International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(3): May-June 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 29-04-2016; Revised: 04-05-2016; Accepted: 05-05-2016

MOUTH DISSOLVING TABLETS: INNOVATION IN FORMULATION FOR IMPROVING PATIENT COMPLIANCE

Mehta N*, Bala R, Banerjee A

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, Ropar (Punjab), India.

Keywords:

Microspheres, controlled release, analgesic, sedatives hormones, cardiovascular drugs, vaccines

For Correspondence:

Mehta N

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, Ropar (Punjab), India

E-mail:

mehtanidhi077@gmail.com

ABSTRACT

The convenience of administration and improved patient compliance are important in the design of oral drug delivery system which remains the preferred route of drug delivery in spite of various disadvantages one such problem can be solved in the novel drug delivery system by formulating "mouth dissolving tablets" (MDTs) which disintegrates or dissolves rapidly without water within few seconds in the mouth[1-3]. In today's scenario MDTs are more preferred for patients suffering from diseases like antacids; muscle relaxants; hypertension; depression; nausea and vomiting (generally occurs in patients who are following chemotherapy, radiation therapy and surgery); heart attacks etc. The treatment of major disorder requires prolonged pharmacotherapy in order to resolve the current episode and reduce the risk for recurrence of disease symptoms. Such prolonged therapy requires considerable commitment on the part of patients to take their medication as prescribed. Medication compliance is often poor among psychiatric patients, geriatric and pediatric patients including those with major disorder; this can result in poor long-term outcomes and, ultimately, treatment failure. The onus lies with the prescribing physician to support patients in complying with their medication regimen. Establishing and maintaining a supportive therapeutic relationship is an essential foundation for ensuring patient compliance. Difficulty in swallowing conventional tablets and capsules has emerged as an additional factor in medication noncompliance and has led to the development of alternative drug delivery strategies such as mouth dissolving tablets (MDTs). MDTs are associated with improved medication compliance compared with traditional tablet formulations.

1. INTRODUCTION

The concept of mouth dissolving dosage forms has emerged from the desire to provide patients with more conventional mean of taking their medication. Interestingly, the demand for MDTs has enormously increased during the last decades partially for geriatric and pediatric patients who experience difficulty in swallowing conventional tablets and capsules, patients suffering from mental disorders such as (depression, psychiatric patients). Hence, they do not comply with prescription which results in high incidence of ineffective therapy[4].MDTs are also been essential for patients suffering from dysphagia, motion sickness, repeated emesis, cardic diseases(heart attacks) since MDTs can be given when someone is unconcious[5]. A variety of dosage form like tablets, film, wafers, chewing gum, microparticles, nanoparticles etc have been developed for enhancing the performance attributed in the MDTs. Advancement in the technology are for manufacturing these system include freeze drying, cotton candy, melt extraction, sublimation, direct compression beside the classical wet granulation processes[6, 7]. MDTs when put in mouth these dosage forms disintegrate instantly to release the drug which dissolve or disperses in the saliva[8]. Thereafter, the drug may get absorbed from the pharynx and oesophagus or from other section of g.i.t as the saliva travels down. The mouth dissolving tablets are not only indicated for people having difficulty in swallowing but also ideal for unfavourable condition of administration where water is not available. Syrups are best for pediatric but they are bulky and drugs are not as stable in liquids forms as in solid form like tablets[9]. Mouth dissolving tablets are also known as fast dissolving, orodispersible, rapid dissolve, rapimelt, fast melt, porous tablets, EFVDAS or Effervescent Drug Absorption system (Elan Corporation), Orosolv (Cima Labs Inc., USA), Zydis (R.P Scherer, U.K) etc. In order to allow fast disintegrating tablets to dissolve in the mouth, they are made of very porous and soft molded matrices or compressed into tablets with very low compression forces[10,11]. To increase the tablet disintegration, super disintegrant are added in it, which are very helpful to increase the bioavailability of tablet and to increase the disintegration property of tablet in saliva. Disintegrants are mainly added in the tablets by three methods:

(a) Extra granular
(b) Intra granular
(c) Partially extra granular and intra granular methods.

