1.1 INTRODUCTION

The development of an appropriate dosage form for older people, children, bedridden patients, mentally retarded, uncooperative, nauseated patients been widely desired as it become difficult for these patients to swallow conventional tablets (Kremzar L. et al, 1998). Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration, leading to high level of patient compliance (Kremzar L et al, 1998, Hanawa T, 1995). To the make the best use of oral cavity we are going for ODTs production to ensure maximum absorption via mucous membrane.

Orodispersable tablets (ODTs), being best alternative of conventional tablets, defined as a solid dosage form containing medicinal substance that disintegrates within a matter of seconds when placed upon tongue (Hanawa et al, 1995). Two different types of dispersible tablets distinguished as one that disintegrates/dissolves instantaneously in the mouth and to be swallowed without the need for drinking water (Bi Y Sunada et al, 1996), while the other tablet formulation can be readily be dispersed in water to form a dispersion (Brown D et al, 2003) which is easy to ingest by the patient (Sandri G et al, 2006). The ODTs formulations have interesting features like exceptional taste masking ability (Fu Y Yang, et al 2004), extremely low disintegration time, and pleasant mouth feel (Orjales Venero, et al, 1993). The drugs which are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach and in such cases bioavailability of the drug is increased, pre-gastric absorption can result in improved bioavailability (Martin T.P et al, 1993 ) and as result of reduced dosage, improved clinical performance through a reduction of unwanted effects (Pandya, H et al,1998).

United States Food and Drug Administration (FDA) (Watanabe Y et al,1995) defined mouth dissolving and mouth disintegrating tablets are “A solid dosage form containing medicinal substances or active ingredients which disintegrate rapidly usually within a matter
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of seconds when placed in mouth and its contact with saliva. Mouth dissolving and mouth disintegrating tablets are offering the combined advantages of both liquid and conventional dosage form but our aim of this review is to provide the basic difference between mouth dissolving and mouth disintegrating tablets. One of the major problems with this drug is its very poor solubility in biological fluids that results into poor bioavailability after oral administration. The solubility enhancement of poorly soluble compounds can be induced by changes in temperature, solvation properties using different cosolvent compositions, and by inclusion compound formation.

1.2 Mouth Dissolving Tablets (MDT)

Currently oral delivery is the gold standard in the pharmaceutical industry, where it is regarded as the safest being most convenient and economical method of drug delivery that having the highest patient compliance. Tablets designed to dissolve on the buccal (cheek) mucous membrane were a precursor to the MDT. Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. A fast disintegration time and a small tablet weight both can enhance absorption in the buccal area.

The first MDTs disintegrated through effervescence rather than dissolution, and were designed to make taking vitamins more pleasant for children. Dissolution became more effective than effervescence through improved manufacturing processes and incorporation of ingredients (such as the addition of mannitol which increase the binding and decrease dissolution time (Blank et al, 1990).

The first ODT form of a drug to get approval from the U.S. Food and Drug Administration (FDA) was a Zydis ODT formation of Claritin (Loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (Clonazepam) in December 1997 and a Zydis ODT formulation of Maxalt (Rizatriptan) in June 1998. (FDA guidance issued in Dec 2008 is that ODT drugs should disintegrate in less than 30 seconds) (Wehling Fred et al, 1993).
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1.2.1 Advantages of Mouth Dissolving Tablets

a. Ease of Swallowing: Dysphagic population is 35% of the general population, since this disorder is associated with a number of medical conditions such as stroke, Parkinson’s disease, AIDS, Head and Neck Radiation Therapy and other neurological disorders. Easily administered by the patients who cannot swallow, such as bed ridden patients, elderly and stroke victims; patients who could not swallow, such as renal failure; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients. Increase the bioavailability of the drug and rapid absorption through pregastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down (Behnke K, Sogaard J, et al, 2003, Dollo G, et al, 2003).

b. Good mouth feel property of true mouth dissolving tablets helps to change the perception of medication as “bitter pill” (Brown, 2003)

c. Convenience of administration and accurate dosing, as compared to liquid formulations.

d. Patient Convenience for bedridden patients and for travelling and busy people who do not have ready access to water (Gafitanu A, 1991). The mouth dissolving dosage forms do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water.

e. New Business opportunity comes in the market like line extension, product differentiation, patent extension and life cycle management.

f. Rapid Action: Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

g. Obstruction Free: No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

h. Enhanced Palatability: Good mouth feel, especially for paediatric patients as taste masking technique is used to avoid the bitter taste of drug.

i. Superior Taste: Most mouth dissolve dosage forms contains taste masking active ingredient, usually, sweetening agent and a flavour.
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j. Accurate Dosing: Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.

k. Rapid drug therapy intervention is possible.

