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THE REVIEW ON PATIENT COMPLIANCE WITH MOUTH DISSOLVING TABLETS

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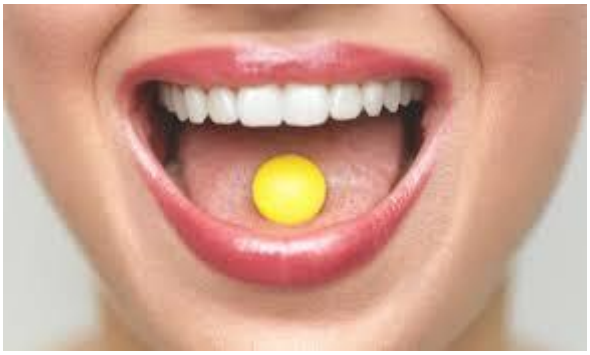
Abstract:

Fast dissolving tablet (FDT) is one such type of innovative and unique drug delivery system which is swiftly gaining much attention in the research field of rapid dissolving technology. The oral route is the most expedient and safest route of drug delivery because of a wide range of drugs are administered through this route. Recently researchers have developed a fast dissolving tablet (FDT) which dissolves or disintegrate rapidly in mouth saliva without the intake of water. This novel drug delivery such as FDT or MDT (mouth dissolving tablet) has overcome many disadvantages like dysphagia or non-accessibility of water while traveling. When compared with the conventional dosage form FDT can be a useful alternative as well. FDTs formulations contain super disintegrants to enhance the disintegration rate of a tablet in the buccal cavity. FDTs have advantages such as easy portability and manufacturing, accurate dosing, good chemical and physical stability and an ideal alternative for geriatric and pediatric patients. FDTs have disintegrated quickly, absorb faster so, in vitro drug release time improves and this property of drugs (dosage form) enhanced bioavailability. FDT formulations have the advantage of both conventional tablet formulation and liquid dosage form. There are several technologies that are conventional or patented based on spray drying, cotton candy process, sublimation, melt granulation, direct compression freezes drying/lyophilization, phase transition process, mass extrusion, etc. have been developed for manufacturing of FDTs. In this review contain brief information about FDTs including definition, advantages, needs or requirements of FDTs, salient features of FDTs, limitations, challenges to developing FDT, marketed formulations of fast dissolving tablets, etc.

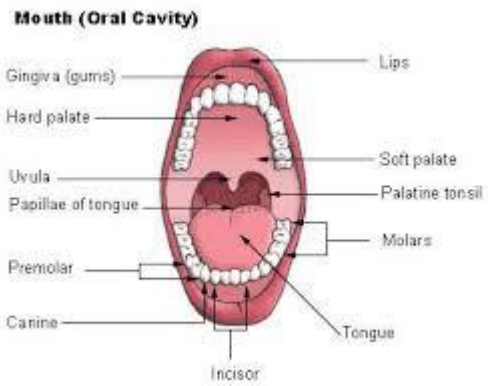
Keywords:

Fast dissolving tablets, FDTs, Superdisintegrants, Mouth dissolving tablets, MDTs



INTRODUCTION:

Formulation of drugs into a presentable form is the basic requirement and need of today. The dosage form is a mean of drug delivery system, used for the application of the drug to a living body. Various type of dosage forms are available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having different type of drug delivery mechanisms. These classical/ modern dosage forms have some advantages and disadvantages. Therefore, the development of an ideal drug delivery system is a big challenge to the pharmacist in the present scenario. In order to get the desired effect, the drug should be delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected [1]. Oral routes of drug administration have wide acceptance up to 50- 60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [2]. The problem of swallowing is a common phenomenon in a geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Approximately one-third of the population (mainly paediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [3]. United States Food and Drug Administration (USFDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue" [3]. Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds [5]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets(MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds,without the need to take water. Recent market studies indicate that more than half of the patient population prefers FDTs to other dosage forms. Mouth dissolving tablets are formulated mainly by two techniques first use of super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone. Another method is maximising pore structure of the tablets by freeze drying and vacuum drying [5]. In all methods, direct compression is preferred because of its effortlessness, quick procedure and cost-effectiveness [1]. 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 subjected to first pass metabolism is reduced as compared to standard tablets [5].