Time for MDTs disintegration is normally assumed to be less than 1 min[12].

2.1 Patient factors: Mouth dissolving dosage forms are particularly suitable for patients, who for one reason or the other find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Travelling patients suffering from mot ion sickness that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bedridden patients and psychiatric patients.

2.2 MDTs used to overcome several diseases:

Nausea and vomiting: Nausea and vomiting following the administration of chemotherapy, radiation therapy, or surgery remain significant and distressing complications associated with these therapies.[13,14]. Despite these noteworthy achievements, several therapeutic challenges and unaddressed needs continue to impact the control of emesis. Episodes of chemotherapy-induced and radiation induced nausea and vomiting (CINV and RINV, respectively) remain frequent among patients undergoing any of these treatment modalities, often occurring in up to 80% of cases.[13,15,16]. In addition to the creation of non traditional drug delivery systems, oral delivery formulations have continued to evolve to promote rapid dissolution and absorption while maintaining the convenience and portability intrinsic with oral agents.[17,18,19,20]. Mouth dissolving tablets (MDTs) have been designed to allow a solid dose to be rapidly dissolved by saliva in the oral cavity without the need for drinking water.[17,18.19.20] Although these drugs are effective in delivering their antiemetic medications particularly among patients who experience difficulty swallowing conventional oral medications, such as pediatric, geriatric, bedridden, or developmentally disabled patients[17,21.22.23] there are notable challenges to their use. Patients must be specifically educated not to chew, swallow, or drink water with the tablet.[24] Also, because administering bitter-tasting antiemetic as an MDT formulation would offset their use, taste masking is required.[18,20] Currently, the only antiemetics available in MDT formulations are ondansetron, metoclopramide, and olanzapine.

Depression: As noted above, daily medication consumption requires a considerable commitment on the part of the patient and acceptability of the route of administration may play a role in determining ongoing compliance with a given medication. MDTs are among the most common alternative oral treatment formulation currently prescribed and are designed to dissolve without water. MDTs are used in a variety of indications to address specific medical issues such as the need for rapid onset of effect (eg, pain, fever, migraine, diarrhea, anxiety, or nausea); for critical conditions where comprehension and cooperation may be an issue (eg, Parkinson's disease, Alzheimer's disease, psychosis, schizophrenia); for patients with repeated emesis (eg, patients receiving chemotherapy/ radiotherapy); or for pediatric patients who are unable to tolerate a standard tablet formulation. All MDTs disintegrate in the mouth, meaning that the drug may be absorbed in the buccal, pharyngeal, or gastric regions, so avoiding first-pass metabolism and potentially leading to an earlier onset of action.[25] If a large proportion of the drug is usually eliminated during first-pass metabolism, then reformulation as an MDT presents the possibility that the dose can be reduced. Some drugs that have been reformulated as MDTs have reported benefits related to the altered pharmacokinetics. For example, the benzodiazepine clonazepam demonstrates fivefold faster drug release as an MDT compared with the standard formulation.[26]

Cardiovascular diseases

Hypertension: Hypertension is still one of the most significant risk factors for cardiovascular disease, especially in the adult population[27].The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1.56 billion[28]. Thus; the development of an appropriate dosage form is desirable. The most desirable formulation for use by the elderly is one that's easy to swallow and easy to handle[29]. Ease of swallowing and no need for water; only the small volume of saliva of these formulations, result in making fast disintegrating tablets' primary benefit is improvement the patient compliance[30]. As the patients with sudden increase blood pressure and acute angina attack, have markedly reduced functional ability and extremely restless, in such cases rapid onset of action is of prime importance. So the patients would be benefited from acute treatment by using proposed drug delivery system. This may help them to return to normal state and resume their functional activities. To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without need of water[31]. "Mouth Dissolving Tablets". This tablet disintegrates

instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva. Produce rapid onset of action in such a cases Bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (Wilson, 1987).

