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MOUTH DISSOLVING TABLETS

ABSTRACT

The drug administration through oral routes has greater acceptability as 50-60% of drugs are administered through this route. Among them the solid dosage forms are widely used due to the easiness in administration, accuracy in dosage forms, advantages of self-medication, avoidance of pain, and last but not the least the high patient compliance**.** But some patients have a problem regarding swallowing named 'Dysphagia'**.** Mouth dissolving tablets are disintegrating and dissolve rapidly in the saliva without the need for water .Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water.

Keywords

Fast Dissolving tablets, Super disintegrants, Preparative Methods, Marketed Products, Patented Technologies.

Introduction[2]

Mouth Dissolving tablets disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast- dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes.

The formulation is more useful for the bed- ridden and patients who have the swallowing problem

Target populations for these new mouth dissolving/disintegrating dosage forms:

- Ease of administration to patients who refuse to swallow tablet, pediatric, geriatric, and bedridden or developmentally disabled patients.
- Patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates for MDTs.
- The ease of administration of a fast dissolving/disintegrating tablet, along with its pleasant taste, may encourage a patient to adhere to a daily medication regimen.
- Fast-dissolving/disintegrating dosage forms increasingly available, it will be likely that prescribers will recommend such products for their noncompliant patients.
- In the near future, other patient populations will also be targeted. A novel application for MDTs is in veterinary medicine, for example, to avoid pilling a cat.
- MDTs/FDDTs is increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those cases where the drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption of the many formulations. However, other formulations show nearly identical plasma concentration profiles.
- Pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is disputable, it is clear that the major advantage of these formulations is convenience.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

DEFINITION[3]

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 sec to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

Ideal properties of MDT[3]

Mouth Dissolving Tablet should

- Not require water or other liquid to swallow.
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasant mouth feel
- Have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be harder and less friable.
- Be portable and easy to transport.
- Be able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity etc.
- Not require water or other liquid to swallow**(3)**

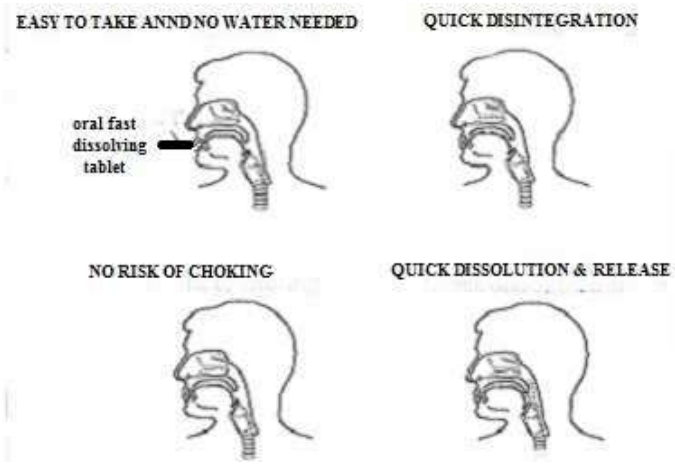
- Easily dissolve or disintegrate in saliva within a few seconds.
- Have a pleasing taste.
- Leave negligible or no residue in the mouth when administered.
- Be portable and easy to transport.
- Be able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity.

Salient Features :[3]

1. Administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients.
2. Convenience of administration and accurate dosing as compared to liquids.
3. Rapid dissolution of drug and absorption which may produce rapid, onset of action
4. Some drugs are absorbed from the pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

ADVANTAGES OF MOUTH DISSOLVING TABLETS[4]

a. No need of water to swallow the tablet.
b.Can be easily administered to pediatric, elderly and mentally disabled patients.
c. Accurate dosing as compared to liquids.
d.Dissolution and absorption of drug is fast, offering rapid onset of action.
e.Bioavailability of drugs is increased10time as some drugs are absorbed from mouth, pharynx and oesophagus through saliva passing down into the stomach
f.Advantageous over liquid medication in terms of administration as well as transportation
g.First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
h.Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety



DISADVANTAGES OF MOUTH DISSOLVING TABLET'S[1]

The tablet should handle carefully due to its low mechanical strength.

