

MOUTH DISSOLVING TABLETS : AN OVERVIEW

Vikrant K Nikam*¹, Kiran B Kotade², Vinayak M Gaware³, Ramdas T Dolas¹,
Kiran B Dhamak³, Sachin B Somwanshi¹, , Atul N Khadse³, Vivek A. Kashid¹

1. Department of Pharmaceutics, College of Pharmacy Chincholi, Sinnar, Nashik, M.S, 422101.
2. Department of Pharmacology, College of Pharmacy Chincholi, Sinnar, Nashik, M.S, 422101.
3. Department of Pharmaceutical Chemistry, College of Pharmacy Chincholi, Sinnar, Nashik, M.S, 422101.

Corresponding author*:

Vikrant K. Nikam
Lecturer, Department of Pharmaceutics,
College of Pharmacy, Chincholi, Sinnar, Nashik, M.S (422101)
E-mail: vikrantnikam@gmail.com

SUMMARY

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performances. Over the past three decades, orally disintegrating tablets have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. Mouth dissolving tablets are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds when placed on the tongue. Ie. Fast dissolving Tablets are disintegrating 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. The new technology has encouraged both academia and industry to generate new formulations and technological approaches in this field. The purpose of this article is to review the development, advantages, and challenges in formulation, evaluation methods and future prospects.

Key Words: Mouth dissolving tablets, super disintegrants, Sublimation, orally disintegrating tablets, Conventional tablets.

INTRODUCTION:

(1) Mouth Dissolving Tablets: A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.⁴⁻⁵

These are also called melt-in-mouth tablets, repimelts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets.



Conventional tablets cannot be swallowed without water. However, water or any other fluid is needed, by the patients, in most of the cases to swallow the capsule or tablet. The difficulty in swallowing, more commonly termed as dysphagia, is apparent in patients of all age groups, especially the pediatrics and geriatrics. The result is a high incidence of non compliance and ineffective therapy. In case of patients who are mentally ill, uncooperative, nauseated patients and those with acute episodes of coughing or asthma the time of response should be very rapid which indicates that the drug should be absorbed into the systemic circulation as early as possible.

All the foresaid problems led to the development of an oral novel drug delivery system called 'The Mouth Dissolving Tablets' are defined as the solid dosage forms that dissolve or disintegrate quickly in the oral cavity, resulting in solution or suspension form without the need of water for the administration. They are also known as Rapid mouth dissolving tablet, Rapid melt, rapid dissolve, fast dissolve and quick disintegrating tablets. Thus, the mouth dissolving tablets have a significant impact on the overall patient compliance. Some Oral dissolving tablets

can be given, to psychiatric patients, in the crushed form added in tea, there by decreasing the refusal rate by psychiatric patients for the administration of oral dosages.

(2) Need of MDT:

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance¹.



To overcome these drawbacks, mouth dissolving tablets (MDT) or orally disintegrating tablets; (ODT) has emerged as alternative oral dosage forms. These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds'. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach used in development of MDT is the use of superdisintegrants like Cross linked carboxymethylcellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab). Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets.

(3) Superdisintegrants:



Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Although various compounds have been proposed and evaluated as disintegrants, relatively few are in common usage today. Traditionally, starch has been the disintegrant of choice in tablet formulations, and it is still widely used. However, starch is far from ideal. For instance, starch generally has to be present at levels greater than 5% to adversely affect compactibility, especially in direct compression. Moreover, intragranular starch in wet granulations is not as effective as dry starch. In more recent years, several newer disintegrants have been developed. Often called “super disintegrants,” these newer substances can be used at lower levels than starch. Because they can be a smaller part of the overall formulation than starch, any possible adverse effect on fluidity or compactibility would be minimized. These newer disintegrants may be organized into three classes based on their chemical structure.⁷

DIFFERENT ASPECTS OF MOUTH DISSOLVING TABLETS

(1) An ideal MDT should:

- 1) Require no water for oral administration, yet dissolve / disperse/disintegrate in mouth in a matter of seconds.
- 2) Have a pleasing mouth feel.
- 3) Have an acceptable taste masking property.
- 4) Be harder and less friable
- 5) Leave minimal or no residue in mouth after administration
- 6) Exhibit low sensitivity to environmental conditions (temperature and humidity).
- 7) Allow the manufacture of tablet using conventional processing and packaging equipments.

