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ORO DISPERSIBLE TABLETS: A NOVEL APPROACH

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ABSTRACT

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of physico-chemical and biochemical parameters pertinent to their performance. Novel ODT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatrics, geriatrics and psychiatric patients who have difficulty in swallowing (dysphagia) conventional tablets and capsules. Aim of this article is to review the development of ODTs, challenges in formulation, new ODT technologies and evaluation methodologies, suitability of drug candidates and future prospects.

Key Words: Disintegrating time, Oral disintegrating tablets, Patented technologies, Superdisintegrants.

INTRODUCTION

The drug which intended to produce the therapeutic effect in systemic circulation, the oral route of drug delivery is preferred. These include traditional and conventional dosage form that is tablet. Tablets are most widely used dosage form because of its convenience in terms of self-administration compactness and unit dosage. However geriatric, pediatric, bedridden, mentally disabled who may face difficulty in swallowing conventional tablets and also those having persistent nausea sudden episode of allergic attacks or coughing leads to ineffectiveness of therapy (Narmada GY *et al.*, 2009). It is estimated that 50% of population is affected by this problem (Na Zhao *et al.*, 2005). To overcome this weakness pharmaceutical technologists have designed innovative drug delivery system known as oral disintegrating tablet (Jaysukh J Hirani *et al.*, 2009). Rapid disintegrating tablets are those solid dosage forms when put on tongue disintegrate or dissolve instantaneously releasing the drug within few seconds without the need of water. When this type of tablet is placed in mouth the saliva will serve to rapid disintegration of the

tablet (Kuldeep M *et al.*, 2010). However the proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets (Na Zhao *et al.*, 2005).

Rapid disintegrating tablets (RDT) are also known as 'fast dissolving', 'mouth dissolving', 'rapid-dissolve', 'quick disintegrating', 'orally disintegrating', 'rapimelt', 'fast melts', 'orodispersible', 'melt-in-mouth', 'quick dissolving', 'porous tablets', 'EFVDAS' or 'Effervescent Drug Absorption System'. USFDA defined OD tablet as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". RDT release drug in the mouth for absorption through local oromucosal tissues and through pregastric (i.e., oral cavity, pharynx and esophagus), gastric (i.e., stomach) and postgastric (i.e., small and large intestine). In such cases, 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 are significantly greater than those observed from conventional dosage forms (Kuldeep Mehta *et al.*, 2010).

When RDT is placed in the mouth saliva causes it to dissolve rapidly within 60 seconds and disperse the dosage form into saliva containing drug medicament. From

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this the active pharmaceutical ingredient is absorbed in to blood stream (Deepak K *et al.*).

The aim of rapid disintegrating tablets (RDT) drug delivery is to produce good- tasting tablets that disintegrate in a reasonable time without the need for water. Drugs have varying levels of bitterness and dosage. It may be acceptable to have a small amount of drug taste present in the final product. Clearly, patient compliance must be taken into account when developing any new drug products and this is where RDT products have a clear benefit for patients.

Creating an Oro-Dispersible Tablet version of an existing immediate-release product means that the two formulations must be bioequivalent (create the same therapeutic effect in the same time frame). This can be challenging, especially if the method of taste masking retards the dissolution rate of the active ingredient after disintegration of the Oro-dispersible tablet. Contrary to some patients' perceptions, shorter disintegration times do not necessarily mean quicker absorption. Typically, depending on the regulatory strategy, the pharmaceutical company wants to see drug dissolution rates for an Oro-dispersible tablet that are similar to the immediate-release innovator, at least until an In Vivo In Vitro Correlation can be made. Oro-dispersible tablet formulations are designed to disintegrate quicker than their counterparts, and this can lead to difficulties finding a discriminating dissolution test method. If, for example, 90% of the drug is released in 5 minutes, any small batch-to-batch changes may be difficult to identify. Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