Heart attacks: The relationship between blood pressure and risk of cardiovascular disease is continuous, consistent and independent of other risks. The higher the blood pressure, the greater is the chance of ischemic heart disease, stroke, heart failure and kidney diseases. Therefore prevention, detection, treatment and control of hypertension should receive high priority. It is used in patients with type 2 diabetes (non-insulin-dependent diabetes)[27]. It works by stimulating the release of your body's natural insulin. Controlling high blood sugar helps prevent heart disease, strokes, kidney disease, blindness, and circulation problems, as well as sexual function problems (impotence).

Tablet 1 Examples of fast dissolving tablets currently available on the market

Drug product	Active ingredient	Indication	Technology	Company
Zofran ODT	Ondansetron	Nausea	Zydis technology	Cardinal Health
Remeron Sol Tab	Mirtazapine	Depression	Durasolv technology	Cima labs
Zomig ZMT	Zolmitriptan	Migrane	Orasolv and dursolv technology	Cima labs
Zyprexa zydis	Olanzapine	Schizophrenia	Zydis technology	Cardinal health

2.4 CHALLENGES IN FORMULATION OF MOUTH DISSOLVING TABLETS (MDTS)

Taste masking: As most drugs are not pleasant, mouth dissolving drugs usually contain the medicament in a taste-masked form. The rapid disintegrating drugs dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste masking of the drugs becomes critical to patient compliance[32].

Amount of drug: For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Size of tablet: It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve[33].

Mouth feel: MDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the MDTs should be as small as possible. Moreover addition of flavours and cooling agents like menthol improve the mouth feel[34].

Aqueous solubility: Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite[35,36].

Hygroscopicity: Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging[37].

2.5 Ideal properties of Mouth Dissolving Tablets:

(1) A MDT should be dissolve or disintegrate in the mouth (in saliva) within seconds.

(2) It should not require any liquid or water to show its action[38.39].

(3) Be compatible with taste masking and Have a pleasing mouth feel.

(4) Be portable without fragility concern.

(5) It should not leave Leave minimal or no residue in the mouth after oral administration of the tablet.

(6) The excipients should have high wettability, and the tablet structure should also have a highly porous network.

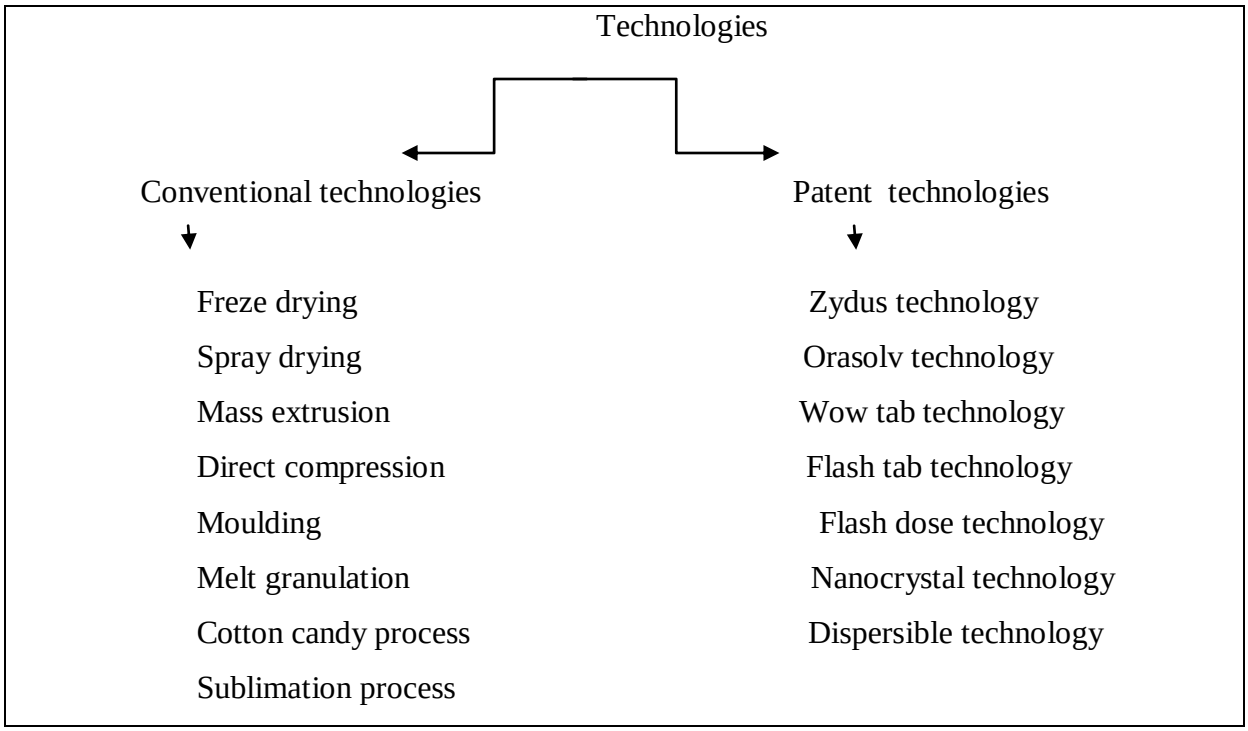
(7) It should be less effective by environmental conditions like humidity, temperature etc.