- MDT must be kept in a dry place as it dissolves rapidly and hygroscopic
- If the tablet is not formulated properly then it may result in an unpleasant taste.
- It requires proper packaging of tablets otherwise it will get unstable.
- If there is any problem regarding the formulation of mouth dissolving tablets, the taste will be unpleasant and sandy.
- There is another problem regarding formulation. As the main characteristics of the mouth dissolving tablets are fast disintegration so large doses of tablets are not formulated properly
- There's also an additional limitation like if any patients have suffered from the disorder like dryness of mouth, it would be difficult

for them to administer mouth dissolving tablets for less saliva production.

- It is also not applicable to those patients who are taking anticholinergic drugs continuously.

THE NEED FOR DEVELOPMENTOF MDTS[5]

The requirement of non-invasive delivery systems persists due to patient's poor acceptance of, and compliance with, existing delivery regimes. The pediatrics and geriatric populations are the primary targets, as both the groups found it difficult to swallow conventional tablets.

- The patient related factors for development of MDTs include the following:
- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety. Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.

The effectiveness factors are:

- Increased bioavailability and faster onset of action are a major claim of these formulations. Because the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions.
- The pre-gastric drug absorption avoids the first-pass metabolism and drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.
- Safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism.

Ingredients used :[1]

There are various excipients which are used to formulate mouth dissolving tablets like super disintegrants, flavours, fillers, binders, sugar-based excipients, surface-active agents, lubricants, color, etc. The important properties of those excipients are the rapid release of drugs and faster dissolution. The temperature range of excipients must be between 30-35°c.

a. Super disintegrants: The super disintegrants plays a key role in the formulation of mouth dissolving tablets. It helps the tablets to disintegrate quickly in the mouth, hence dissolves rapidly. The chosen of desirable super disintegrants depends upon its optimum concentration because at this concentration rapid disintegration and dissolution take place. The critical concentration of disintegrants is very much important in the formulation. Below the critical concentration of disintegrants, the disintegration time of tablets is inversely proportional to the super disintegrants concentration above the critical concentration, the disintegration time remains constant or increase. The rapid disintegration is the result of the combined effect of swelling and water absorption of the formulation. The disintegration and dissolution enhance due to the swelling effects of disintegrants as it increases the wetting property and dispersibility of the system. The examples of super disintegrants are – microcrystalline cellulose, crospovidone, sodium starch glycolate, croscarmellose sodium, pre-gelatinized starch, magnesium aluminium silicate(veegum).

b. Flavors: Flavoring agents are mainly used in the formulation of any dosage forms to increase its palatability and patient's compliance. It is also known as taste-masking agents as it conceals the bitterness or any undesirable tastes of active pharmaceutical ingredients. There are various types of flavoring agents like peppermint oil, clove oil, aromatic oil, anise oil etc.

c. Fillers: Fillers also play an important role in the formulation of mouth dissolving tablets as it helps in

calculating the disintegration time. The examples of fillers used are Sorbitol, Magnesium carbonate, Mannitol, Calcium carbonate etc.

d. Binders: Binders are used in the formulation to increase the cohesiveness of the powder and it forms granules. Those granules form a compact mass or cohesive mass of tablets after compaction. Examples of those binding agents are – Polyvinyl alcohol, Polyvinyl pyrrolidone, HPMC (Hydroxypropyl methylcellulose), etc**.**

e. Sugar-based excipients: Sugar-based excipients are also known as bulking agents or taste-masking agents. MDTs should have a pleasant taste so it is necessary for the formulation. But there are some limitations like all sugar-based excipients do not have good compatibility and rapid dissolution rate. The sugar-based excipients which also having the bulk property like fructose, sorbitol, maltose is highly soluble in aqueous medium and also act as a sweetening agent which helps to avoid the bitter taste.

f. Surface active agents: Surface-active agents plays an important role in the formulation of MDTs. Examples of surface-active agents are polyoxymethylene sorbitan fatty acid esters, sodium lauryl sulfate, and sodium dodecyl sulfate.