CONVENTIONAL TECHNOLOGIES FOR PREPARING MOUTH DISSOLVING TABLETS

Freeze drying Freeze drying is a process of sublimation of water content from the product through freezing. Thus formed freeze dried forms shows more rapid dissolution compared to other conventional dosage forms. Glossy amorphous structural appearance is due to lyophilisation of the drug; thereby enhancing the dissolution characteristics of the formulation. Due to its high economic equipment the usage of freeze drying became limited [6] Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying of the tablet above its collapse temperature rather than freeze drying below its collapse temperature provides a method for manufacturing tablets with increased structural integrity, which disintegrates rapidly in saliva [7-11] . Moulding Solid dispersions are the tablets which are produced by moulding technique. Extent or amount of the drug it dissolves in the molten carrier depends on the physical form of the drug [58]. The drug can exist as discrete particles or micro particles dispersed in the matrix. It may dissolve completely/ partially in the molten carrier to form solid solution and the remaining particles stay undissolved and dispersed in the matrix [12]. Disintegration time, drug dissolution rate will depend on the type of dispersion or dissolution. Moulded tablets generally made from water-soluble sugars thus offers rapid disintegration and improved taste. These moulded tablets were subjected to erosion and breakage during handling and opening of blister packs because of its lesser mechanical strength [13-17] . Sublimation Tablets containing highly water soluble excipients as a matrix material show slow dissolution in water because of its low porosity. Tablets with high porosity and rapid dissolution have been developed by adding inert solid volatile substances (urea, urethane, ammonium carbonate, camphor, naphthalene) to other excipients of the tablet and this blend was subjected to tableting. Porosity of the tablet can be achieved by removal of solid volatile substance through sublimation [18]. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. Thus formed tablets exhibits good mechanical strength and also shows a rapid dissolution i.e, 10-20 seconds.

Challenges in formulating Fast dissolving tablets:

Palatability

As most drugs are unpalatable, FDTs usually contain the medicament in a taste-masked form. Upon administration, it disintegrate or 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 **.**

Mechanical strength

In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, andoften requiring specialized peel-off blister packing that may add to the cost. Only Wow tab and durasolv technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi-dose bottles.[19]

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**.**

Amount of drug

The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be less than 400 mg for insoluble drugs and 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

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 that can induce crystallinity and hence, impart rigidity to the amorphous composite

Size of tablet

The ease of administration of a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.[20]

FORMULATION OF MDTs:

Drug:

The ultimate characteristics of a drug for dissolution in the mouth and pre gastric absorption from MDTs include:

1)Free from bitter taste

2)Dose lower than 20 mg

3)Small to Moderate molecular weight

4) Good solubility in saliva

5)Ability to permeate through oral mucosal tissue.

Bulking materials:

Bulking materials are significant in the formulation of fastmelting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.[21]

Emulsifying agents:

Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.[22]

Lubricants:

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.[23]

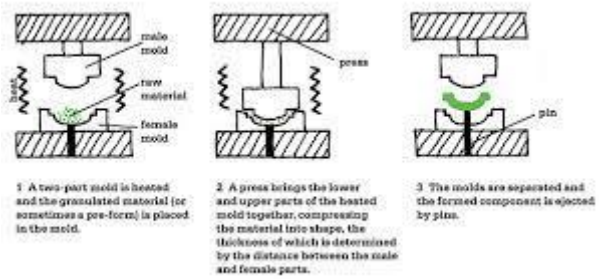
Flavours and sweeteners: Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients.[24]

Tablet Moulding:

Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly. Following are the different tablet moulding techniques:

Compression Moulding Process

This manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.



Heat-Moulding Process

Heat-moulding process involves setting the molten mass containing a dispersed drug. This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C under vacuum.[25]

Moulding by Vacuum Evaporation without Lyophilization

This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process.[26]

Mechanisms of Superdisintegrants:

They work by four basic mechanisms

Swelling:

By this mechanism, certain disintegrating agents (like starch) impart the disintegrating effect upon contact with water, cause the tablet breakdown. e.g. Sodium starch glycolate, Plantago Ovata.[27]

Porosity and Capillary Action (Wicking): The disintegration action of some superdisintegrants is by the capillary action and porosity. The disintegrated particles act to enhance porosity which conveys ways for the permeation of fluid into tablets. After that via capillary action or wicking action, the liquid is tired up, this results in inter particulate bonds breakdown and ultimately tablet disintegration. e.g. Crosspovidone, Crosscarmellose.[28]

Deformation:

When the pressure applied to the starch grains they deformed and when pressure removed they will come into original shape. But when they compressed into tablets they deformed permanently which release their energy when coming in contact with water.[29]

Due to Disintegrating Particle/Particle Repulsive Forces:

This mechanism is associated with non-swell able disintegrants. For that Guyot-Hermann has given particle repulsion theory. According to that disintegration electric repulsive forces between particles are responsible for the water. It is believed that no single mechanism is responsible for the action of most disintegrants. But, it is the result of inter-relationships between these major mechanisms.[30]

Evaluation of Mouth Dissolving Tablets:

Mouth dissolving tablets are evaluated for the various parameters like hardness, friability, weight variation, drug content, etc. Apart from these conventional evaluation parameters, there are some specific parameters that are important in order to establish the effectiveness of MDTs for the drug delivery purpose. These parameters include wetting time, disintegration time, dissolution study and moisture uptake study. The wetting time of the mouth dissolving tablets is very considerable because when we place MDT in the mouth it gets dissolve within a few seconds. Lower wetting time gives very fast disintegration of the MDT, So, it plays an important role in the manufacturing of mouth dissolving tablets. For the assessment of wetting time 10 ml of distilled water containing eosin, a water-soluble dye was placed in a Petri dish of 10 cm diameter. Tablets were carefully placed in the center of the Petri dish and the time vital for water to touch the higher superficial of the tablet was noted. This is called wetting time.[31]

The disintegration test is also widely employed for MDT"s. Disintegration time is measured using the USP disintegration test apparatus. Six tablets per batch are used for disintegration test. The disintegration test is performed in 900 ml simulated saliva fluid pH 6.8 at 37 ± 0.5 °C temperature and at the rate of 30 ± 2 cycles/min.[32]

A dissolution study is very important for mouth dissolving tablets. In-vitro dissolution study of mouth dissolving tablets is carried out using the tablet dissolution test apparatus (USP XXII type) at 50 rpm. Phosphate buffer pH 6.8 is used as the dissolution media and temperature maintained at 37 ± 0.5 °C. Samples are withdrawn at different time intervals and analyzed by suitable analytical method. [33]

Apart from these mouth dissolving tablets also taken for moisture uptake studies because numerous excipients are hygroscopic in nature. In the desiccator with calcium chloride randomly ten tablets are taken up and reserved at 37 °C for 24 h. For two weeks the tablets are then weighed and open to 75% relative humidity at room temperature. At the bottom of the desiccators, sodium chloride is kept for the attainment of 75% relative humidity for three days. As a control group, one superdisintegrant deficit tablet is kept for the evaluation of other excipients moisture uptake in the tablet.[34]

IDEAL CHARACTERISTICS OF FAST DISSOLVING TABLETS

They should not require water for administration, yet dissolve or disintegrate in the mouth within a few seconds. [35,36]

- Should compatible with sweetening agents for masking of taste
- Should have acceptable taste
- Should leave minimal residue in the mouth after its administration
- Should compatible for high drug loading
- Should withstand to humidity and temperature
- Manufacturing and packaging should be economic To attain the tablet's fast dissolving character, water should quickly egress into the tablet matrix to cause rapid disintegration and instant dissolution of the tablet [37]. Increase in the porous structure of the tablet matrix and incorporating appropriate disintegrating agents or extremely water soluble agents in the tablet formulation are the fundamental approaches employed in current fast dissolving tablet technologies. Basically, the disintegrates major activity is to oppose the affectivity of the tablet binder and therefore the physical forces that act under compression to make the tablet [38]. The mechanism by which tablet disintegrates into smaller particles and then produces a homogeneous suspension or solution is based on: I) Capillary action II) High swell ability of disintegrates III) Capillary action and high swell ability IV) Chemical reaction (Release of Gases). By capillary action

First step of disintegration is always done by capillary action. Once the tablet comes in contact with the aqueous medium it replaces the air adsorbed on the tablet by penetration of aqueous medium into the tablet. There by it weakens the intermolecular bonding and breaks the tablet into fine particles. Hydrophilicity of the drug /excipient decides the water uptake by the tablet [39]. For these types of disintegrates 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. By swelling Disintegration of tablets can be achieved by swelling mechanism. Tablets show poor disintegration with less swelling force and high porosity. On the other hand, sufficient swelling force is exerted in the tablet with low porosity [40-44]. 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. Because of heat of wetting (air expansion) Wetting of disintegrates with exothermic properties exhibits localized stress due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrates and cannot describe the action of most recent disintegrating agents [45]. Due to disintegrating particle/particle repulsive forces Guyot-Hermann has proposed that non-swelling particle also cause disintegration of tablets by particle repulsion theory [45]. 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. Due to deformation Hess had proved that disintegrated particles gets deformed during tablet compression and these deformed particles when they come in contact with aqueous media or water they get into their normal structure. Moreover, when granules were extensively deformed during compression the swelling capacity of starch also improved. Thus increased deformed particles produce a breakup of the tablet This may be a mechanism of starch and has only recently begun to be studied

.

CONCLUSION:

Due to the increasing demand for novel drug delivery, the quickdisintegrating drug delivery a system has become one in the entire milestone within the novel drug delivery system. The introduction of quick-dissolving drug delivery system has encountered the delivery of standard dosage form. Mouth dissolving tablets are cost-effective with the addition of advantage to dysphasic patients as they disintegrate and dissolve in mouth within a few minutes and release active agents. The new technologies of manufacturing provide tablets with rapid onset of action, increased bioavailability, low side effects and better safety.

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