SELECTION OF DRUGS FOR THE ODT FORMULATIONS

Generally, ODTs are formulated as bio-equivalent extensions of existing oral dosage forms. Under these circumstances, it is assumed that the absorption of drugs from ODTs occurs in the postgastric gastrointestinal tract segments, similar to the conventional oral dosage form. Nevertheless, this scenario may not always be the case. An ODT may have varying degrees of pregastric absorption of drugs and thus, the pharmacokinetic profiles of drugs will vary. Therefore, the ODTs will not be bioequivalent to the conventional dosage forms. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profile

compared with the name dose administered in a conventional dosage form. If significantly higher plasma levels have been observed, pregastric absorption leading to the avoidance of first-pass liver metabolism may play a significant role. This situation may have implications for drug delivery and efficacy, which may need to be addressed and assessed in a marketing application for an ODT. The ideal characteristics of a drug for *in vivo* dissolution from an ODT include (Amit Kumar N *et al.*, 2011):

- i. No bitter taste.
 - ii. Small to moderate molecular weight.
 - iii. Good stability in water and saliva.
 - iv. Partially non-ionized at the oral cavities pH.
 - v. Ability to diffuse and partition into the epithelium of the upper GIT ($\log P > 1$, or preferably > 2).
 - vi. Ability to permeate oral mucosal tissue.
- Unsuitable drug characteristic for ODTs:
- i. Short half-life and frequent dosing.
 - ii. Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
 - iii. Required controlled or sustained release.

ADVANTAGES (Velmurugan S *et al.*, 2010)

- Easy to administer to the patient who cannot swallow such as pediatric, geriatric, bedridden, stroke victim and institutionalized patient (specially for mentally retarded and psychiatric patients)
- 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.
- Convenient for administration to traveling patients and busy people who do not have access to water.
- Excellent mouth feel properly produced by use of flavours and sweeteners help to change the perception of "medication as bitter pill" especially in pediatric population.
- Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action.
- ODTs offer all the advantages of solid dosage forms and liquid dosage forms.
- Convenience of administration and accurate dosing compared to liquids.

DESIRED CRITERIA FOR ODTs (Velmurugan S *et al.*, 2010)

- ODT should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
- Effective taste masking technologies should be adopted for bitter taste drugs.
- Exhibit low sensitivity to environment condition such as humidity and temperature.

- ODTs should dissolve / disintegrate in the mouth in matter of seconds without water.
- Have sufficient mechanical strength and good package design.
- The drug and excipients property should not affect the orally disintegrating tablets.
- Be portable and without fragility concern.

IMPORTANT CRITERIA FOR EXCIPIENTS USED IN THE FORMULATION OF ODTs (Rangasamy M, 2005)

- It must be able to disintegrate quickly.
- Their individual properties should not affect the ODTs.
- It should not have any interactions with drug and other excipients.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When selecting binder a (single or combination of binders) care must be taken in the final integrity and stability of the product.
- The melting points of excipients used will be in the range of 30-35°C.
- The binders may be in liquid, semi liquid, solid or polymeric mixtures. (Ex: Polyethylene glycol, cocoa butter, hydrogenated vegetable oils).

TECHNOLOGIES FOR PREPARING ODTs

Various processes employed in formulating ODT's including conventional technologies and patented technologies.

CONVENTIONAL TECHNOLOGIES

Lyophilization or Freeze-drying

Freeze-drying or lyophilization is a process in which solvent is removed from a frozen drug solution or suspension containing structure-forming excipients. This technology consists of three phases (Amit Kumar Nayak *et al.*, 2011):

1. Freezing to bring the material below its eutectic zone
2. Sublimation or primary drying to reduce moisture to around 4 % w/w of dry product.
3. Desorption or secondary drying to reduce bound moisture to the required final value.

The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermolabile substances. This technology forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture ODTs.

The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspensions. Primary problems associated with water-soluble drugs are formation of

eutectic mixture, because of freezing point depression (FPD) and formation of glassy solid on freezing which might collapse on sublimation. The addition of cryoprotectants like mannitol, crystal-forming materials induces crystallinity and imparts rigidity to amorphous material and can prevent collapse of structure and mask the bitter taste. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at non-elevated temperature, thereby eliminating adverse thermal effects. However, high cost of equipment and processing limits the use of this process. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms.