(8) It should not leave Leave minimal/no residue in the mouth after oral administration of tablet.

(9) More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action[40].

2. Technologies used for manufacturing of MDTs:

In the recent past, several new advanced technologies have been introduced for the manufacturing of MDTs with ideal properties like less disintegration time, pleasant mouth feel, exceptional taste masking and sugar free tablets for diabetic patients. The technologies used for manufacturing of MDTs broadly classified in two category one is patented another one is non patented technologies[41,42].



(a) Lyophilization or Freeze-drying:

Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. This technique creates an amorphous porous structure that can dissolve rapidly. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has Rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug. However, the MDTs formed by lyophilization have low

mechanical strength, poor stability at higher temperature, and humidity. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying[43]. The disadvantage of lyophilized drug is that have poor stability when stored under stressed condition. 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[44].

(b) Melt granulation method: In this process, MDTs can be prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate is a waxy material with an m. pt. of 33- 37°C and a hydrophilic- lipophilic balance of 9. It not only acts as a binder and increases the physical resistance of tablets, but also helps in the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of MDTs by melt granulation method where granules are formed by the molten form of this material[50].

Advantages

(1) Neither solvent nor water used in this process.
(2) Fewer processing steps needed thus time consuming drying steps eliminated.
(3) There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
(4) Uniform dispersion of fine particle occurs.
(5) Good stability at varying pH and moisture levels.

(c) Spray Drying: This method involves spray drying of a blend containing solution/dispersion for spray comprises hydrolyzed and unhydrolyzed gelatine as supporting agent for the matrix, mannitol as bulking agent, and sodium starch glycolate or crosscarmellose as disintegrant these are to enhance disintegration and dissolution.. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium[45, 46].

(d) Mass-Extrusion: In this method active blend is softened using the solvent mixture of water-soluble polyethylene glycol and methanol and then subsequent expulsion of softened mass through the extruder or syringe is made to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking[47].

(e) Tablet Molding: Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent it dissolves in the molten carrier. Molding process is of two type's i.e. solvent method and heat method[48, 49].

- **Solvent method:** This method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution.
- **Heat method:** This process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

(f) Cotton candy process: This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially re-crystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to MDTs[51].

(g) Sublimation process: The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of MDTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process. Developed MDTs utilizing camphor, a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets[52].

