCS, CP, SSG	Direct Compression	48
7	Domperidone	Camphor, CP	Sublimation method	49
8	Celecoxib	SSG	Holt Melt Extrusion, Direct Compression	50
9	Amlodipine Besylate	Ac-Di-Sol, SSG, Kollidon-CL Camphor	Sublimation Method	51
10	Lornoxicam	KYRON T-314 (Polacrillin Potassium), Menthol	Wet Granulation Technique	52
11	Nimesulide	CCS, CP	Direct Compression	53
12	Promethazine HCL	SSG, CP,CCS, Pregelatinised Starch	Direct Compression	54
13	Salbutamol Sulphate	Primojel, Kollidon-CL, L-HPC	Direct Compression	55
14	Tramadol HCl	SSG, D-mannitol	Extrusion/ Spheronization Process	56
15	Cinnarizine	CP,CCS, L-HPC	Sublimation Method	57
16	Rosiglitazone	SSG, CP, CCS	Direct Compression	58
17	Meloxicam	CP, SSG	Sublimation	59
18	Promethazine Theoclate	CP	Direct compression	60
19	Zopiclone	CCS, polyplasdone XL 10, MCC	Direct compression	61
20	Levocetrizine HCl	SSG, CP,CCS	Direct compression	62
21	Chlorpromazine HCl	SSG, CP,CCS, L-HPC, Pregelatinised Starch	Direct compression	63
22	Etoricoxib	CP, CCS, L-HPC, L-HPMC, SSG	Direct Compression	64
23	Ibuprofen	CCS, MCC, SSG	Direct Compression	65
24	Metronidazole	CP, Pregelatinised Starch, L-HPC	Direct Compression	66
25	Nimesulide	CP	Direct Compression	67
26	Ketorolac Tromethamine	Ac-Di-Sol, Polyplasdone XL, Explotab	Direct Compression	68
27	Omeprazole & domperidone	SSG, Ac-Di-Sol, Kollidon CL,	Direct Compression	69
28	Tizanidine Hydrochloride	CCS, SSG, CP	Granules – Mass Extrusion	70
29	Metronidazole	SSG, Chitosan, Bamboomanna, & Combination	Direct Compression	71
30	Oxcarbazepine	CP, CCS, MCC	Direct Compression	72
31	granisetron hydrochloride	SSG,CCS, CP	Direct Compression	73
32	Aloe vera	CCS, CP, SSG	Dry Granulation Method	74
33	Famotidine	CCS, SSG, Camphor	Sublimation	75
34	Granisetron	SSG, CP,CCS	Wet Granulation	76
35	Aceclofenac	SSG, CCS, Starch 1500	Wet Granulation method	77
36	Haloperidol	CCS, SSG, CP	Direct Compression Method	78
37	Furosemide	CCS, Xylitol	Direct Compression	79
38	Etoricoxib	Menthol, CP	Sublimation Technique	80

CP – Crospovidone, CCS - Croscarmellose Sodium, SSG - Sodium Starch Glycolate, MCC - Microcrystalline Cellulose, L-HPC - L- Hydroxy Propyl Cellulose

Table 3: List of Currently Available Mouth Dissolving Tablets

Product	Manufactured by/for	Active ingredient	Category
Abilify Discmelt	Otsuka America/ Bristol-Myers Squibb	Aripiprazole	Atypical antipsychotics
Alavert Quick Dissolving Tablets	Wyeth	Loratadine	Anti-histamines
Allegra ODT	Sanofi Aventis	Fexofenadine	Anti-histamines
Aricept ODT	Eisai Co.	Donepezil	Acetylcholinesterase inhibitors
Benadryl Fast Melt	Pfizer	Diphenhydramine	Anti-histamines
Calpol Fast Melts	McNeil Healthcare UK	Paracetamol	Analgesics
Clarinex RediTabs	Schering-Plough	Desloratadine	Anti-histamines
Claritin RediTabs	Schering-Plough	Loratadine	Anti-histamines
Clonazepam ODT	Par Pharmaceutical	Clonazepam	Benzodiazepines (Anxiety, Seizure Disorders)
FazaClo	AzurPharma	Clozapine	Antipsychotics
Jr. Tylenol Meltaways	McNeil Consumer Healthcare	Acetaminophen	Analgesics, Anti-pyretics
Klonopin Wafers	Roche	Clonazepam	Benzodiazepines
Loratadine Redidose	Ranbaxy	Loratadine	Antihistamines
Maxalt-MLT	Merck & Co.	Rizatriptan	Triptans/Serotonin agonists (acute Migraine)
Mirtazapine ODT	Teva Pharmaceuticals	Mirtazapine	Antidepressants
Nurofen Meltlets	Reckitt Benckiser	Ibuprofen	NSAIDs
Ondansetron ODT	Teva Pharmaceuticals	Ondansetron	Antiemetics
Orapred ODT	Sciele Pharma	Prednisolone	Corticosteroids
Parcopa	Schwarz Pharma	Carbidopa/levodopa	Parkinson's disease
Prevacid SoluTab	Takeda Pharmaceuticals	Lansoprazole	Proton pump inhibitors
Remeron SolTab	Schering-Plough	Mirtazapine	Antidepressants
Risperdal M-Tab	Janssen	Risperidone	Atypical antipsychotics
Unisom SleepMelts	Chattem	Diphenhydramine	Anticholinergic (Nighttime Sleep Aid)
Zelapar	Valeant Pharmaceuticals Int'l	Selegiline	Parkinson's disease (MAOIs)
Zofran ODT	GlaxoSmithKline	Ondansetron	Antiemetics
Zomig-ZMT	AstraZeneca	Zolmitriptan	Triptans/Serotonin agonists (Migraine)
Zyprexa Zydis	Eli Lilly and Company	Olanzapine	Atypical antipsychotics
Citalopram ODT	Biovail	Citalopram	Major Depressive Disorder
Metoclopramide Zydis	Salix Pharmaceuticals	Metoclopramide	Antiemetics
Reglan ODT	Schwarz Pharma	Metoclopramide	Antiemetics
Tramadol/Acetaminophen ODT	Biovail	Tramadol/Acetaminophen	Opioid analgesic
Zolpidem ODT	Biovail	Zolpidem	Hypnotics