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently, more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for paediatric and geriatric patients (Bhusan SY, 2000, Wadhwani AR, 2004). Many patients, elderly people and person with dysphagia find it difficult to swallow the tablets and hard gelatine capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy. Addition of effervescent system in the formulation is one of the approach by which mouth dissolving tablets can be prepared (Michaelson 1983, F Wehling 1996). The major advantages with effervescent formulation approach that it is a well established, easy to implement and mask the bitter taste of drug. The effervescent system is generally composed of a dry acid and dry base which when react facilitate a mild effervescent reaction when the tablets contacts saliva. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to evolution of carbon dioxide the bitter taste of drug is also masked and a pleasant mouth feel is felt (Banker G S et al, 1990). Soluble effervescent tablets get quickly dissolved when put in water to give a sparkling solution with good taste which can be easily consumed by patients with dysphagia. Citric acid (CA) is very hygroscopic and it poses challenge to formulators hence, it was selected. Also market preparations like ENO and DISPIRIN contain CA and hence they were selected so that comparison of humidity resistance of our formulation can be made. It is also helpful for patients having prolonged illness who are prone to nauseatic sensations if they have to swallow a tablet. The added advantage of this formulation is faster onset of action as compared to standard compressed tablet. The properties of the water dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity
after dispersion are necessary to investigate during manufacturing which decides the product performance (Chang R et al, 2000)

1.2.2 Essential Requirement of MDTs

1. No need of water for administration as it should disintegrate, disperse and dissolves in mouth within seconds. (Susijit Sahoo et al, 2010)

2. Should have a pleasant mouth feel
   a. with improved taste
   b. without any residue in the mouth after disintegration to avoid rough texture of tablet.

3. Patient compliance should be one of the most valuable requirements.

4. Adequate mechanical strength should be posses and durable to withstand the rigors of manufacturing and handling.

5. It should have low sensitivity to environmental conditions (temperature and humidity).

6. It should be cost effective also an should be Adaptable and amenable to existing process and packaging machinery.

1.2.3 Important criteria for excipients used in the formulation of MDTs

1) It must be able to disintegrate quickly. (Seager H, 1998)

2) It should not have any interaction with the drug and other ingredients or excipients such as agents used for taste masking of bitter drug.

3) It should not interfere in the efficacy and organoleptic properties of the product.

4) The concentration of the binder must be in adequate range and the binder should not affect the final integrity means disintegration and stability of the product.

5) The properties of all the ingredients should not affect the MDTs.

6) The excipients used to formulate MDTs should have melting point in range of 30-35°C.
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1.3 CHALLENGES IN FORMULATION OF MDTs:

1.3.1 Taste masking of drugs

MDT technology is relatively new to the industry and had a significant impact on patients of all ages and taste masking being an essential requirement for MDTs for commercial success. Taste-masking of bitter or with objectionable-tasting drug substances is critical for any orally-administered dosage form. Less commonly, active pharmaceutical ingredients to be incorporated are tasteless and do not require taste masking. Taste masking of bitter drugs become necessity in case of oral administration and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug.

1.3.2 Quick disintegration of tablets

In the case of MDTs, the total stay time of tablet in mouth remains few seconds (less than 60sec.) and has to disintegrate and dissolve within mouth in the salivary fluid so quick disintegration of MDTs being an important step for success of MDTs and may be achieved by different mechanism as(Mitrevej, A 1982, Shangraw, RF., Mitrevej A et al,1980)

a. Swelling and Deformation:

Swelling and deformation believed to be a mechanism in which disintegrant (superdisintegrant) impart the disintegration when added to the tablet formulation and works on the mechanism that disintegrant swells upon water absorption, breaks the tablet matrix due to induced localized stress within the tablet (figure 1.1) and thereby increasing the available space area and also promoting a more rapid release of the drug substance.

![Figure 1.1: Tablet disintegration by swelling and deformation of disintegrating agents](image-url)
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b. Porosity and Capillary Action (Wicking)

This mechanism imparts its action by making the tablet porous and provides the pathway for penetration of fluid into the tablet (figure 1.2). With low cohesiveness and compressibility, fluid tends to be drawn or wicked into these porous pathways through capillary action and rupturing of the particular bonds causes the tablet to break apart.

Figure 1.2 Quick Dissolution mechanism using porosity

c. Enzymatic Reaction

Enzymes present in the body break the bond between particle and help in disintegration by accelerated absorption of water leading to enormous increase in the volume of granules to promote disintegration for example, in colon targeted drug delivery, tablets prepared using guar gum disintegrated in the colon by \textit{E. coli}

d. Release of Gases

Interaction between Sodium bicarbonate and citric acid produces carbon dioxide which generates pressure within the tablet and causes the disintegration of the tablet and must be added to the formulation either immediately prior to compression or can be added in two separate fractions of formulation.

It is believed that no single mechanism is responsible for disintegration, but rather, it is more likely the result of inter-relationships between these major mechanisms.
1.3.3 Industrial Adaptability

To make adaptable at industrial manufacturing, MDTSs should have adequate mechanical strength and durable to withstand the rigors of manufacturing (Chang, R.K et al, 2000), handling and low sensitivity to environmental conditions (temperature and humidity) as well as cost effectiveness with adaptable and amenable to existing process and instruments (Dobetti L et al, 2000).

1.3.4 Patient compliance

MDTs overcome all the genuine swallowing problems and prevent convert refusal in uncooperative patients in acute setting (Dowson, AJ. et al, 2003.), potentially reducing conformation with medical staff and must be compatible in term of taste (Carpay J et al, 2004), appearance, absence of grittiness (undissolved particles), no water requirement along with minimum time of stay in mouth.