(h) Direct compression method: Direct compression is viewed as the technique of choice for the manufacturing of tablets containing thermolabile and moisture sensitive drugs[51]. This method is not as popular as wet granulation method. Substance, such a micro crystalline

cellulose undergoes plastic deformation while dicalcium phosphate undergoes brittle fracture during direct compression. The excipents could be ranked in descending order in terms of their brittleness: microcrystalline cellulose> spray-dried lactose> β-lactose> α-lactose monohydrate> dicalcium phosphates dehydrate. Micro crystalline cellulose (MCC) is a good excipent for direct compression processing[51]. Microcrystalline cellulose has inherently high compatibility due to plastic deformation and limited elastic recovery and it usually provides good dispersion and uniform mixing with the drug[53,54]. Material flow properties are relatively poor for most grades of MCC. Intermittent and non- uniform flow can occureas the formulation moves from hopper to die on a tablet press. This non-uniform flow can lead to drug content variation in the finished tablet dosage form.

Advantages of direct compression method:

(1) Cost effective production.

(2) Better stability of active pharmaceutical ingredient.

(3) Faster dissolution.

(4) Less wear and tear of punches.

(5) Simple validation.

(6) Low microbial contamination[51,55,56].

3.1 Patented technologies for Mouth dissolving tablets (MDTs):

1. **Zydis Technology:** Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of mouth 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 material designed to achieve a number of objectives. These form a glossy amorphous structure, which imparts strength. 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. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Zydis products are packed in blister packs to protect the formulation from moisture in the environment[57].

Drawbacks:

(a) A water insoluble drug can be incorporated only up to 400 mg per tablet or less. On

the other hand water soluble drug can be incorporated only up to 60 mg.

(b) Fragility and poor stability of dosage form during storage under stressful conditions.

2. **Flash Tab Technology:** Prographarm laboratories have patented the Flash tab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like Coacervation microencapsulation, and extrusion spheronisation. All the processing utilized conventional tabletting technology. This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of microcrystal. The micro crystals or micro granules of the active ingredients are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets[58].
3. **Flash Dose technology:** Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self binding shear form matrix termed as floss. Shear form matrices are prepared by flash heat processing.

Drawbacks:

(a) The dosage form can accommodate only up to 600 mg of drug.

(b) Tablets produced are highly friable, soft and moisture sensitive. Therefore specialized packing is required.

4. **Cotton candy technology:** It is patented by Fuisz. Cotton candy technology utilizes a unique spinning mechanism to produce floss like crystalline structure. The cotton candy process forms the basis of thetechnologies such as Flash Dose (Fuisz Technology). A specially designed machine head produces long, cotton candy-like fibers (referred to as "floss"). Shear form matrices are of two types. Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol. The candyfloss can then be milled and blended with active ingredients and other excipients and subsequently compressed into MDT. However the high processing temperature limits the use of this technology to thermostable compounds Flash Dose tablets can accommodate up to 600mg of active ingredient, and typically dissolve in the oral cavity within 5-15 seconds[59,60].

5. **Nanocrystal technology:** This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water soluble ingredients filled into blister pockets. This method avoids manufacturing process such as granulation, blending and tabletting which is more advantages for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug[61].

4. EVALUATION:

4.1 General Appearance: The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance and tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

4.2 Hardness: The test is done as per the standard methods. The hardness of three randomly selected tablets from each formulation is determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale is noted down in Kg/cm^2 [62,63].

4.3 Thickness: The thickness of three randomly selected tablets from each formulation is determined in mm using a Vernier caliper. The average values is calculated.

4.4 Friability (F): Friability of the tablet is determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre – weighted sample of tablets is placed in the friabilator and were subjected to the 100 revolutions. The friability (F) is given by the formula.

$$F = \frac{W_{int} - W_{final}}{W_{int}}$$

Where, Wint - Weight of tablets before friability.

W_{final} - Weight of tablets after friability.

4.5 Weight variation: 20 tablets are selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in the table below.

Table 2 : I.P. Specification for uniformity of weight

Average Weight of Tablet	**% Deviation**
80 mg or less	±10
80 mg to 250 mg	±7.5
250 mg or more	±5

4.6 Wetting Time: Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured.

4.7 Water absorption Ratio: A piece of tissue paper folded twice is placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, is determined using following equation[66].

$$R = 10 (wa/wb)$$

Where, **wa** is weight of tablet before water absorption &

wb is weight of tablet after water absorption.