(2) Advantages of MDT^{4,6}:

- 1) Administration to the patients who can not swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- 2) Rapid drug therapy intervention.
- 3) Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
- 4) Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- 5) Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- 6) The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- 7) New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

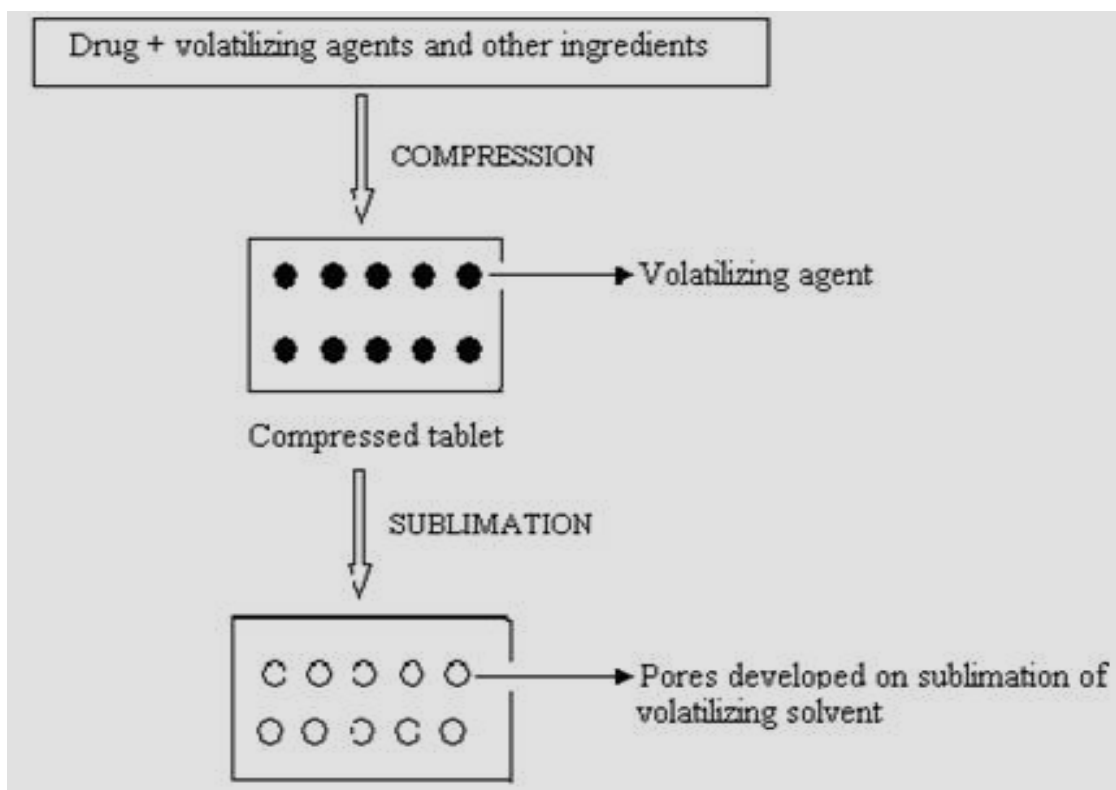
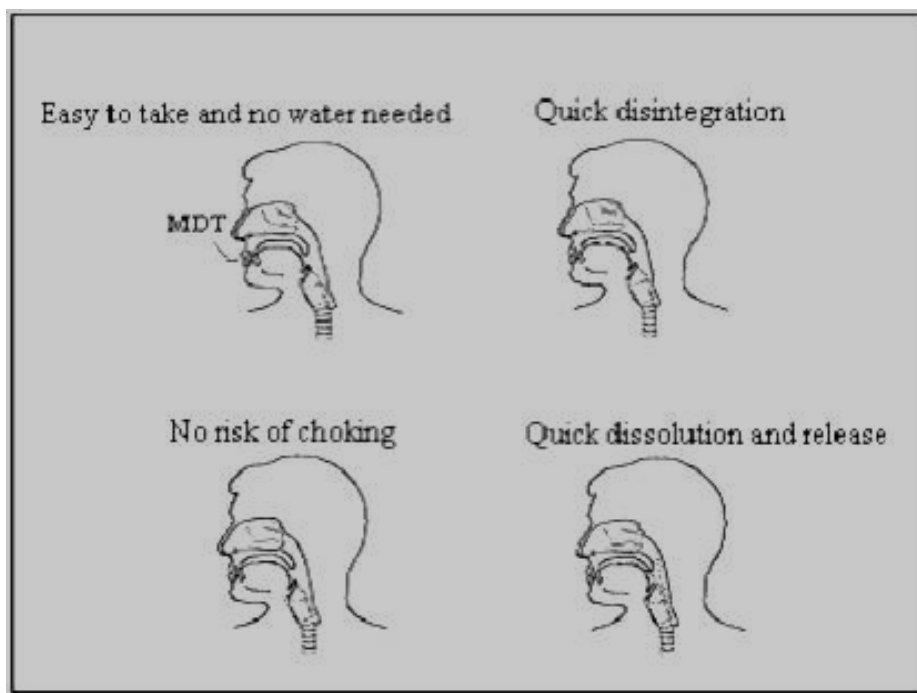