g. Lubricants: Lubricants are not as essential as any other excipients. It is used to improve the mechanism of the transportation of drugs through the gastrointestinal tract and remove granular properties. Some lubricants are talc, magnesium stearate, calcium stearate, etc.

h. Color: Various colors are used like yellow, pink, purplish blue, etc

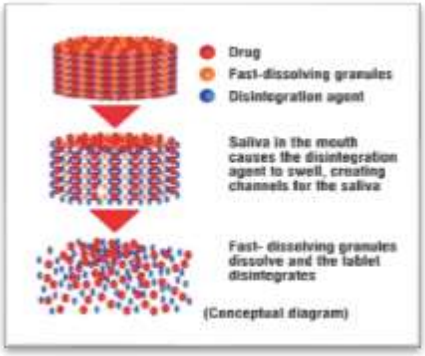


Fig: Mechanism of Drug ,fast Dissolving granules and disintegration granules

Techniques for Preparing Fast dissolving Tablets.[6]

Many techniques have been reported for the formulation of Fast dissolving tablets or Orodispersible tablets. Here we have discussed the six major techniques which are widely used for the formulation of these tablets.

1. Freeze drying/ Lyophilisation
2. Tablet moulding
3. Spray drying
4. Direct Compression
5. Sublimation
6. Mass Extrusion

5.1 Freeze-Drying or Lyophilization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of FDT using this technique is mentioned here.

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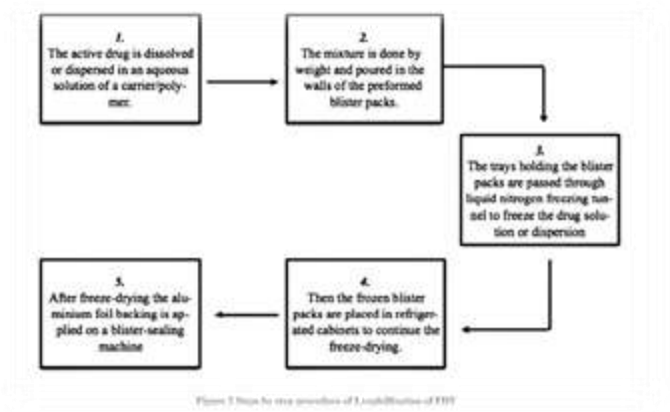

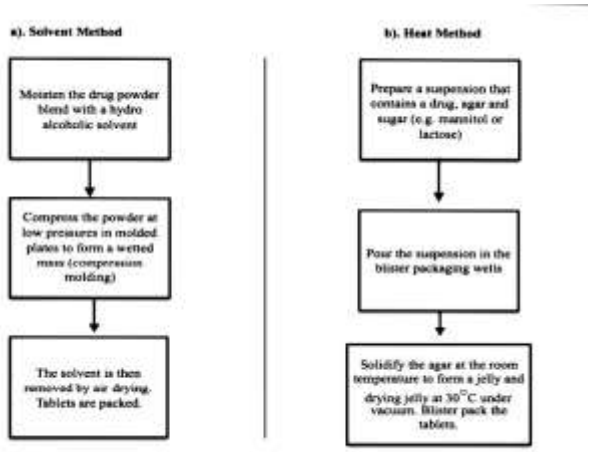

Figure 3 Procedure of Tablet Molding

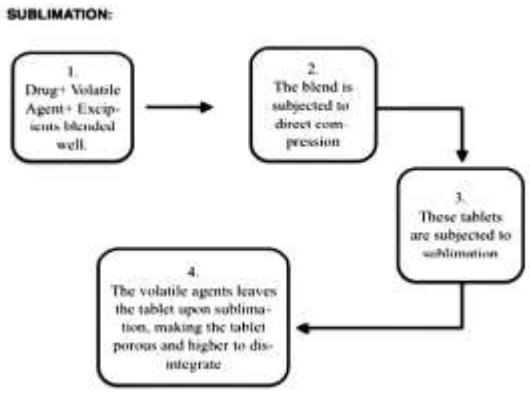

Figure 4 Step by Step Formation of FDT's by sublimation

8) Drugs to be promising in corporate in Mouth dissolving tablets

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient

Analgesics and Anti-inflammatory Agents:

Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac.