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 effervescent 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 super disintegrants 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. Super disintegrants 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 (Velmurugan S *et al.*, 2010).

Molding

Molding process is of two type's i.e. solvent method and heat method.

Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to

form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution.

The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture (Debjit B *et al.*, 2009).

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 shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with different super disintegrate e.g. sodium starch glycolate, croscarmellose sodium and crosspovidone etc (Velmurugan S *et al.*, 2010).

Melt granulation

Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder that can be a molten liquid, a solid, or a solid that melts during the process. 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. Abdelbary *et al.* prepared orally disintegrating tablet by incorporating a hydrophilic waxy binder PEG 6-stearate (Superpolystate®) in the formulation. It has melting point of 33-37°C and HLB value of 9. It acts as a binder and increases the physical resistance of tablet. It helps for fast disintegration of tablet when placed in mouth and leaving no residue in oral cavity. Perissutti *et al.* developed the orally disintegrating tablets of carbamazepine by melt granulation technique. The granules were prepared by using polyethylene glycol (PEG-4000) as a melting binder and lactose monohydrate

as hydrophilic filler without using solvents or water. The dissolution profiles of granules containing crosspovidone as an intragranulating agent were found to be superimposable to those prepared without it. In addition, the extragranular addition of a small amount of crosspovidone gave rise to a further increase in disintegration rate and dissolution performances (Amit Kumar N *et al.*, 2011).

Phase transition process

In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. The combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, is important for making ODTs without any special apparatus. Here, tablet produced by compressing the powder containing two sugar alcohols of high and low melting point and subsequently heating at temperature between their two melting points. Orally disintegrating tablets were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol. Before heating process, tablet did not have sufficient hardness because of low compatibility but after heating, increase in interparticulate bonding or binding surface area occurs which then increased tablet hardness (Amit Kumar N *et al.*, 2011).

Sublimation

This technique is based on the use of volatile ingredients (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc.) to other tablet excipients and the mixture is then compressed into tablets. Entrapped volatile material is then removed via sublimation, which leads to formation of a porous structure. These compressed tablets which have high porosity (approximately 30 %) rapidly dissolved within 15 seconds in saliva. Several solvents like cyclohexane, benzene etc, can also be used as pore forming agents. Orodispersible tablets with highly porous structure and good mechanical strength have been developed by this method. Makino *et al.* described a method of producing a fast dissolving tablet using water as a pore forming material. They used a mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc) which then moistened with water (1-3 % w/w) and compressed into tablets. Then water was removed, yielding highly porous tablet (Amit Kumar N *et al.*, 2011).

Spray Drying

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated

during this process. Spray drying process was employed by Allen and Wang to prepare ODT. Hydrolyzed and non-hydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent, sodium starch glycolate as superdisintegrant, citric acid and sodium bicarbonate were used to enhance disintegration and dissolution (Rangasamy M 2005).

Oral Disintegrating Thin Films

It is a newer developing front in ODT that provides a very suitable means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.) drug and other taste masking ingredients are dissolved in non aqueous solvent to prepare non-aqueous solution, which forms a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. After placing this film in mouth, it melts or dissolves rapidly and releases the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 seconds with instant drug delivery and flavoured taste (Amit Kumar N *et al.*, 2011).

Taste Masking Technologies

Pharmaceutically active ingredients may leave an unpleasant taste after administration. A new generation of rapidly dissolving and safely swallowable tablets films etc. that are being developed should have sweet and pleasant taste. Various types of orally disintegrating formulation containing drugs in the taste masked form are available like chewing gums or tablets, multiparticulates or microparticulates, microspheres or comestible units, microcapsules, nanocrystals etc (Amit Kumar Nayak *et al.*, 2011).