1.4 TASTE MASKING

Organoleptic properties are important considerations for development of a solid oral dosage form that can influence consumer preference and compliance. In the case of bitter drugs, taste is one of the most important parameter governing patient compliance (Patel et al, 2009) and oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers especially for pediatric and geriatric (Sohi et al, 2004). Chewing large pieces of gum or tablet is difficult for elderly patient and sometimes experiences the bitter or unpleasant taste of drug if the taste masking coatings rupture during mastication. Bitter sensation is the result of signal transduction from the receptor organs containing very sensitive nerve endings, which produce and transmit electrical impulses (Reilly et al, 2002). Masking the bitter taste of drugs by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste.
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1.4.1 Taste Masking Technologies

Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor (Brahmankar et al, 1995). Popular approaches in the development of taste masking in liquid dosage form include use of flavor followed by viscosity modification and if failed, by ion exchange resin (Fig. 1.3). In case of solid dosage form, chemical modification (Prodrugs and salt formation), Host Guest locking, solid dispersion method effectively masked the unpleasant taste. Drug particle coating technique successfully masks the taste in all type of formulation.

Fig. 1.3 Taste Masking Technologies uses in liquid and solid dosage forms
a. **Flavor Modification and Sweeteners**

Using flavors from natural or synthetic sources, being simplest approach for taste masking, unpleasant taste of drugs modified (Pokharkar *et al.*, 2005). Flavors and sweeteners overwhelm the unpleasant taste by occupying the taste buds and thus suppressing the taste of drug. Traditionally, slight bitter and sour taste of drugs are effectively masked by the citrus fruits, however, this method fails in case of highly bitter drugs and used to improve the palatability of formulations. Flavors and sweeteners chosen based on their specific taste and release profiles e.g. Sweeteners like sodium saccharin, acesulfame potassium (aspartame) give instant sweetness, whereas sweeteners like monoammonium glycyrrhizate give lingering sweetness and used either alone or in combination.

b. **Viscosity Modification**

Enhancement of viscosity in liquid formulations by thickening agents such as natural gums or carbohydrates can mask the unpleasant taste of drug by formulating a covering layer on the tongue and act as barrier between drug particles and taste buds, thus lowering the diffusion of drug from saliva into the taste buds (Popescu *et al.*, 1991). For viscosity enhancement in liquid formulations, polyethylene glycols and carboxy methylcellulose are induced which not only increases the stability of liquid formulation but surprisingly, provides taste masking of unpleasant tasting medicines. For examples, in cough syrups, terbutaline given in doses of 4mg/5ml can be effectively administered by increasing the viscosity of the formulation.

c. **Host Guest Locking Method**

In host guest locking method, host molecule has a cavity in which the guest drug occupies and the taste of the guest drug masked by two approaches (Lachman *et al.*, 1976) as

a. By decreasing its oral solubility on ingestion and

b. By decreasing the amount of drug particles exposed to taste buds, reducing the perception of bitter taste.
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Cyclodextrins are widely used in industry due to their ability to form inclusion complexes with a variety of molecules. Cyclodextrins are cyclic oligosaccharides composed of 6, 7, 8 glucose molecules (alpha-beta or gamma respectively) having supramolecular structures that involve intramolecular interactions (Martin, 2004). Bitterness elimination is depend upon the extent of Complexation of guest molecule with host, value of complex association constant, temperature and the host / guest ratio. For bitter drug forming a 1:1 complex with cyclodextrins, more than 99% of the bitter drug is complexed with cyclodextrins and as complexed molecule cannot react with the taste bud in the buccal cavity, no bitter taste perceived (Szejtli et al, 2005) and suppression of bitter taste by cyclodextrin was increase in increasing order of alpha, gamma, and beta cyclodextrin.

d. Drug Particle coating

Involves the covering total surface of particle with enough coating so that the taste is not apparent to the users and mask the bitter taste of drug. Any nontoxic polymer that is insoluble at pH 6.2 and soluble at acidic pH would be acceptable to coat the bitter drugs and should be inert in nature.

Methods used for polymer coating are

i. Fluidized Bed / Spray Coating: In fluidized bed coating, powders as fine as fifty micrometer fluidized in an expansion chamber by means of heated, high velocity air and the drug particles coated with a coating solution as a spray through the nozzle.

ii. Microencapsulation: is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Different methods used for Microencapsulation are air suspension, coacervation phase separation, solvent evaporation, spray drying and congealing, pan coating technique (Bakan, 1986) (Rattes et al, 2007). In practice Microencapsulation by spray drying is conducted by dispersing a core material in coating solution in which the coating solution is dissolved and then by atomizing the mixture into an air stream.

iii. Extrusion coating: technology involves softening of active blend using the solvent mixture of water soluble PEG, menthol and expulsion of softened mass through the
extruder or syringe to get a cylindrical product and these cylindrical shaped products used to coat granules of bitter taste drugs and masks the taste (Katsuragi et al., 1995).