4.8 In vitro dispersion time: In vitro dispersion time is measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation are randomly selected and in vitro dispersion time is performed. Time required for complete dispersion of a tablet is then measured[64].

4.9 In- vitro drug release: In-vitro release rate of sublingual tablets is carried out using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus. The dissolution test is carried out using 900 ml of 6.8 pH phosphate buffer or 0.1 N HCl, at 37± 20C and 50 rpm. A sample (5 ml) of the solution is withdrawn from the dissolution apparatus at different time

intervals (min). The sample is replaced with fresh dissolution medium of same quantity. The sample is filtered and analysed for drug after appropriate dilution by UV spectrophotometer at respective wave length. The percentage drug release is calculated using an equation obtained from the calibration curve.

5.0 Stability testing of drug (temperature dependent stability studies): The fast disintegrating tablets is packed in a suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(1) 40 ± 1 ℃

(2) 50 ± 1°c

(3) 37 ±1 ° C and RH 75% ± 5%

The tablet is withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C[64, 65].

5. **Acknowledgement:** The authors are highly thankful to DFE Pharma for providing all the necessary support or information regarding the excipents.

REFERENCES

(1) Habib W, Khankari R, Hontz J, Fast-dissolving drug delivery systems, Critical review in therapeutics, Drug Carrier Systems, 2000, 17(1):61- 72.

(2) Chang R, Guo X, Burnside B.A, Couch R, Fast-dissolving tablets, Pharm. Tech, 2000, 24(6):52-58.

(3) Dobetti L, Fast-Melting Tablets: Developments and Technologies, Pharm. Tech., (Suppl.), 2001, 44-50.

(4) Seager H, Drug delivery products and the Zydis fast-dissolving dosage form. J Pharm Pharmacol, 1998, 50: 375-382.

(5) Goel H, Rai P, Rana V, Orally disintegrating systems:Innovation in formulation and technologies; Recent patent on drug delivery and formulation, 2008 (2):258-274.

(6) Lailla J.K, Sharma A.H, Freeze-drying and its applications, Indian Drugs, 1993 (31),503-513.

(7) Allen L.V, Wang B, Process for making a particulate support matrix for making rapidly dissolving tablets. 1996 US Patent No. 5, 587,180.

(8) Bachynsky M.O, Infeld M.H, Rashed M, Shah N.H,: US20080085310 (2008).

(9) Robert D, Hans D, Ole N, Michael R, Helle E, Ken L,: W007036169A2 (2007).

(10) Hirani J.J, Rathod D.K, Vadalia R, Orally Disintegrating Tablet, A Review, Trop. J. Pharm. Res, 2009 8(2), 161-172.

(11) Slowson M, Slowson S, What to do When Patients Cannot Swallow their Medication, Pharma. Times,1985, 51, 90-96.

(12) Seager H, Drug-Delivery Products and the Zydis Fast Dissolving Dosage Form, J. Pharm. Pharmacol, 1998, 50, 375-382.

(13) Roila F, Hesketh P.J, Herrstedt J, Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol 2006, 17:20−28. [16314401].

(14) Watcha M.F, White P.F. Postoperative nausea and vomiting, its etiology, treatment, and prevention. Anesthesiology 1992;77:162−184. [1609990].

(15) Jenns K. Importance of nausea, Cancer Nurs 1994;17:488−493. [7820827].

(16) Radiation-induced emesis: a prospective observational multicenter Italian trial. The Italian Group for Antiemetic Research in Radiotherapy. Int J Radiat Oncol Biol Phys 1999; 44:619−625. [10348292].

(17) Chang R.K, Guo X, Burnside B.A, Couch R.A, Fast-dissolving tablets, Pharmaceutical Technology 2000, 24:52−58.

(18) Khan S, Kataria P, Nakhat P, Yeole P, Taste masking of ondansetron hydrochloride by polymer carrier system formulation of rapid-disintegrating tablets, AAPS PharmSciTech 2007; 8:E1−E7. [17622121]

(19) Habib W, Khankari R, Hontz J. Fast-dissolve drug delivery systems, Crit Rev Ther Drug Carrier Syst, 2000;17:61−72. [10755211]

(20) Doijad R.C, Manvi F.V, Khalandar K.S, A comparative study on mouth dissolving tablets of granisetron with different super disintegrants, formulation and evaluation. Internet J Pharmacol 2008;5.