EVALUATION OF MOUTH DISSOLVING TABLETS [2,41,42]

Evaluation of MDTs is done using various tests and parameters. Following tests are performed to evaluate MDTs:

1) Weight Variation: According to I.P. procedure for uniformity of weight, twenty tablets are taken and their weight is determined individually and collectively on an electronic weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Average weight of Tablets (mg)	Maximum percentage deviation allowed
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

2) Thickness: Thickness of tablets is determined using Vernier caliper. An average value is calculated by using tablets in triplicate and then the mean ± standard deviation values of thickness are notified.

3) Tablet Hardness: Hardness of tablet is defined as the 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 on its hardness. Hardness in case of MDTs is kept low to allow rapid disintegration in mouth. It is done by using hardness tester like Pfizer hardness tester or Monsanto tablet hardness tester.

4) Friability: Friability is measured of mechanical strength of tablets. Roche friabilator is used to determine the friability by following procedure. A preweighed tablet is placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for 4 minutes for 100 revolutions. At the end of test, tablets are reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as;

% Friability = Loss in weight / Initial weight x 100

5) Disintegration Time: The test is carried out using the disintegration apparatus. Phosphate buffer (pH 6.8) maintained at 37ºC ± 2ºC is used as a disintegration media and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured.

6) Wetting Time: A piece of tissue paper folded twice is placed in a small petridish containing 6ml. of distilled water. A tablet is carefully placed on the surface of the paper and the time required for water to reach the upper

surface of the tablet is noted as the wetting time. Less is the wetting time, indicates more porous the tablet[6].

7) Water Absorption Ratio: Water absorption ratio 'R' was determined using the equation, R=100 (Wb-Wa) / Wa Where,

Wa is weight of tablet before water absorption and Wb is weight of tablet after water absorption[6].

8) *In vitro* Drug Release Studies: The *in vitro* drug release is studied using USP dissolution apparatus II (paddle type) at 50 rpm in 900 ml of phosphate buffer (pH 6.8) at 37±0.5ºC. At different time intervals, 10 ml of sample is withdrawn and filtered. An equal volume of the medium is introduced into the container after each withdrawal to maintain a constant volume. The absorbance of the samples is determined by UV Spectrophotometer at given λ_{max}. The mean values of drug released are plotted as cumulative % drug release vs. time.

FUTURE PROSPECTIVES

Future prospectives in the development of mouth dissolving tablets is bright and the various technologies used are still relatively new. Tablets prepared by these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. Various drugs which have limited bioavailability, low-molecular weight, high permeability or which degrade rapidly in the stomach can be successfully formulated in the form of mouth dissolving tablets as these tablets are absorbed through oral cavity and thus pregastric absorption of drugs avoid hepatic metabolism, which reduces the dose and increases the bioavailability. Thus MDT may be developed for most of the drugs like anti-coagulants, anti-gout agents, anti-hypertensive agents, anti-neoplastic agents & immunosuppressants, anti-thyroid agents, corticosteroids, lipid regulating agents, proteins, peptides and recombinant drugs, nutritional agents, neuro -muscular agents, in the near future. Now days due to advancement in technology, various manufacturing and evaluation techniques for MDTs are available and research is in process to develop other categories of drugs (which are not available in the form of MDTs) in such dosage forms.

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