ABSTRACT

Researchers throughout the world are focusing intensively on the methods for the development of new drug delivery systems to enhance patient’s compliance. Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Oral delivery (viz., solutions, suspensions, tablets, and capsules) is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery.

A Fast dissolving tablet, orally disintegrating tablet or orodispersible tablet (ODT) is a drug dosage form available for a limited amount of over-the-counter (OTC) and prescription medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. FDDT formulation combines the advantage of both liquid and conventional tablet formulation while also offering advantage over both traditional dosage forms.

KEYWORDS: ODT, Over the counter, Oral disintegrating tablets, Fast dissolving tablet (FDT).

INTRODUCTION

Fast-dissolving drug-delivery systems were initially developed in the late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who
experiences difficulties in swallowing traditional oral solid-dosage forms. The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients.

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population.

The conventional tablet seems to be most popular because of its ease of transportability and comparatively low manufacturing cost but poor patient compliance in case of paediatrics and geriatrics patients because of hand tremors and dysphasia that experienced difficulties in swallowing. 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. To overcome these problems, scientists have developed innovative drug delivery system known as fast dissolving/disintegrating tablets (FDTs). These are novel types of tablets that dissolve/disintegrate/disperse in saliva within few seconds. There are several factors that should be considered while selecting an appropriate drug candidate for development of orally disintegrating dosage forms. The ultimate characteristics of a drug for dissolution in the mouth and pregastric absorption from ODTs include:

1. Ability to permeate oral mucosal tissue.
2. Good solubility in water and saliva.
3. Free from bitter taste.
4. Dose lower than 20 mg.
5. Ability to diffuse and partition into the epithelium of the upper GIT (log P >1, or preferably>2).
7. Partially non-ionized at the oral cavity's pH.

Advantages of Fast Dissolving Tablets\textsuperscript{[6, 7]}
1. Easy to administer to the patient who cannot swallow such as paediatric, geriatric, bedridden, stroke victim and institutionalized patient (specially for mentally retarded and psychiatric patients)
2. Pregastric absorption leading to increased bioavailability/ rapid absorption of drugs from mouth, pharynx and oesophagus as saliva passes down to stomach, also avoids hepatic metabolism.
3. Convenient for administration to traveling patients and busy people who do not have accesses to water.
4. Excellent mouths feel property produced by use of flavours and sweeteners help to change the perception of “medication as bitter pill” especially in paediatric population.
5. Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action.
6. ODTs offer all the advantages of solid dosage forms and liquid dosage forms.
7. Convenience of administration and accurate dosing compared to liquids.

Disadvantages of Fast Dissolving Tablets\textsuperscript{[8, 9]}
1. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
2. Formulations are hygroscopic, fragile and effervescence in nature.

Drug selection criteria for ODT
The ideal characteristics of a drug for oral dispersible tablet include \textsuperscript{[10]}
1. Ability to permeate the oral mucosa.
2. At least partially non-ionized at the oral cavity pH.
3. Have the ability to diffuse and partition into the epithelium of the upper GIT.
4. Small to moderate molecular weight.
5. Low dose drugs preferably less than 50 mg.
6. Short half-life and frequent dosing drugs are unsuitable for ODT.
7. Drug should have good stability in saliva and water.
8. Very bitter or unacceptable taste and odour drugs are unsuitable for ODT.
9. Drugs with different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. The drugs that produce toxic metabolites by first pass liver metabolism.

10. Drugs that diffuse into the epithelium of the upper GIT and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.

EXCIPIENTS TO BE USED IN FAST DISOLVING [11-17]

Tablets
Important ingredients that are used in the formulation of fast-disintegrating tablets should allow quick release of the drug, resulting in faster dissolution. This includes both the active and inactive ingredients. Excipient balances the properties of the actives in fast-disintegrating tablets.

Binders
During the compression, binders keep the composition of these fast dissolving tablets together. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. Binders can either be liquid, semi-solid, solid or mixtures of varying molecular weights.

Lubricants
Lubrications are used for to reduce the friction during compaction and ejection of tablets in present study magnesium stearate and talc were used as lubricant.

Bulking agent
The material contributes functions of a diluents, 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 manifold.

Flavours and Sweeteners
The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sugar alcohols and sucralose.
Superdisintegrants / Role of superdisintegrants

Superdisintegrants are effective at low concentration, have greater disintegrating efficiency and they are more effective intra granularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. Various Superdisintegrants which can be used in the formulation of fast dissolving tablets.