e. **Taste Masking by Ion Exchange Resins**

Ion exchange resins are water insoluble, cross linked high molecular weight polyelectrolytes containing salt forming groups in repeating position on the polymer chain which exchange their mobile ion of equal charge with the drug molecule (Shishu et al., 2009). As taste perception of bitter drugs is experienced in the mouth at taste buds, complexed drugs resinate does not release drug in mouth due of scarcity of exchangeable ions (at pH 6.7) in the saliva and when complex comes in contact with GIT fluids (at acidic pH), complex is broken down quickly and drug is release (Swarbik et al., 2003). Resins being polyelectrolyte have extensive binding sites leading to very high drug loading ability (Bhalekar et al., 2004, Pisal et al., 2004). Ion exchange resins have received considerable attention because of their versatile properties as drug delivery vehicles, chemically inert and free from local and systematic side effects (Manhas et al., 2004) (Spinger et al., 1981) possess long-term safety even while ingesting large doses and also compatible with all conventional solid, semisolid and liquid dosage forms (Jain, 2001). Ion exchange resin classified in four major groups, strong acid cation exchange resin, weak acid cation exchange resin, strong base anion exchange resin, weak base anion exchange resin (Chandira et al., 2009). Majority of oral preparation containing bitter drugs use cation exchange resins for taste masking (Manek et al., 1998). Bitter cationic drugs get absorbed on to weak cationic exchange resins of carboxylic acid functionally to form the complex, which is not bitter. To bind the drug with resin, the drug repeatedly exposed with resin for prolonged contact and drug attached to the oppositely charged resin through weak ionic bond, so the dissociation of the drug-resin complex dose not occurs under salivary pH conditions, which suitably masks the unpleasant taste of drug. Strong acid cation exchange resins used for masking the taste of basic drug functions through out the entire pH range whereas weak acid cation exchange resin functions at pH more then six. Strong base cation exchange resin function through out the entire pH range (Satpathy, 2007).
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f. Solid Dispersion:

Dispersion of one or more active ingredients in an inert carrier or matrix in solid state is utilizes in solid dispersion for masking the bitter drugs (Liberman et al, 1987) and approaches used are melting method, solvent method and melting solvent method. Chiou and Riegelman defined solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixture”. In melting method, drug and solid carrier melted together, cooled and solidified whereas in solvent method, taste masking done by dissolving the drug and carrier in common solvent followed by evaporation. For example, taste masking of artemether (Chaudhari, 2006) (ether derivative of artemisinin, a well known antimalarial drug) carried by solid dispersion technique using monoammonium glycyrrhizinate pentahydrate.

g. Multiple Emulsions

Multiple emulsions are complex poly dispersed systems having oil in water and water in oil emulsion simultaneously existence, stabilized by lipophillic and hydrophilic surfactants respectively (Khan et al, 2006), prepared by dissolution of drug in inner aqueous phase of w/o/w emulsion under good shelf stability condition (Rosoff et al, 1988). This technique successfully utilizes in masking the bitter taste of chloroquine (Rao et al, 1993) (broad-spectrum antimalarial drug).

h. Chemical Modification

i) Formation of salt or derivatives: Decreasing the solubility of drug by its salt formation makes the drug as tasteless as become less soluble in saliva so less sensitive to taste buds. For example Penicillin modified as N, N- di benzyl ethylenediamine diacetate salts or N, N bis (dehydroabiety) ethylene diamine salts is tasteless.

ii) Prodrug formation: Prodrug, a chemically modified inert drug precursors, which upon biotransformation converts into pharmacologically active parent compound shows its activity
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i. **Desensitizing agents**

Desensitizing agents like phenols, sodium phenolates desensitize the taste buds by interfering with taste transduction, the process by which taste message from the mouth to the brain and thus mask the taste of drug.

j. **Use of lipoproteins**

Lipoprotein composed of lipids (phosphatidic acid) and protein (β lactoglobulin) reduces the bitter taste of drugs most effectively by suppressing bitter taste (Katsuragi *et al*, 1995). Basic and hydrophobic drugs such as quinine, papaverine, denatortium, caffeine and L-Leucine and propranolol, theophylline are very bitter in taste and their taste is effectively suppressed by phosphatidic acid- lactoglobulin due to binding to the hydrophobic region of the receptor membranes leading to suppression of the responses to the bitter substances.

k. **Use of amino acids**

Amino acids and their salts (alanine, taurine, glutamic acid, glycine) in combination with bitter drugs reduces the bitterness of the drugs for example, taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets (Meyer *et al*, 1997).

1.4.2 **EVALUATION OF TASTE MASKING**

Evaluation of taste masking is tedious work as the taste sensation varies person to person and involves taste masking efficiency as quality control parameter and determining the rate of release of drug from taste-masked complex and asses by *in vivo* and *in vitro*.

1.4.2.1 **In vivo Evaluation** (*Hukla et al*, 2007)

*In vivo* taste evaluation carried out on a trained taste panel of healthy volunteers with organoleptic sense, with their prior consent. On placing the dosage form in mouth for 60 seconds, bitterness recorded against pure drug using a numerical scale. The numerical scale
may bear values as 0 = pleasant, 1 = Tasteless, 2 = No bitter but after taste give bitterness, 3= immediately gives bitterness, 4 = slightly bitter, 5 = extremely bitter.

*In vivo* assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues and can be time consuming and expensive.