PATENTED TECHNOLOGIES (Rangasamy M 2005)

Zydis technology

Zydis is a unique freeze dried oral solid dosage form that can be administered without water and it dissolves instantly on tongue in less than 3 sec. The drug is physically trapped in a water soluble matrix, and then freeze dried to produce a product that rapidly dissolves. The matrix consists of water soluble saccharides and polymer (gelatin, dextran, alginates) to provide rapid dissolution and to allow sufficient physical strength to withstand handling. Water is used during the process to produce porous units for rapid disintegration. Various gums are used to eliminate sedimentation problem of dispersed drug. Glycine is used to prevent the shrinkage of zydis unit during the process and long term storage. As the zydis dosage form is weak in physical strength, unit is contained in peelable blister pack, which allows removal of

product without damaging it. An ideal drug candidate for zydis would be chemically stable and water insoluble and should have small particle size (Less than 50 microns). Water soluble drugs might form eutectic mixtures and not freeze adequately, hence the dose is limited to 60mg. larger drug particles might present sedimentation problem during processing.

Orasolv technology

It is CIMA lab's first fast dissolving formulation. Tablets are prepared by direct compression at low compression force in order to minimize oral disintegration and dissolution time. Orasolv technology is an example of slightly effervescent tablet that rapidly dissolve in mouth. The active medicaments are taste masked and dispersed in saliva due to the action of effervescent agents. It provides the pleasant sensation in mouth of the patient. The major disadvantage of Orasolv technology is its low mechanical strength. The tablets produced are soft and friable and need to be packaged in specially designed pack.

Durasolv technology

It is also a patented technology by CIMA lab, producing second generation ODT's. The tablets prepared by this technology contain drug, fillers, lubricant and tablets prepared by conventional equipments. Durasolv formulations have higher mechanical strength than its predecessors due to application of higher compaction pressure. Durasolv product is so durable that it can be packed in either traditional blister pack or vials. It is one of the appropriate technologies for product requiring low amounts of active ingredients.

Wow tab technology

It is patented by yamanouchi Wow means "without water". Wow tab is an intra buccally soluble, compressed tablets consisting of granules made with saccharides of low and high mouldability. It is used to obtain a tablet of adequate hardness and fast dissolution rate. Mouldability is that capacity of the compound to be compressed. Low mouldability means the compound shows reduced compressibility for tableting and rapid dissolution rate. But in case of high mouldability compounds this context is reversed. In this the active ingredients is mixed with low mouldability saccharides and then compressed into tablet. The wow tab formulation is stable to environment due to its significant hardness than zydis and Orasolv. Wow tab product is suitable for both conventional bottle and blister package.

Cotton candy technology

It is patented by Fuisz. Cotton candy technology utilizes a unique spinning mechanism to produce floss like crystalline structure. This crystalline sugar can incorporate the active drug into a tablet. A final product has a very

high surface area for dissolution. Once placed on the tongue it disperses and dissolves quickly.

Oraquick technology

The oraquick ODT formulation utilizes a patented taste masking technology by KV Pharmaceutical Company, who claims that its taste masking technology i.e., microsphere technology (Micromask) 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 superior efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression. Oraquick claims quick dissolution in matter of seconds with good taste masking. There are no products yet in the market using oraquick technology, but KV pharmaceutical has products, having different classes of drugs such as analgesics, cough and cold, psychotics and ant infective, in developmental stage.

Nanocrystal technology

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

Shearform technology

It is based on preparation of floss that is known as shear form matrix, which is produced by subjecting a feedstock containing a sugar carrier by flash heat processing. In this process, 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 mass. The flowing mass exists through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide uniform flow properties and thus facilitate blending. The recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet. The active ingredient and other excipients can be blended with floss before carrying out recrystallisation. The shear form floss, when blended with the coated or uncoated microspheres, is compressed into flash dose or EZ chew tablets.

Pharmaburst technology

SPI Pharma, New castle, patents this technology. It utilizes the coprocessed excipients to develop ODT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by

compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and coprocessing at low pressure to produce strong tablets with high porosity. Plastic granules composed of:

1. Porous and plastic material
2. 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. There are several commercial products available in market for orally disintegrating tablets (Yourong Fu *et al.*, 2004) that are given in Table 1. Specific properties of the various ODT technologies (Jaysukh J Hirani *et al.*, 2009) are listed in Table 2

EVALUATION OF ODT's

Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests are discussed here (Velmurugan S *et al.*, 2010)

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.