(21) Carnaby M.G, Crary M, Pill swallowing by adults with dysphagia, Arch Otolaryngol Head Neck Surg, 2005;131:970−975. [16301368].

(22) Kaushik D, Dureja H, Saini T.R. Mouth dissolving tablets: a review, Indian Drugs (Bombay) 2004;41:187−193.

(23) Shu T, Suzuki H, Hironaka K, Ito K.Studies of rapidly disintegrating tablets in oral cavity using co-ground mixtures of mannitol with crospovidone. Chem Pharm Bull (Tokyo) 2002;50:193−198. [11848208].

(24) Hariharan M, Bogue A, Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms, Drug Delivery Technol 2009;9:24−29.

(25) Fu Y, Schicheng Y, Jeong S.H, Kimura S, Park K, Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies, Crit Rev Ther Drug Carrier Syst, 2004;21:433-475.

(26) Shirsand S.B, Suresh S, Swamy O.V, Formulation design and optimization of fast dissolving clonazepam tablets, Indian J Pharm Sci. 2009;71:567-572.

(27) Verma S, Rawat A, Kaul M, Saini S, Solid dispersion: astrategy for solubility enhancement, Int JPharm Tech 2011;3:1062–99.

(28) The fundamental variables of the biopharmaceutics classification system(BCS) acommentary, Eur JPharmSci 1998;7:1–3.

(29) Choudhary A, Aggarwal G, Zakir F, Kumar V, Minireview: journey of solid dispersion technique from bench to scale, Int Res J Pharm 2011;2:46–51.

(30) Sekiguchi K, Obi N, Studieson absorption of eutectic mixtures. A comparison of behavioro feutectic mixtures of sulphathiazole and that of ordinary sulphathiazoleinman. Chem Pharm Bull 1961;9:866–72.

(31) Bikiaris D.N, Solid dispersions, part I: recent evolutions and future opportunities in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs, Expert Opin Drug Deliv 2011;8:1501–19.

(32) Reddy L.H, Ghosh B.R, Fast dissolving drug delivery systems: A review of the literature, Indian Journal of Pharmaceutical Sciences 2002; 64(4) : 331-336.

(33) Sugihara M, Hidaka M, Saitou A, Discriminatory features of dosage form and package, Japanese Journal of Hospital Pharmacy 1986; 12 : 322-328.

(34) Bhandari S, Mittapalli R.K, Gannu R, Rao Y.M, Orodispersible tablet: An overview, Asian Journal of Pharmaceutics 2008 : 2-10.

(35) Seager H. Drug-delivery products and Zydis Fast dissolving dosage form. J Pharm Pharmacol, 1998; 50: 375-382.

(36) Lies M.C, Atherton A.D, Copping N.M, Freeze-dried dosage forms and methods for preparing same.1993 US Patent 5,188,825.

(37) Hirani J.J, Rathod D.A, Vadalia K.R, Orally disintegrating tablets: A Review: Tropical Journal of Pharmaceutical Research, April 2009; 8 (2): 161-172

(38) Brown D, Orally Disintegrating Tablet: Taste Over Speed, Drug Delivery Tech, 2001, 3(6), 58-61.

(39) www. ElanNanoCrystal_Technology.html

(40) Fix J.A, Advances in Quick-Dissolving Tablets Technology Employing Wowtab' Paper Presented at: IIR Conference on Drug Delivery Systems, Oct.; Washington DC, USA (1998).

(41) Bagul U.S, Bagul N.S, Kulkarni M.S, Dr Sawant S.D, Dr Gujjar K.N and Bidkar A.A, Manufacturing technologies for mouth dissolving tablets; Vol 1 334-335.