1.4.2.2 *In vitro* Evaluation

Invention of “E-Tongue” electronic sensor array technology overcomes this problem, which is a device for recognition, quantitative multicomponent analysis and artificial assessment of taste and flavor. It recognizes three levels of biological taste including receptor level (Taste buds in humans, probe membranes in E-Tongue), circuit level (neural transmission in humans, transducer in E-Tongue), and perceptual level (cognition in the thalamus humans, computer and statistical analysis in the E-Tongue) (Murray, *et al*., 2004) (Krantz-Rulcker *et al*., 2005). The probes consist of a silicon transistor with proprietary organic coatings, which govern the probe’s sensitivity and selectivity, and measurement done potentiometrically. Each probe is cross selective to allow coverage of full taste profile and statistical software interprets the sensor data into taste patterns (Anand *et al*., 2007). Liquid samples directly analyzed without any preparation, whereas solids require a preliminary dissolution before measurement. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds. A potentiometric difference between each sensor and a reference electrode measured and analyzed by the E-Tongue software. Sensory analysis employs to measure and control taste and flavor quality during manufacturing process development, clinical use, stability studies, validation, commercial manufacturing and batch release (Anand, Vikas. *et al*., 2008). These data represent the input for mathematical treatment that will deliver results. The E-Tongue enables us to test taste accurately without the need for human volunteers at earlier stages of drug development. Furthermore, the E-Tongue cannot be poisoned and it won’t fatigue or lose its sense of taste after long periods of testing.

Taste masking of bitter drugs become necessity in case of oral administration and lot of technologies available that effectively mask the objectionable taste of drug but require
skillful application, which can improve product preference largely and selection of technology depends upon the bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug. Extensive work had been carried out till date in order to taste masking of bitter drugs and their evaluation. Despite the effect that a lot of dosage forms available in the market, still a lot of work needs to be done to standardize the techniques.

1.5. MANUFACTURING TECHNOLOGY FOR MDTs

1.5.1 Freeze Drying

A process in which water is sublimated from the product after freezing is called freeze-drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation. However, the use of freeze-drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs (Dobetti L 2001).

A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva (Gole. D.J,1993, Walter, 1994).

1.5.2 Moulding

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depend whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix (Dobetti L, 2001). It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix.
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Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution (Makino Yamada, 1993)

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is, in general, made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs. Moulded tablets usually are prepared from soluble ingredients by compressing a powder mixture previously moistened with solvent (usually water or ethanol) into mould plates to form wetted mass (compression moulding). Recently moulded forms also have been prepared directly from the molten matrix in which the drug is dissolved or dispersed (heat moulding) or by evaporating the solvent from the suspension at standard pressure (no-vacuum lyophilization).

Mouldability is defined as the capacity of the compound to get moulded or compressed. Wowtab is an intrabuccally dissolving compressed moulding comprising granules made with saccharides having low and high mouldability. Low mouldability means that the saccharides show reduced compressibility by tableting and rapid dissolution. By contrast, high moulding saccharides show excellent compressibility and slow dissolution. Wowtab can accommodate high doses of multiparticulate water soluble or insoluble drug and has adequate hardness.

1.5.3 Sublimation

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed by Heinnemann & Rose, (Heinemann H et al, 1976). Inert solid ingredients (ex. urea, urethane, ammonium carbonate, camphor, and naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure.
A method of producing fast dissolving tablet using water as the pore forming material has been described by Makino (Makino T Yamada et al, 1998). Compressed tablets containing D-Mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Koizumi, (Koizumi K et al, 1997), have developed a new method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material.

1.5.4 Spray-Drying

Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. Spray drying technique has been employed by Allen and Wang (Allen L V, 1998), to prepare fast dissolving tablets. They developed formulation by using mannitol as bulking agent, hydrolyzed and non-hydrolyzed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (ex. citric acid) and/or alkali material (ex. NaHCO3) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds.

1.5.5 Mass-Extrusion

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.

1.5.6 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
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exceed that of other production methods. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent (Caramella et al, 1990). Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance (Kamdar N.M, 2002).

Disintegrants have major role in the disintegration and dissolution process of Mouth Dissolving Tablets made by direct compression. 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 further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature.

The understanding of disintegrant properties and their effect on formulation has advanced during last few years; particularly regarding so called super-disintegrants. Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrant concentration and above that disintegration time remains approximately constant or even increases.

The simultaneous presence of disintegrant with a high swelling force called disintegrating agent and substances with low swelling force (starch, cellulose and direct compression sugar) defined as, "swelling agent" was claimed to be a key factor for rapid disintegration of tablet, which also offers physical resistance (Reddy, L.H et al, 2002).
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1.6 PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING TABLETS

1.6.1 Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When Zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The Zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength (Seager H, 1998).

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of Zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

1.6.2 Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

1.6.3 Orasolv Technology

CIMA labs have developed Orasolv Technology (Misra et al, 1999). In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral
dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

**1.6.4 Flash Dose Technology**

Fuisz has patented flash dose technology. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology (Yarwood, 1998) is the first commercial product launched by Biovail Corporation. Flash dose tablets consists of self-binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

**1.6.5 Wowtab Technology**

Wowtab Technology (Yarwood, 1998) is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

**1.6.6 Flashtab Technology**

Prographarm laboratories have patented the Flashtab technology (Mizumoto et al, 1996). Tablets prepared by this system consist of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, and extrusion-spheronisation. All the processing utilized conventional tableting technology.

**1.6.7 Frosta® Technology For Making Fast-Melting Tablets**

Akina has developed a new fast-melting tablet technology, called "Frosta®". The Frosta® approach utilizes conventional wet granulation processing and tablet machines for cost-effective production of fast-melting tablets. Frosta tablets are strong with friability much
1. Introduction

less than 1% and stable in open air environment. Conventional tablet machines are used for production of Frosta tablets, and no other special instruments are necessary.