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%).

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 determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

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 tablet 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.

Determination of Disintegration Time (Yourong Fu *et al.*, 2004)

FDTs should be strong enough to survive rough handling during manufacturing and shipping processes, and yet friable enough to instantly dissolve or disintegrate into small particles for easy swallowing by the patient. Conventional disintegration tests for ordinary tablets may not allow precise measurement of the disintegration time of FDTs because of their fast disintegration. It is also hard to distinguish among FDTs, which release their ingredients very quickly. In vitro testing may not always reflect the real in vivo disintegration of tablets. In general, the method described in the US Pharmacopoeia can produce data for

evaluation of the disintegration time; however, no additional information might be extracted. It is also possible to evaluate the tendency of the disintegration kinetics by visual examination. However, these evaluations are not sufficiently objective. When developing FDT formulations, it is important to evaluate the effect of different excipients on the disintegration time. In order to predict the disintegration time of FDTs and the effects of different formulation parameters, a few methods have been proposed. It is important to define a suitable method to better distinguish between the disintegration times of different FDTs and to find better correlation between in vitro and in vivo data. To achieve this goal, a modified dissolution apparatus was applied to FDTs with disintegration times too fast to distinguish the differences between the tablets when the conventional methods were used.

In Vivo Determination of Disintegration Time

In vivo disintegration tests of FDTs can be conducted on volunteers who are usually randomized to receive the treatments and then directed to clean their mouths with water. Tablets are placed on their tongues, and the time for disintegration is measured by immediately starting a stopwatch. The volunteers are allowed to move FDTs against the upper roof of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable granule has disintegrated, the stopwatch is stopped and the time recorded.

IN VITRO DETERMINATION OF DISINTEGRATION TIME

Modified US Pharmacopoeia Method

Instead of using the disintegration apparatus described in the US Pharmacopoeia, a modified method has been proposed. The disintegration apparatus was the same as the USP dissolution test Apparatus 2, which uses a paddle stirring element and 1000-mL cylindrical vessel at 37°C. Distilled water was chosen for the disintegration medium instead of a buffer solution. A tablet to be tested was put on the bottom of a sinker, which was placed in the middle of the vessel and hung by a hook to the lid of the vessel with a distance of 6–8.5 cm. Disintegration time was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely. The opening of mesh of the sinker was 3–3.5 mm in height and 3.5–4 mm in width.

Texture Analyzer Method

The Texture Analyzer (Stable Micro Systems, U.K.) was applied to measure the beginning and ending time of disintegration. A tablet was adhered to the bottom of a probe, which was attached to the load cell with a very thin layer of glue or double-sided tape. A small amount of water, usually 0.4 mL, in a beaker or petri dish was used as

a disintegration medium at room temperature. The tablet was submerged in water and compressed against the bottom of the beaker or petri dish with a constant pressure. The beaker size could be varied, and the beaker could even be a water bath to keep the temperature constant.

The instrument was programmed to apply a moderate force for up to 60 seconds so that the penetration distance could be measured as the tablet was compressed while submerged in the water. The probe distance would be steady as the tablet remained cohesive.

However, as the tablet disintegrated, the compression distances increased, because the probe had to keep the pressure constant. The time for the tablet to disintegrate was determined by measuring the distance the probe travelled into the tablet. Typical time-distance profiles generated by the Texture Analyzer software enabled the calculation of beginning and ending of disintegration time.

CCD Camera Method

The CCD camera apparatus comprises two distinct sections—a disintegration component and a measurement device. The mode of measurement involves the continuous acquisition of pictures by the CCD camera to record the time course of disintegration. The acquired pictures are simultaneously transferred to the computer and stored. The key point of this apparatus is to combine the detailed pictures obtained by the CCD camera.

The disintegration apparatus consists of a plastic cell partitioned into two parts: one component comprises an inner tank containing a stirring bar, a grid fabricated from stainless-steel, and a disintegration medium (distilled water, 200 mL, 37 ± 2 °C); the second component is an outer tank of thermostated water. The grid is constructed of three hollow areas equidistant from the centre.