Fig. Sublimation

(3) Salient Features of Fast Dissolving Drug Delivery System :

- 1) Ease of administration to patients who refuse to swallow a tablet, such as paediatric and geriatric patients and, psychiatric patients.
- 2) Convenience of administration and accurate dosing as compared to liquids.
- 3) No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- 4) Good mouth feels properly of MDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients.
- 5) Rapid dissolution of drug and absorption which may produce rapid, onset of action.
- 6) Some drugs are absorbed from the mouth pharynx and oesophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- 7) Ability to provide advantages of liquid medication in the form of solid preparation.
- 8) Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.



METHODS OF PREPARATION OF MDT

1) Tablet Molding:

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet.

To overcome poor taste masking characteristic Van Scoik³ incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

2) Direct Compression Method:

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology^{4,5,6} is cost effective and easy to implement at industrial level.

Cousin et al,⁷ using carboxymethyl cellulose as disintegrating agent and one swelling agent consisting of modified starch or microcrystalline cellulose formulated rapidly disintegrable multi particular tablets. The tablets disintegrate in the mouth in less than 60 seconds.

Gas Evolving disintegrants have been used to formulate fast dissolving tablets. The evolution of carbon dioxide as a disintegration mechanism called OROSOLV and DURASOLV have been described in two US Patents assigned to CIMA Labs

J. Michaelson⁸ describe the use of intimate mixture of alginic acid and a water-soluble metal carbonic acid to prepare tablets. When tablet was placed in water, an acid base reaction takes place forming a metal alginic acid salt and carbonic acid. The salt caused the tablet to swell and the carbonic acid produced carbon dioxide within the swelling tablet whereby rapid disintegration of tablet was effected.

3) Freeze Drying Technology (Zydis Technology⁹):

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth.

The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless.

Corveleyn and Remon^{10, 11} investigated the influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in lyophilized form using hydrochlorthiazide as a model drug. They have concluded that maltodextrins are useful in the formulation of fast dissolving tablets made by freeze-drying.

Lyophilization is relatively expensive and time consuming manufacturing process. Other drawback includes fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition.

4) Spray Drying:

Spray dryers are widely used in pharmaceuticals and biochemical processes. Due to processing solvent is evaporated rapidly; spray drying can produce highly porous, fine powder. Spray drying can be used to prepare rapidly disintegrating tablets. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets.

Allen et al¹² used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 seconds.

5) Sublimation Technology:

The basis of this technique is to add inert solid ingredients that volatilize readily, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.