1.6.8. Pharmaburst

Pharmaburst is SPI Pharma’s new easy to use “quick dissolve” tablet delivery platform. Pharmaburst is an “off the self” excipient, which allows developments of quick dissolve formulations in-house quickly and much more cost effectively.

1.7 COMPARATIVE STUDY

1.7.1 Mouth disintegrating tablets

Tablet that contains insoluble taste masking resins and super disintegrant to enhance the palatability and rate of tablet disintegration in the mouth and does not dissolve in saliva but formulate dispersion which is easy to swallow without the need for drinking water, can be well termed as Mouth Disintegration tablet rather than Mouth Dissolving Tablets. In mouth disintegrating tablets, the basic challenges in formulating MDTs handled as

1.7.1.1 Taste masking

Taste masking in mouth disintegrating tablets normally done by ion exchange resins (table 1.1), water insoluble cross linked high molecular weight polyelectrolytes containing salt forming groups in repeating position on the polymer chain (Swarbik J et al 2003.), chemically inert, free from local and systemic side effect which have the ability to exchange counterions in aqueous solution surrounding them.

As taste perception of bitter drugs is experienced in the mouth at taste buds, drug resinate complex does not release drug in mouth due of scarcity of exchangeable ions (at pH 6.7) in the saliva and when comes in contact with GIT fluids (at acidic pH), complex is broken down quickly and drug is release. Majority of MDTs containing bitter drugs use cation exchange resins for taste masking (table 1.1). Bitter cationic drugs get absorbed on to weak cationic exchange resins of carboxylic acid functionally to form the complex, which is not bitter. For complete taste masking of drug, higher concentration of resins (300-400 %) are exposed with drug for prolonged contact and drug attached to the oppositely charged
resin through weak ionic bond, so the dissociation of the drug-resin complex does not occur under salivary pH conditions, which suitably masks the unpleasant taste of the drug.

**Table 1.1: Commonly used ion exchange resins for taste masking of MDTs**

<table>
<thead>
<tr>
<th>Type</th>
<th>Matrix Structure</th>
<th>Commercial Resins</th>
<th>Taste masked drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weak cation</strong></td>
<td>Methacrylic acid Divinylbenzene</td>
<td>Indion 204, Tulsion T-335, Amberlite IRC 50</td>
<td>Gatifloxacin, Tramadol, Ondansterone, Norfloxacin, Ofloxacin, Roxithromycin,</td>
</tr>
<tr>
<td></td>
<td>Methacrylic acid Divinylbenzene</td>
<td>Tulsion T-339, Indion 234, Amberlite IRP 88</td>
<td>Diphenhydramine HCl, Ciprofloxacin, Chloroquine</td>
</tr>
<tr>
<td><strong>Strong cation</strong></td>
<td>Polystyrene Divinylbenzene</td>
<td>Indion 244, Dowex 50, Amberlite IR 120</td>
<td>Chlorpheneramine maleate, Ephedrine Hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Sodium polystyrene Divinylbenzene</td>
<td>Tulsion T-3, Amberlite IRP 69, Indion 254</td>
<td>Dicyclomine, Dextromethorphen, Pseudoephedrine, Buflomedil, Rantidine</td>
</tr>
</tbody>
</table>

**1.7.1.2 Quick Disintegration**

The basic principle in formulating mouth disintegrating tablets involved super disintegrant addition technique at optimum concentration to achieve rapid disintegration. Super disintegrants in comparison to classical disintegrant (starch) swell to many times their original size when placed in water while producing minimal viscosity effects (Gissinge, D. *et al*, 1980) for example Isapghula seeds have high swellability, gives uniform and rapid disintegration at concentration of 5-15% (Gorman, EA. *et al*, 1982). Commonly used super disintegrants are modified starch, sodium carboxymethyl starch, sodium starch glycolate, modified cellulose includes crystalline cellulose (Avicel) and low substituted hydroxy propyl cellulose (HPC), crosslinked polyvinylpyrrolidone (Kollidone) (Lalla, JK *et al*, 2004).
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Table 1.2: Few commercially available mouth disintegrating tablets