These hollow points represent the position of the tablets, and a support is added for each tablet to avoid movement during the disintegration test. The CCD camera method permits documentation of the disintegration time course with sequentially obtained pictures.

The computer enables calculation of the surface area of each tablet at any time point, as well as the design of graphs that show decrease in the tablet surface area as a function of time. The disintegration time and the area under the curve can be calculated from these graphs as qualitative parameters that can be correlated to the oral disintegration time. Consequently, results depend on the direction and focal length of the camera relative to the tablet.

The disadvantage of the method involves difficulty associated with the application of mechanical stress to test tablets. Thus, the time required for a single test is several minutes, which is greater than that for the *in vivo* disintegration time.

Rotary-Shaft Method

FDTs generally receive some mechanical stress produced by the tongue in the human mouth. Narazaki *et al.* developed a suitable disintegration method for FDTs. In this method, the FDT is placed on stainless steel wire gauze, which is slightly immersed in test medium, and a rotary shaft is employed to provide mechanical stress to the tablet by means of its rotation and weight. The critical parameters of this method are the rotation speed and the mechanical stress. To assess our method, several placebo FDTs were prepared and exposed to severe storage conditions (60 °C/75% RH for 1 week) in order to obtain FDTs with a wide range of disintegration times. These placebo FDTs were used to compare the disintegration times obtained by several methods, including the proposed Rotary-Shaft method. The disintegration time of the placebo FDTs in human sensory test varied widely after storage. The disintegration times determined by the conventional disintegration test were in good correlation to those in the human sensory test, but the slope was 0.241, far from 1.

There was no correlation between the disintegration time of FDTs in the human sensory test and those determined by the conventional dissolution test. In contrast, a good correlation between the disintegration times was obtained with the new Rotary-Shaft method and the human sensory test, and the slope was 0.858, very close to 1. It was concluded that the proposed Rotary-Shaft method was suitable for the measurement of the disintegration time of FDTs. This new method might provide a valuable approach for establishing the official disintegration test for FDTs in the future.

Sieve Method

A simple device based on a shaking water bath was designed to measure the disintegration time of FDTs. The device is composed of a 10-mesh sieve and a glass cylinder. The sieve is placed into the cylinder at a certain position so that 2 mL of disintegration medium fills the space below the sieve of the cylinder. Then, 1 mL of the medium is added into the device, so that it is available for an FDT to be tested. The device is in a reciprocal shaking water bath keeping the temperature at 37°C.

While the shaker is running in horizontal back-and-forth motions with 150 rpm, an FDT is placed onto the top of the sieve immersed in the disintegration medium. The FDT starts disintegration into small particles and/or dissolution, and the time at which the particles of the tablet go through the sieve completely is determined as the disintegration time. The disintegration time is measured using a stopwatch, and this quick method gives reproducible data that are highly useful in screening various formulations and testing many formulation variables.

Table 1. Examples of Commercially Available, Preapproval, or Submitted ODT Products