Anthelminitics:

Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Ivermectin, Mebendazole, Oxarniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Pyrantel Embonate, Thiabendazole.

Anti-Arrhythmic Agents:

Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate.

Anti-bacterial Agents:

Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixic Acid, Nitrofurantoin, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxine, Sulphamerazine, Sulphacetamide, Sulphadiazine

Anti-Fungal Agents:

Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole Nitrate, Terbinafine, Terconazole, Tioconazole, Undecenoic Acid. Anti-Gout Agents: Allopurinol, Probenecid, Sulphinpyrazone.

Anti-Hypertensive Agents:

Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidii, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin**.**

Anti-Malarials:

Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate.

Anti-Migraine Agents:

Dihydroergotamine Mesyiate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate. Anti-Neoplastic Agents and Immunosuppressants: Aminoglutethimide, Amsacrine, Azathiopnne, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitotane, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone.

Anti-Thyroid Agents:
Carbimazole, Propylthiouracil. Nutritional Agents: Betacarotene, Vitamin A, Vitamin B 2 , Vitamin D, Vitamin E, Vitamin K.

Opioid Analgesics:
Codeine, Dextropropyoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine**.**

Oral Vaccines:
Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a Representative Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, Aids, Measles, Lyme Disease, Travellers Diarrhea, Hepatitis A, B And C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhegic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Urinary Tract Infection Caused By E.Coli, Pneumoccoccal Disease, Mumps, File://H:\Gits Mdt\Fast Dissolving Tablet The Future Of Compaction And Chikungunya.

Proteins, Peptides and Recombinant Drugs:
Insulin (Hexameric/Dimeric/Monomeric Forms), Glucagon, Growth Hormone (Somatotropin), Polypeptides or Their Derivatives, (Preferably With A Molecular Weight from 1000 To 300,000), Calcitonins And Synthetic Modifications Thereof, Enkephalins, Interferons (Especially Alpha-2 Inter Feron For Treatment Of Common Colds).

Sex Hormones:
Clomiphene Citrate, Danazol, Ethinyloestradiol, Medroxyprogesterone Acetate, Mestranol, Methyltestosterone, Norethisterone, Norgestrel, Oestradiol, Conjugated Oestrogens, Progesterone, Stanozolol, Stiboestrol, Testosterone, Tibolone.

9) Preformulation studies mouth dissolving tablet :

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

1. Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by Db = M/ Vb
Where, M is the mass of powder Vb is the bulk volume of the powder.

2. Tapped Density (Dt): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the expressed in g/ml and given by Dt = M / Vt Where, M is the mass of powder Vt is the tapped volume of the powder.

3. Angle of Repose (q): The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane $\tan (q) = h / r$ $q = \tan^{-1} (h / r)$ Where, q is the angle of repose. h is the height in cm r is the radius in cm. The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through

the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 1: Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose	Type of Flow
1.	<20	Excellent
2.	20-30	Good
3.	30-34	Passable
4.	>34	Very poor

4. Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair Passable
23-35	Poor
33-38	Very poor
>40	Very Very Poor

Evaluation test for mouth Dissolving Tablets :[7]

1) **Weight variation**: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in Table 3.

Table 3: Weight Variation Specification as per IP

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

2) Hardness: Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

3) Friability (F): Friability of the tablet determined using Roche friabilator or Electro lab 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 I height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$\text{Friability (\%)} = \frac{\text{W initial} - \text{W final}}{\text{W initial}} \times 100$$

4) Mechanical Strength: Tablets should possess adequate strength to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameter to evaluate a tablet for its mechanical strength.

5) Crushing Strength: It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported.

6) Wetting time: Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder

bed is proportional to the pore radius and is affected by the hydrophilicity of the powders. dl/dt = r¡cosq/(4hl) Where l is the length of penetration, r is the capillary radius, ¡ is the surface tension, h is the liquid viscosity, t is the time, and q is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37º. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

7) In vitro dispersion time: Tablet was placed in 10 ml phosphate buffer solution, pH 6.8±0.5°C. Time required for complete dispersion of a tablet was measured.