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active Drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alavert</td>
<td>Loratadine</td>
<td>Wyeth</td>
</tr>
<tr>
<td>Allegra ODT</td>
<td>Fexofenadine</td>
<td>Sanofi Aventis</td>
</tr>
<tr>
<td>Clarinex RediTabs</td>
<td>Desloratadine</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Claritin RediTabs</td>
<td>Loratadine</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Clonazepam ODT</td>
<td>Clonazepam</td>
<td>Par Pharmaceutical</td>
</tr>
<tr>
<td>FazaClo</td>
<td>Clozapine</td>
<td>AzurPharma</td>
</tr>
<tr>
<td>Klonopin Wafers</td>
<td>clonazepam</td>
<td>Roche</td>
</tr>
<tr>
<td>Lamictal ODT</td>
<td>lamotrigine</td>
<td>Eurand / GlaxoSmithKline</td>
</tr>
<tr>
<td>Loratadine Redidose</td>
<td>loratadine</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Maxalt-MLT</td>
<td>Rizatriptan</td>
<td>Merck &amp; Co.</td>
</tr>
<tr>
<td>Mosid-MT</td>
<td>Mosapride Citrate</td>
<td>Torrent pharmaceuticals</td>
</tr>
<tr>
<td>Nimulide-MD</td>
<td>Nimuslide</td>
<td>Panacea Biotech</td>
</tr>
<tr>
<td>Niravam</td>
<td>Alprazolam</td>
<td>Schwarz Pharma</td>
</tr>
<tr>
<td>Nurofen Meltlets</td>
<td>Ibuprofen</td>
<td>Reckitt Benckiser</td>
</tr>
<tr>
<td>Olanex Instab</td>
<td>Olanzapine</td>
<td>Ranbaxy Labs Ltd</td>
</tr>
<tr>
<td>Ondansetron ODT</td>
<td>Ondansetron</td>
<td>Teva Pharmaceuticals</td>
</tr>
<tr>
<td>Orapred ODT</td>
<td>Prednisolone</td>
<td>Sciele Pharma</td>
</tr>
<tr>
<td>Parcopa</td>
<td>Carbidopa/levodopa</td>
<td>Schwarz Pharma</td>
</tr>
<tr>
<td>Prevacid SoluTab</td>
<td>Lansoprazole</td>
<td>Takeda Pharmaceuticals</td>
</tr>
<tr>
<td>Remeron SolTab</td>
<td>Mirtazapine</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>Romilast</td>
<td>Montelukcast</td>
<td>Ranbaxy Labs Ltd</td>
</tr>
<tr>
<td>Torrox MT</td>
<td>Rofecoxib</td>
<td>Torrent pharmaceuticals</td>
</tr>
<tr>
<td>Zelapar</td>
<td>Selegiline</td>
<td>Valeant Pharmaceuticals Int'l</td>
</tr>
<tr>
<td>Zofran ODT</td>
<td>Ondansterone</td>
<td>Glaxowellcome Middlesex, UK</td>
</tr>
<tr>
<td>Zyprexa Zydis</td>
<td>Olanzepine</td>
<td>Eli Lilly and Company</td>
</tr>
</tbody>
</table>
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1.7.1.3 Industrial Strength

Industries generally follow adaptable, easy techniques to produce a product so manufacturing of mouth disintegrating tablets widely produced at commercial level due to their higher mechanical strength, ease of production and all of this done at low cost. The mechanical strength of these tablets gives better results in respect to its hardness, better handling, and ordinary packing (Dobetti L et al, 2000).

1.7.1.4 Patient compliance

In Patient compliance, absence of rough texture, grittiness being an important considerations and Mouth disintegrating tablets not up to the mark, that to be disintegrate using the salivary fluid within mouth. These MDTs consist of more than 70% insoluble ingredients including insoluble resins (20-30% w/w), Superdisintegrants (35-45% w/w) which on disintegration makes suspension of the whole slurry rather than solution and giving rough texture to mouth and patient incompliance (Dowson, AJ et al, 2003).

1.7.2 Mouth dissolving tablets

Mouth dissolving tablets comprises highly water-soluble excipients rather than insoluble taste masking and disintegrating excipients and concentrated on complete dissolution of all ingredients in saliva within few seconds giving good patient compliance. The basic principle for mouth dissolving tablets involves absence of any insoluble ingredients and major focus on maximizing the porous structure of the tablet matrix and incorporation of highly water soluble excipients (Lindgren S et al, 1993). Mouth dissolving tablets are easily administered by the patients who cannot swallow, such as bed ridden patients, elderly and stroke victims; patients who could not swallow, such as renal failure; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients. Good mouth feel property of true mouth dissolving tablets helps to change the perception of medication as bitter pill (Mallet L et al, 1996.)
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1.7.2.1 Taste masking

In mouth dissolving tablets, slight unpalatable taste can be masked successfully using flavors and sweeteners (table 1.3) for examples, Wowtab® used the so-called “smoothmelt action” of sugar and sugar like (e.g., mannitol) excipients (Mizumoto T., 2005.) and the Zydis® dosage form also uses these sweeteners and flavors to mask the bitter taste of tablets(Chang R.K., et al, 2000). In the DuraSolv® tablet, the low dose of hyoscyamine sulfate(Khankari RK. et al, 2001) was sufficiently taste-masked by incorporation of sweetener and a flavor(Misra TK, et al, 2000).

Table 1.3: Commonly used natural flavoring agents for taste masking

<table>
<thead>
<tr>
<th>Taste</th>
<th>Masking agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter</td>
<td>Lemon, Orange, Cheery, Grapefruit, Raspberry, Lime, Coffee, Chocolate</td>
</tr>
<tr>
<td>Sour</td>
<td>Lemon, Lime, Orange, Cherry, Grapefruit</td>
</tr>
<tr>
<td>Salty</td>
<td>Berries, Mints, Fennel, Anise, Grape</td>
</tr>
</tbody>
</table>

In case of highly bitter drug, taste masking being an obstacle in formulation of mouth dissolving tablets(Myers, GL et al, 1998.). In selective cases, Herbal excipients like Licorice, Coco powder effectively masked the taste, for example, taste masking of artemether by monoaminoglycyrrhizinate pentahydrate (extract of glycyrrhiza) (Chiou, WL, et al, 1971). Another rarely used but effective technique for soluble taste masking is solid dispersion technique which refers to solid products derived from at least two different components, generally a hydrophilic matrix and a drug, done by dissolving the drug and carrier in common solvent followed by evaporation (Cilurzo F. et al, 2002). For example, solid dispersion of bitter drugs with Cyclodextrins in ethanol produces a water soluble matrix which effectively masked the bitter taste.