Koizumi et al ¹³ applied the sublimation technique to prepare highly porous compressed tablets that were rapidly soluble in saliva. Mannitol and camphor were used as a tablet matrix material and subliming the material respectively. Camphor was iminated by subliming in vacuum at 80 C for 30 minutes to develop pores in the tablets.

Makino et al ¹⁴ described a method of producing a fast dissolving tablet using water as a pore forming material. A mixture containing active ingredient and carbohydrates (glucose, manitol, xylitol etc) were moistened with water (1- 3 %w/w) and compressed into tablets. The water was then removed yielding highly porous tablet that exhibited excellent.

INGREDIENTS MOSTLY USED IN MDT

An excipient is generally a pharmacologically inactive substance used as a carrier for the active ingredient of a medication. In many cases, an "active" substance (such as acetylsalicylic acid) may not be easily administered and absorbed by the human body; in such cases the substance in question may be dissolved into or mixed with an excipient. Excipients are also sometimes used to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid in the handling of the active substance concerned. Depending on the route of administration, and form of medication, different excipients may be used. For oral administration tablets and capsules are used. Suppositories are used for rectal administration.

Often, once an active ingredient has been purified, it cannot stay in purified form for long. In many cases it will denature, fall out of solution, or stick to the sides of the container. To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time that the shelf-life of the product makes it competitive with other products. Thus, the formulation of excipients in many cases is considered a trade secret.

Pharmaceutical codes require that all ingredients in drugs, as well as their chemical decomposition products are identified and guaranteed to be safe. For this reason, excipients are only used when absolutely necessary and in the smallest amounts possible.

1) Super Disintegrants:

Use of disintegrants is the basic approach in development of MDTs. Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates¹⁵.

Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases¹⁶.

Sodium starch glycolate, Ac-di-sol(crosscarmellose sodium), Crospovidone, Microcrystalline cellulose, Pregelatinised starch are some of examples of disintegrants.

2) Sugar Based Excipients:

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. And the basic requirement for designing MDTs is that the drug should not have disagreeable taste. So taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose, fructose, etc. are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking²⁹. But not all sugar-based materials have fast dissolution rate and good compressibility or compactability. However technologies are developed to make use of the sugar based excipients in the design of fast dissolving tablets¹⁵⁻¹⁷.

Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, binders, colors and flavors¹⁸⁻¹⁹.

3) Antiadherents:

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches. They are also used to help protect tablets from sticking. Most commonly used is magnesium stearate.

4) Binders:

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets. Binders are usually:

- Saccharides and their derivatives:
 - Disaccharides: sucrose, lactose;
 - Polysaccharides and their derivatives: starches, cellulose or modified cellulose such as microcrystalline cellulose and cellulose ethers such as hydroxypropyl cellulose (HPC);
 - Sugar alcohols such as xylitol, sorbitol or maltitol;
- Protein: gelatin;
- Synthetic polymers: polyvinylpyrrolidone (PVP), polyethylene glycol (PEG).

Binders are classified according to their application:

- Solution binders are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose and polyethylene glycol.
- Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone and polyethylene glycol.

5) Disintegrants:

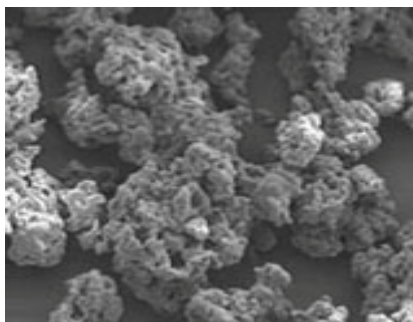
Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. Disintegrant types include:

- Water uptake facilitators
- Tablet rupture promoters

They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution.

Examples of disintegrants include:

- Crosslinked polymers: crosslinked polyvinylpyrrolidone (crospovidone), crosslinked sodium carboxymethyl cellulose (croscarmellose sodium).
- The modified starch sodium starch glycolate.



6) Fillers or diluents:

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling.

A good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, relatively cheap, compactible, and preferably tasteless or pleasant tasting.

Plant cellulose (pure plant filler) is a popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is another popular tablet filler. A range of vegetable fats and oils can be used in soft gelatin capsules.

Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate.

7) Flavours:

Flavours can be used to mask unpleasant tasting active ingredients and improve the likelihood that the patient will complete a course of medication. Flavourings may be natural (e.g. fruit extract) or artificial. For example, to improve:

- a bitter product - mint, cherry or anise may be used
- a salty product - peach, apricot or liquorice may be used
- a sour product - raspberry or liquorice may be used
- an excessively sweet product - vanilla may be used

8) Colours:

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication.

9) Lubricants:

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall.

Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

10) Glidants:

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction. Examples include fumed silica, talc, and magnesium carbonate.

11) Preservatives:

Some typical preservatives used in pharmaceutical formulations are

- Antioxidants like vitamin A, vitamin E, vitamin C, retinyl palmitate, and selenium
- The amino acids cysteine and methionine
- Citric acid and sodium citrate
- Synthetic preservatives like the parabens: methyl paraben and propyl paraben.

12) Sweeteners:

Sweeteners are added to make the ingredients more palatable, especially in chewable tablets such as antacids or liquids like cough syrup. Therefore, tooth decay is sometimes associated with cough syrup abuse. Sugar can be used to disguise unpleasant tastes or smells.

13) Sublimating Agents:

The use of sublimating agents including camphor, menthol, and thymol was explored. The

addition of camphor lowered the disintegration time (~30 s) further, but the percent friability

was increased.

SUPER DISINTEGRANTS

Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the

dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Although various compounds have been proposed and evaluated as disintegrants, relatively few are in common usage today. Traditionally, starch has been the disintegrant of choice in tablet formulations, and it is still widely used. However, starch is far from ideal. For instance, starch generally has to be present at levels greater than 5% to adversely affect compactibility, especially in direct compression. Moreover, intragranular starch in wet granulations is not as effective as dry starch. In more recent years, several newer disintegrants have been developed. Often called “super disintegrants,” these newer substances can be used at lower levels than starch. Because they can be a smaller part of the overall formulation than starch, any possible adverse effect on fluidity or compactibility would be minimized. These newer disintegrants may be organized into three classes based on their chemical structure.

MECHANISM OF ACTION OF SUPERDISINTEGRANTS²⁰⁻²² :

(1) By Capillary Action:

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

(2) By Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

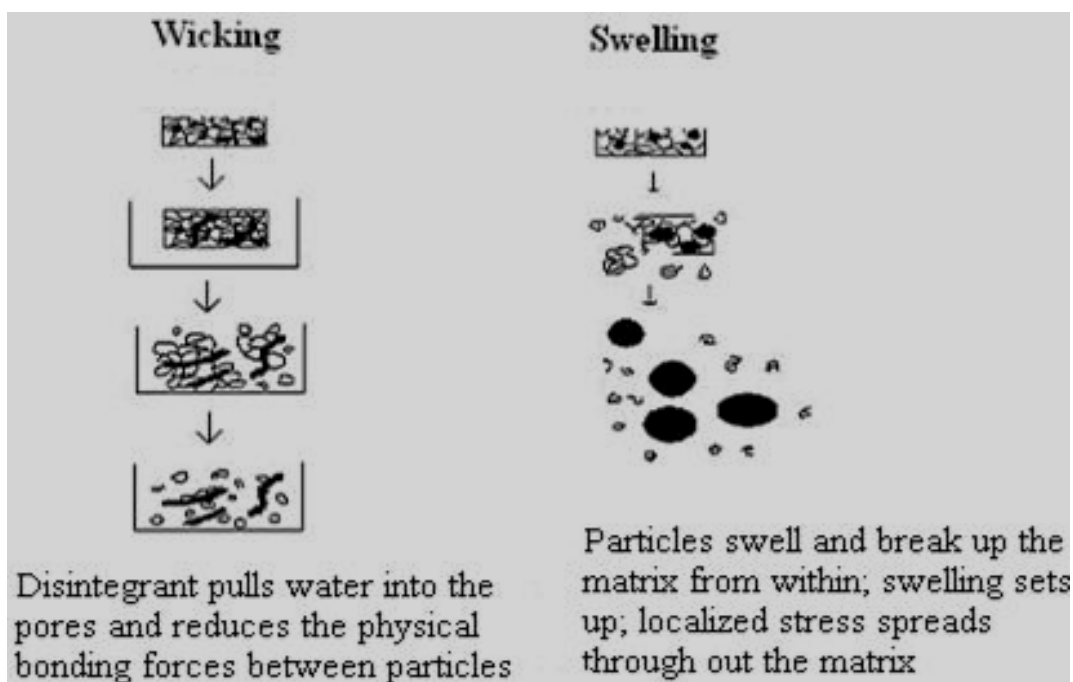


Fig. Disintegration of Tablet by Wicking and Swelling

(3) Because of Heat of Wetting (Air Expansion):

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

(4) Due to Release of Gases:

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

(5) By Enzymatic Reaction:

Enzymes presents in the body also act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

(6) Due to Disintegrating Particle/Particle Repulsive Forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with ‘non-swelling’ disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

(7) Due to Deformation:

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

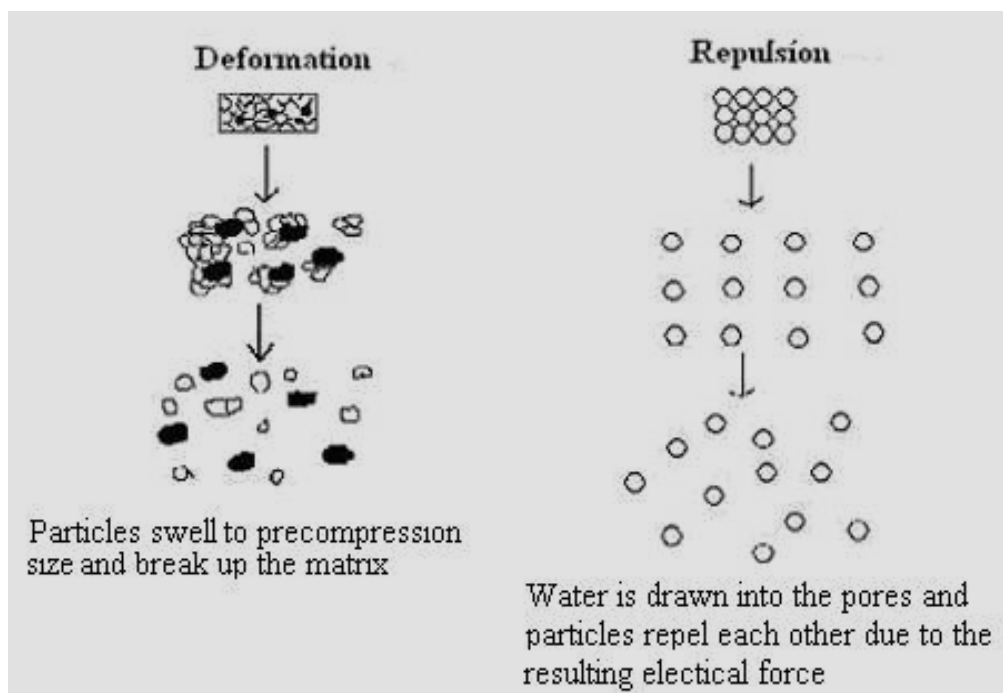


Fig. Disintegration by Deformation and Repulsion

EVALUATION OF MOUTH DISSOLVING TABLETS

I) Evaluation Of Blends⁸

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics-of blends produced.



The various characteristics of blends tested are as given below:

1. Angle of Repose:

The frictional force in a loose powder can be measured by the angle of repose θ . It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ , is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where θ = Angle of repose
h = height of the cone
r = Radius of the cone base

Angle of Repose less than 30° shows the free flowing of the material.

2. Bulk Density:

Density is defined as weight per unit volume. Bulk density, p_b , is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3 .

The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. There are two types of bulk density.

The particles are packed in such a way so as to leave large gaps between their surfaces resulting in light powder of low bulk density.

Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. A standard procedure used for obtaining bulk density or its reciprocal bulkiness is given, below

A sample of about 50 cm³ (blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm³.

$$P_b = M/V_p$$

Where

p_b = Bulk Density "

M = Weight of sample in gm

V = Final volume of blend in cm³

3. Bulkiness:

Specific bulk volume or reciprocal of bulk density is called bulkiness or bulk.

Bulkiness increases with a decrease in particle size. In mixture of material of different sizes, however the smaller particle shifts between the larger particles and tends to reduce the bulkiness.

The bulkiness can be calculated by the following formula

Bulkiness = $1/p_b$ where, p_b = Bulk Density.

Loose bulk density

It is defined as the ratio of weight of blend in gms to the loose bulk volume (untapped volume) in cm³ Loose bulk density is given by

Loose bulk density p_u = Weight in gms / V_b

Where V_b = Bulk volume (untapped volume)

4. Void Volume:

The volume of the spaces is known as the void volume "v" and is given by the formula

$$V = V_b - V_p$$

Where V_b = Bulk volume (volume before tapping)

V = True volume (volume after tapping)

5. Porosity:

The porosity ϵ of powder is defined as the ratio of void volume to the bulk volume of the packaging.

The porosity of the powder is given by

$$\epsilon = \frac{V_b - V_p}{V_p} = 1 - \frac{V_p}{V_b}$$

Porosity is frequently expressed in percentage and is given as

$$\% \epsilon = (1 - \frac{V_p}{V_b}) \times 100$$

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.



6. Percent Compressibility:

It is an important measure obtained from bulk density and is defined as,

$$C = \frac{P_b - P_u}{P_b} \times 100$$

If the bed of particles is more compressible the blend will be less flowable and flowing materials.

II) Evaluation Of Fast Dissolving Tablet⁹⁻¹²

Tablets from all the formulation were subjected to following quality control test.

1. General Appearance:

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



2. Size and Shape:

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

3. Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4. Uniformity of weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.



Average weight of
Tablets (mg)
1. 130 or less
2. 130-324

Maximum percentage
difference allowed
10
7.5

5. Tablet hardness:

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

6. Friability:

It is measured of mechanical strength of tablets. Roche fribaiator was used to determine the friability by following procedure. A preweighed tablet was placed in the fribaiator. Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. At the end of test tablets were dusied and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{Friability} = \text{loss in weight} / \text{Initial weight} \times 100$$

7. In Vivo Dsintegration test:



The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

8. Wetting time:

The method reported by yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for

complete wetting was measured. Three trials for each batch and the standard deviation was also determined.



9. In vitro dispersion time:

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

Stability testing of drug (temperature dependent stability studies)

The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C

(ii) 50 ± 1 °C

(iii) 37 ± 1 °C and RH $75\% \pm 5\%$

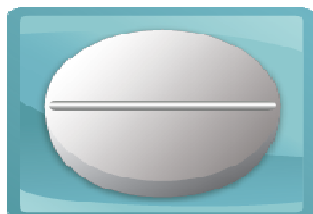
The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation.

Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 °C.



FUTURE ASPECTS IN MDT:

Orodispersible 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 pregastric 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 drugs²³⁻²⁷.



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.^{28,29}

CONCLUSION

Mouth dissolving tablets have better patient compliance and acceptance and may offer improved biopharmaceutical properties, improved efficacy and better safety compared with conventional oral dosage forms. Mouth dissolving tablets are more widely used for the treatment of allergies and asthmatic attacks since these are quickly dissolved and can help in case of emergency. Therefore, the potential for such dosage forms is promising because of the availability of newer and advanced technologies with strong market acceptance and increasing patient demands. Since incorporating an existing medicine in a new drug delivery system can significantly improve its performance and patient compliance, Mouth dissolving tablets have always attracted scientists towards development of fancy oral drug delivery systems and have acquired an important position in the market by overcoming previously encountered administration problems and contributing to betterment of patient's life.