8) In-vitro disintegration time The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±2ºC as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±2ºC. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

9) Thickness Variation: Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer. The mean SD values were calculated

FACTORS TO BE CONSIDERED FOR SELECTION OF SUPERDISINTEGRANTS

Disintegration: The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressure necessary to provide rapid disintegration in the mouth.

Compatibility: It is desirable to have ODT with acceptable hardness and less friability at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed.

Mouth feel: Large particles can result in a gritty feeling in mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water. However, it produces a gummy texture that many consumers find objectionable.

Flow: In typical tablet formulation, superdisintegrants are used at 2-5 wt % of the tablet formulation. With ODT formulation, disintegrant level can be significantly higher.

List of Superdisintegrants[9]

Superdisintegrants	Example	Mechanism Of Action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked -Swells 4-8 folds in < 10 seconds. -Swelling and Wicking both cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and Wicking both	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel	Cross linked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional Products
Calcium silicate		-Wicking Action	Highly porous, Optimum concentration is b/ 20-40%

List of commercially Available Fast dissolving tablets[8]

Trade Name	Active Drug	
Felden fast melt Claritin redi Tab Maxalt MLT Zyprexia Pepcid RPD Zofran ODT Zoming-ZMT Zeplar TM Tempra Quiclets Febrectol Nimulid MDT Torrox MT Olanex instab Romilast Benadryl Fastmelt	Loratidine Rizatriptan Olanzapine Famotidine Ondansetron Zolmitriptan Selegilline Acetaminophen Paracetamol Nimesulide Rofecoxib Olanzapine Montelukast Diphenhydramine and pseudoephedrine	Schering plough Corp., USA Merck and Co., NJ, USA Eli lilly, Indianapolis, USA Merck and Co., NJ, USA Glaxo Wellcome, Middlesex, UK AstraZeneca, Wilmington, USA Amarin Corp., London, UK Bristol myers Squibb, NY, USA Prographarm, Chateauneuf, France Panacea Biotech, New delhi , India Torrent pharmaceuticals , India Ranbaxy lab. Ltd. New-delhi, India Ranbaxy lab. Ltd. New-delhi, India Warner Lambert, NY, USA

PATENTED TECHNOLOGIES:[9]

Zydis Technology: Zydis technology is the first mouth dissolving dosage form in the market. It is a unique freeze dried tablet in which the active drug is incorporated in a water soluble matrix, which is then transformed in to blister pockets and freeze dried to remove water by sublimation. 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. Polymers such as gelatin, dextran or alginates are added to impart strength during handling. These form a glossy and amorphous structure. Mannitol or sorbitol is added to impart Zydis Technology: Zydis technology is the first mouth dissolving dosage form in the market. It is a unique freeze dried tablet in which the active drug is incorporated in a water soluble matrix, which is then transformed in to blister pockets and freeze dried to remove water by sublimation. 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. Polymers such as gelatin, dextran or alginates are added to impart strength during handling. These form a glossy and amorphous structure. Mannitol or sorbitol is added to impart

Orasolv Technology (Cima Labs): This includes use of effervescent disintegrating agents compressed with low pressure to produce the FDTs. This evolution of carbon dioxide from the tablet produces fizzing sensations, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25% of tablet weight. As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop pakslov, a special packing to protect tablets from breaking during storage of transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet within the depression.

Paksolv offers moisture, light and child resistance packing

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

Wowtab Technology: Yamanauchi pharmaceutical company patented this technology. 'wow' means 'without water'. The active ingredients may constitute upto 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mouldability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldabiity saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packsand thus shows slow dissolution. The combination of high and low mouldability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mouldability saccharides and then granulated with high mouldabiity saccharides and then compressed into tablet. The Wowtab product dissolves quickly in 15 s or less. Wowtab product can be packed in both into conventional bottle and blister packs.

Oraquick Technology: The Oraquick fast dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its micro sphere technology, known as Micro Mask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/ disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste-masking Oraquick claims quick dissolution in a matter of seconds, with goodtaste-masking. There are no products using the Oraquick technology currently on the market, but KV pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropic, and anti-infective.