1.7.2.2 Quick Disintegration/dissolution

For tablets to disintegrate and dissolve quickly in saliva, mouth dissolving tablets utilizes highly water soluble porous excipients along with capillaries or pore creation in tablets (Allen LV, 2001). Spray dried excipients posses highly porous structure which when
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compressed into tablets provide quick disintegration and reported to disintegrate within 30 second in aqueous media (Yarwood, R et al, 1998). Freeze drying/sublimation technique, mainly used to formulate mouth dissolving tablets, creates pores on the surface of the tablet and also imparts a glassy amorphous structure to the excipients thereby enhancing the dissolution characteristics of the formulation (Bogner R H, 2002). Release of gases (effervescence) also utilizes in formulating MDTs like Triaminic Softchews using OraSolv® patented technology commercialized by Novartis Consumer Health (Table 1.4) (Gregory GKE et al, 1981, Habib W, et al, 2004)

Table 1.4: -Commercially available mouth dissolving tablets

<table>
<thead>
<tr>
<th>MDTs Techniques</th>
<th>Marketed Products</th>
<th>Brand Name</th>
<th>Active Constituent</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeze Drying/ Sublimation</td>
<td>Zydis</td>
<td>Zubrin</td>
<td>Tepoxalin</td>
<td>Schering Corporation</td>
</tr>
<tr>
<td>Quicksolv</td>
<td>Propulsid quicksolv</td>
<td>Cisapride monohydrate</td>
<td>Janseen Pharmaceutica</td>
<td></td>
</tr>
<tr>
<td>Lyoc</td>
<td>Paralyoc</td>
<td>Acetaminophen</td>
<td>Cephlon</td>
<td></td>
</tr>
<tr>
<td>Nanocrystal</td>
<td>Abbott’s Tricor</td>
<td>Fenofibrate</td>
<td>Elan</td>
<td></td>
</tr>
<tr>
<td>Effervescent</td>
<td>Orasolv</td>
<td>Tempra Quicklets</td>
<td>Acetaminophen</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Spray Drying</td>
<td>Advatab</td>
<td>Unison</td>
<td>Diphenhydramine Hydrochloride</td>
<td>Eurand</td>
</tr>
<tr>
<td>Solid Dispersion</td>
<td>Flash Dose</td>
<td>Zolpidem MDT</td>
<td>Zolpidem Tartrate</td>
<td>Bioavail</td>
</tr>
<tr>
<td>Shear Form</td>
<td>Tiazac</td>
<td>Diltizen Hydrochloride</td>
<td>Bioavail</td>
<td></td>
</tr>
<tr>
<td>Highly Water Soluble Excipients</td>
<td>Durasolv</td>
<td>Alavert</td>
<td>Loratidine</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>Wowtab</td>
<td>Benadryl Fast Melt</td>
<td>Diphenhydramine Citrate</td>
<td>Pfizer</td>
<td></td>
</tr>
</tbody>
</table>
1.7.2.3 Industrial approach

The strength of a tablet related to compression pressure which inversely related to porosity, so porosity that allows fast water absorption while maintaining high mechanical strength being an important parameter. Strategy to increase tablet mechanical strength without sacrificing tablet porosity requires a special packaging to handle fragile tablets thus producing a costly product.

1.7.2.4 Patient compliance

Patient like formulations which have easy administration (small size, pleasant mouth feel, minimum saliva requirement for dissolution, disappear as soon as taken) and most of the mouth dissolving tablets comply with these requirements (table 1.5). Zyprexa Zydis® facilitated antipsychotic medication compliance in ill uncooperative patients.

1.8 CURRENT SCENARIO IN MARKETED MDTs

Commercially available MDTs like Nimulid-MD, Romilast, Torrox MT (table 1.2) nowadays marketed under mouth dissolving tablets are actually mouth disintegrating tablets, which are perfect modified formulation of orodispersible tablets (ODTs) based on rapid disintegration in saliva by using super disintegrates such as Microcrystalline Cellulose, Sodium Starch Glycolate and making slurry in mouth followed by swallowing giving rough texture in mouth rather than complete dissolution and prepared by conventional tableting method using taste masking resins for taste masking of bitter drug, Superdisintegrants for quicker disintegration, flavors, and sweetners for patient compliance.
### Table 1.5: Commonly used techniques in MDTs and comparative evaluation

<table>
<thead>
<tr>
<th>MDTs Techniques</th>
<th>Taste masking</th>
<th>Disintegrant</th>
<th>Industrial Approaches</th>
<th>Patient Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water insoluble agents</td>
<td>Water soluble agents</td>
<td>Swelling &amp; deformation</td>
<td>Porosity</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Disintegration</td>
<td>Disintegration</td>
<td>Disintegration</td>
<td>Dissolution</td>
</tr>
<tr>
<td>Freeze Drying</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td>Sublimation</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td>Effervescent</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Spray Drying</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td>Solid Dispersion</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Direct Compression</td>
<td>√</td>
<td>X</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Moisture Treated Tablets</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>√</td>
</tr>
</tbody>
</table>