(42) Parakh S.R, Gothoskar A.V, A review of mouth dissolving tablet technologies, Pharm Tech, 2003; 27(11):92-98.

(43) Kuchekar B.S, Badhan A.C, Design of fast dissolving tablets, Ind. J. Pharm Edu, 2001; 35-150.

(44) Nail S.L, Gatlin L.A, Freeze Drying: Principles and Practice,Parenteral Medications, in Pharmaceutical Dosage Forms.1993, 2nd ed. Vol. 2. Marcel Dekker, New York:163.

(45) Allen L.V, Wang B, Process for making a particulate support matrix for making a rapidly dissolving dosage form.2001 US Patent 6,207,199.

(46) Kaushik D, Dureja H ,Saini T.R, Mouth dissolving tablets: A Review. Indian Drugs; 2004; 41(4):187-192.

(47) Panigrahi D, Baghel S, Mishra B, Mouth dissolving tablets: An overview of preparation techniques, evaluation and patented technologies. J Pharm Research, 2005; 4(3):35-38.

(48) Shangraw R, Mitrevej A, Shah M, A new era of tablet disintegrants, Pharm Technol,1980 ; 4(10):49-57.

(49) Mizumoto T, Masuda Y and Fukui M. Intrabuccally dissolving compressed moldings and production process thereof. US Patent 1996; No. 5576014.

(50) Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier J.P, Piccerelle P, The preparation of orally disintegrating tablets using a hydrophilic waxy binder, Int J Pharm, 2004; 278:423-33.

(51) Goel H, Rai P, Rana V, Orally disintegrating systems: Innovation in formulation and technologies; Recent patent on drug delivery and formulation, 2008; (2): 258-274.

(52) Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M. New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor: A subliming material. Int J Pharm, 1997 ; 152:127-31.

(53) Tiwary A.K, Sapra B, Jain S. Dissolution, In Preclinical Development Handbook - ADME and Biopharmaceutical Properties, (ed.), Shayne Cox Gad, New Jersey, Wiley Inter science, 2008; 483-544.

(54) Kaushik D, Dureja H, Saini T.R, Mouth dissolving tablets: A Review, Indian Drugs, 2004 ; 41(4):187-192.

(55) Panigrahi D, Baghel S, Mishra B, Mouth dissolving tablets: An overview of preparation techniques, evaluation and patented technologies. J Pharm Research, 2005; 4(3):35-38.

(56) Adel M, Semreen M.K, Qato K.M, et al, Pharm Tech, 2,pg 68(2005).

(57) Mizumoto T, Allen, A, Loyd, V, Method for producing a rapidly dissolving dosage form, US patent, 5,576,014(1996).

(58) Acosta C, Tabare R, Ouali A, et al, US patent, 5, 1998, 807.

(59) Chang R.K, Guo X, Burnside B.A, Couch R.A. Fast dissolving tablets. Pharm Techno, 2000; 24(6):52–58.

(60) Indian Pharmacopoeia 1996. The Controller of Publication, Delhi, Vol-2, p-735.

(61) Gohel M.C, Patel M.M, Amin A.F, Agrawal R, Dave R, Bariya N, Formulation design and optimization of mouth dissolving tablets of nimesulide using vacuum drying technique, AAPS Pharm Sci Tech, 2004 ; 5: 1-8.

(62) Yarwood R. Zydis - a novel fast dissolving dosage forms. Manf Chem 1990; 36-37.

(63) Hamilton E.L, Luts E.M. Advanced Orally disintegrating tablets bring significant benefits to patients and product life cycle. Drug Delivery Technol, 2005; 5(1):34-7.

(64) Sharma S, New Generation of Tablets: Fast Dissolving Tablet.

(65) Hirani J.J, Rathod A.D, Vadalia R.K, Orally Disintegrating Tablets: A Review, Tropical Journal of Pharmaceutical Research, 2009, 8(2), 161-172.

(66) Koizumi K, "New Method of Preparing Highly Porous Rapidly saliva Soluble Tablets by Sublimation Technique". Int. J.Pharm. 152, 1997, 127- 131.