Nanocrystal Technology: For fast disintegrating tablets, Elan's proprietary Nano crystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nano crystal technology. Nano crystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. Nano Crystal Fast dissolving technology provides for:
Pharmacokinetic benefits of orally administered nano particles (<2 microns) in the form of a rapidly disintegrating tablet matrix.
Product differentiation based upon a combination of proprietary & patent-protected technology elements.
Cost-effective manufacturing processes that utilize conventional, scalable unit operations.
Exceptional durability, enabling use of conventional packaging equipment & formats (bottles &/or blisters) Wide range of doses (up to 200mg of API per unit) Use of conventional, compendial inactive components. Employment of non-moisture sensitive inactives.

Quicksolv: In Quicksolv porous solid dosage forms are obtained by freezing an aqueous dispersion/solution of the drug-containing matrix and then drying it by removing the water using excess of alcohol by solvent extraction. The final

form disintegrates very rapidly, but is limited to low drug content and can be used only for those drugs that are insoluble in the extraction solvent. The ideal drug characteristics required for this technology are relative low aqueous solubility, fine particle size <50 μm, and good aqueous stability in the suspension.

Frosta Technology (Akina): It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules composed of Porous and plastic material, Water penetration enhancer and binder. The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30s depending on size of tablet 30. filler reduces porosity of tablets due to which disintegration is lowered.

Dispersible Tablet Technology: Lek in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methanesulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulate ion was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross –linked sodium carboxymethyl cellulose, and cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.

Pharmaburst Technology(Spi Pharma, New Castle): It utilizes the co processed recipients to develop FDTs, which dissolves within 30-40s. This technology involves dry blending of drug, flavour, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

Advatab Technology: Advatab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is distinct from other ODT technologies as it can be combined with Eurand_s complimentary particle technologies like its world leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

Lyo (Pharmalyoc): Oil in watr emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Nonhomogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

Sheaform Technology: The technology is based on the preparation of floss that is also known as, Shearform Matrix, which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide aciform flow properties and this facilitate blending the re-crystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet.

Ceform Technology: In ceform technology microspheres containing active ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a

precision engineered and rapidly spinning machine. The centrifugal force of the rotating head of the ceform machine throws the dry drug blend at high speed through small heated openings. The microspheres are then blended and/or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance.

Future prospects of MDT:[9]

The technologies depicted in this article demonstrate how recent advances in formulation development and processing technologies meet the efforts to achieve more sophisticated drug delivery system (Oral Disintegrating/Mouth Dissolving Tablets). MDT needs to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in traveling, has difficulty in swallowing and may not have access to water. Mouth dissolving tablets can offer several biopharmaceutical advantages such as improved efficiency over conventional dosage forms. For example, they require smaller amounts of active ingredient to be effective, improve absorption profiles, and offer better drug bioavailability than regular tablets and capsules. In addition, MDTs may be suitable for the oral delivery of drugs such as protein and peptide based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Because drugs delivered in MDTs may be absorbed in the pre-gastric sites of highly permeable buccal and mucosal tissues of the oral cavity, they may be suitable for delivering relatively low molecular weight and highly permeable drugs. Future possibilities for improvements in MDTs and drug delivery are bright, but the technology is still relatively new. Several drug delivery technologies that can be leveraged on improving drug therapy from MDTs have yet to be fully realized.

CONCLUSION:[6]

Fast Dissolving tablets are considered to be contemporary dosage forms. These dosage forms and their route of administration results in better efficacy, rapid onset of action, enhanced bioavailability, and improved patient compliance. There are many marketed product of this category which have been introduced in the recent past. Some of the recent product in the Indian and global market are listed in table for ready reference (Table 6). The primary attractive factor of MDT is quick disintegration in oral cavity without the aid of water, along with sufficient mechanical strength. This feature makes this formulation a highly recommendable choice for geriatric and pediatric patients. FDT in the near future is expected to grow at a great and rapid pace, owing to the advancement in the scientific research and discovery of new excipients, resulting in a future-ready, combative area of pharmaceutical drug delivery systems.

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