Brand Name	Active Ingredient	Application	Company	Technology
Claritin [®] RediTabs [®]	Loratadine	Antihistamine	Schering Corporation	Zydis [®]
Feldene Melt [®]	Piroxicam	NSAID	Pfizer	
Maxalt [®] -MLT [®]	Rizatriptan benzoate	Migrane	Merck	
Pepcid [®] ODT	Famotidine	Anti-ulcer	Merck	
Zyprexa [®]	Olanzapine	Psychotic disorders	Eli Lilly	
Zofran [®] ODT [®]	Ondansetron	Anti-emetic	Glaxo Smith Kline	
Risperdal [®] M-Tab [™]	Risperidone	Schizophrenia	Janssen	
Zubrin [™] (Pet drug)	Tepoxalin	Canine NSAID	Schering Corporation	
Zelapar [™]	Selegiline	Parkinson's disease	Elan/Amrian Corporation	
Klonopin [®] Wafers	Clonazepam	Sedation	Roche	
Children's Dimetapp [®] ND	Loratadine	Allergy	Wyeth Consumer Healthcare	Quicksolv [®]
Imodium Instant Melts	Loperamide HCl	Anti-diarrheal	Janseen	
Propulsid [®] Quicksolv [®]	Cisapride monohydrate	Gastrointestinal prokinetic agent	Janssen	OraSolv [®]
Tempra Quicklets Tempra Firs Tabs	Acetaminophen	Analgesic	Bristol-Myers Squibb	
Remeron [®] SolTab [®]	Mirtazapine	Anti-depression	Organon Inc	
Triminic [®] Softchews [®]	Various combinations	Pediatric cold, cough and allergy	Novartis Consumer Health	DuraSolv [®]
Zomig-ZMT [®] and Rapimelt [®]	Zolmitriptan	Anti-migraine	AstraZeneca	
Alavert [®]	Loratadine	Allergy	Wyeth Consumer Healthcare	
NuLev [®]	Hyoscyamine sulphate	Anti-ulcer	Schwarz Pharma	
Kemstro [®]	Baclofen	Anti-spastic analgesic	Schwarz Pharma	WOWTAB [®]
Benadryl [®] Fastmelt [®]	Diphenhydramine citrate	Allergy, sinus pressure relief	Pfizer	
Nasea OD	Ramosetron HCl	Anti-emetic	Yamanouchi	
Gaster D	Famotidine	Anti-ulcer	Yamanouchi	
Excedrin [®] Quick Tabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb	Quick Tabs [™]
Ralivia FlashDose [®]	Tramadol HCl	Analgesic	Biovail	FlashDose [®]
Zolpidem ODT	Zolpidem tartrate	Sleep disorders	Biovail	
Fluoxetine ODT	Fluoxetine	Anti-depression	Biovail	
Nurofen [®] Flashtab [®]	Ibuprofen	NSAID	Boots Healthcare	Flashtab [®]
Hyoscyamine Sulfate ODT	Hyoscyamine sulphate	Anti-ulcer	Ethex Corporation	OraQuick
Cibalginadue Fast	Ibuprofen	NSAID	Novartis Consumer Health	Ziplets [™]

Table 2. Advantage and disadvantage of Patented technologies

Technique	Novelty	Advantage(s)	Disadvantages(s)
Zydis	First to market, Freeze dried	Quick dissolution, Self-preserving, increased bioavailability	Expensive process, poor stability at higher temperatures and humidities
Orasolv	Unique taste-masking, lightly compressed	Taste-masking is twofold, quick dissolution	Low mechanical strength
Durasolv	Compressed dosage form, proprietary taste masking	Higher mechanical strength than Orasolv, good rigidity	Inappropriate with larger doses
Flash Dose	Unique spinning mechanism to	High surface area for	High temperature required to

	produce a floss-like crystalline structure, much like cotton candy.	dissolution	melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity
Flashtab	Compressed dosage form containing drugs as microcrystals.	Only conventional tableting technology is required	--
Wowtab	Combination of low-mouldability and high-mouldability saccharides. SMOOTHMELT action gives superior mouth feel.	Adequate dissolution rate and hardness	No significant change in bioavailability
Oraquick	Uses patented taste-masking technology	Faster and efficient production, appropriate for heat-sensitive drugs	--
Ziplet	Incorporation of water-insoluble inorganic excipients for excellent physical performance	Good mechanical strength, handling problems during manufacturing are avoided, satisfactory properties can be obtained at high dose (450mg) and high weight (850mg)	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution.

CONCLUSION

The area of formulating orally disintegrating dosage forms aims at increasing the patient compliance and decreasing the disintegration time and finally masking the objectionable taste of active ingredients thus making it an attractive drug delivery form. 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 liquids within few seconds of administration. The techniques depicted in this article

demonstrates how advances in formulation development and processing technologies meet the efforts to achieve more sophisticated drug delivery system (ODT). Due to the availability of various formulation techniques several products have already been commercialised. This article also emphasises on how new developments and innovations should be undertaken for the emergence of promising and versatile dosage form with novel performance.

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