As day’s passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

![Figure 1: Mechanism of superdisintegrants by swelling.](image1)
![Figure 2: Disintegration of Tablet by Wicking and Swelling.](image2)
By Capillary Action\textsuperscript{[18]}
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.

Due to deformation: \textsuperscript{[19]}
During tablet compression, disintegrant particles get deformed 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 breakup of the tablet. This may be a mechanism of starch and has only recently begun studied.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{deformation.png}
\caption{Showing deformation of superdisintegrant particles.}
\end{figure}

Due to enzymatic reaction: \textsuperscript{[20]}
Here, enzymes present in the body act as disintegrants. These 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.
Conventional Techniques Used In the Preparation of ODT [21-27]

**Freeze drying or lyophilization**
A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization processes imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristic of the formulation. The entire freeze drying process is done at non-elevated temperature to eliminate adverse thermal effects that may affect drug stability. The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions and their limited ability to accommodate adequate concentration of drugs. [11-15]

**Direct compression**
Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water absorption capacity. Studies revealed that the water insoluble superdisintegrants like sodium starch glycolate and Croscarmellose sodium show better disintegration property than the slightly water soluble agents like Crospovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants. [7, 16]
Molding
In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

Spray Drying
Spray drying is a process by which highly porous, fine powders can be produced. Spray drying technique for preparing fast dissolving tablets. The composition contained a bulking agent (e.g.: mannitol and lactose), a disintegrant (e.g.: sodium starch glycolate and croscarmellose sodium), an acidic ingredients (citric acid), and/or alkaline ingredients (e.g.; sodium bicarbonate) which when compressed into tablets showed fast disintegration and enhanced dissolution. The fast dissolving tablets prepared from spray drying technique disintegrated within 20 seconds.

Mass-Extrusion
This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

Taste Masking
Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking ingredients can be achieved by various techniques; Drugs with unacceptable bitter taste can be microencapsulated into PH sensitive acrylic polymers. Cefuroxime axetile is microencapsulated in various types of acrylic polymers (e.g eudragit E eudragit L-55 and eudragit RL) by solvent evaporation and solvent extraction techniques.

Melt granulation
Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. For accomplishing
this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). Superpolystate© is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilises rapidly leaving no residues.

Sublimation
The slow dissolution of the compressed tablet containing even highly water soluble ingredients is due to the fact that the low porosity of the tablets reduces water penetration into the matrix. When inert volatile solid ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane were added to along with other tablet excipients and the blend was compressed in to a table, which are finally subjected to a process of sublimation resulting in highly porous structures. Sublimation has been used to produce MDTs with high porosity. These compressed tablets exhibit good mechanical strength and have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

EVALUATION OF ODTs [28-33]

Friability
To achieve % friability within limits for an ODT is a challenge for a formulator since all methods of manufacturing of ODT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1-0.9%).

Hardness
A significant strength of ODT is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness test.

Wetting time and water absorption ratio
Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the
disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio, R can be the determined according to the following equation.
\[ R = \frac{100 \times (Wa - Wb)}{Wb} \]

**Disintegration test**
The time for disintegration of ODTs is generally <1min and actual the disintegration time that patients can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents.

**Moisture uptake studies**
Moisture uptake studies for ODT should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a dessicator over calcium chloride at 37°C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator for 3 days. One tablet as control (without super disintegrants) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

**Dissolution test**
The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to
obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets.

**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.

**Accelerated Stability study**

The Orally disintegrating 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 Relative Humidity= 75% ± 5%

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

**Packaging**

Packaging special care is required during manufacturing and storage to protect the dosage of other fast-dissolving dosage forms. Quick-dispersing and/or dissolving oral delivery systems, the system can be packaged using various options, such as single pouch, blister card with multiple units, multiple unit dispenser, and continuous roll dispenser, depending on the application and marketing objectives.
CONCLUSION

Mouth dissolving Tablets is the general form of nomenclature for tablets that disintegrate rapidly or instantly in the oral cavity. They are a very good alternative for drug delivery to geriatric and pediatric patients. They have significant advantages of both solid and liquid dosage forms, as they remain solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration.

The future potential for these products is promising because of the availability of new technologies combined with strong market acceptance and patient demand. Future possibilities for improvements in Rapid disintegrating and drug delivery are bright, but the technology is still relatively new.

REFERENCES