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. Dobbetti, L.,Fast-Melting Tablets: Developments and Technologies, *Pharm. Tech.*, (Suppl.), 2001;44-50.
4. Kuchekar, B. S., Atul, Badhan, C., Mahajan, H. S., Mouth dissolving tablets: A novel drug delivery system, *Pharma Times*, 2003;35:7-9.
5. Allen,L.V. and Wang, B., Particulate support matrix for making a rapidly dissolving tablet, 1997, US Patent 5595761.
6. Bradoo, R., Fast Dissolving Drug Delivery Systems, *JAMA India*, 2001; 4 (10):27-31.
7. Encyclopedia, Larry L. Augsburger^a; Albert W. Brzeczko^b; Umang Shah^c; Huijeong Ashley Hahm^d 2001.
8. Yoshio, K., Masazumi, K., Shuichi A., and Hiroaki N., Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols, *J. Control. Release*, 2005; 105(1-2):16-22.
9. Kuchekar, B. S., Mahajan, S., and Bandhan, A. C., Mouth dissolve tablets of sumatriptan, *Indian Drugs*, 2004; 41(10):592-598.
10. S. Corveleyn, J. P. Remon, “ Formulation and Production of rapidly disintegrating tablets by Lyophilization Technique”, *Int. J. Pharm.*, 1997; 152:215 – 225.
11. S. Corveleyn, J. P. Remon, US patent 6,010,719(2000).
12. Lalla. J K., Mamanian, H. M., Fast dissolving rofecoxib tablets, *Indian J. Pharm. Sci.*,2004;59(4): 23-26.
13. I. K. Koizumi et al, “ New Method of Preparing Highly Porous Rapidly saliva Soluble Tablets by Sublimation Technique”, *Int. J. Pharm.*, 1997;152: 127- 131.
14. T. Makino, M. Yamado, J. I. Kikuta, “ Fast Dissolving Tablet” US patent 5,720,974(1998).
15. Gissinger D, Stamm A. A comparative evaluation of the properties of some tablet disintegrants. *Drug Dev Ind Pharm* 1980; 6(5): 511–536.

16. Gorman EA, Rhodes CT, Rudnic EM. An evaluation of croscarmellose as a tablet disintegrant in direct compression systems. *Drug Dev Ind Pharm* 1982; 8: 397–410.
18. Ganderton D. The effect of distribution of magnesium stearate on the penetration of a tablet by water. *J Pharm Pharmacol* 1969; 21 (Suppl.): 9S–18S.
19. Mullarney MP, Hancock BC, Carlson GT. The powder flow and compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets. *Int J Pharm* 2003; 257(1–2): 227–236.
20. Malke S, Shidhaye S, Kadam VJ. Formulation and evaluation of oxcarbazepine fast dissolving tablets. *Indian J Pharm Sci* 2007; 69(2):211-214.
21. Shangraw RF, Mitrevej A, Shah M. A new era of tablet disintegrants. *Pharm. Technol.* 1980; 4(10): 49-57.
22. Mitrevej A, Hollenbeck RG. Photomicrographic analysis of water vapor sorption and swelling of selected super disintegrants. *Pharm. Technol.* 1982; 6(Oct): 48-50, 53-54.
23. Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS Pharm Sci Tech* 2006; 7(3): 68.
24. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast-dissolving ketoprofen tablet using freeze-drying in blisters technique. *Drug Dev Ind Pharm* 2006; 32(4): 437-442.
25. Cirri M, Valleri M, Mura P, Maestrelli F, Ballerina R. Development of fast-dissolving tablets of flurbiprofen-cyclodextrin complexes. *Drug Dev Ind pharm* 2005; 31(7): 697-707.
26. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reyneir J. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. *Int J Pharm* 2005; 292(1-2):29-41.
27. Takagi H, Kajiyama A, Yangisawa M. Rapidly disintegrable pharmaceutical composition. US Patent 6,899,899; 2005.
28. 44 Lalla JK, Mamania HM. Fast dissolving rofecoxib tablets. *Indian J Pharm Sci* 2004; 59(4):23-26.
29. Rockville. MD, United States Pharmacopoeia: 27 th revision. USP Convention, Inc. 2004; 2302.