Review Article

Oral Disintegrating Tablets: Background and Review on Recent Advancements

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Abstract

Most of the drug products available in the market are for oral drug administration. Oral route is preferred due to ease of administration, versatility, patient compliance and accurate dosing. However, oral administration is not suitable for people with dysphasia, a condition that results in difficulty in swallowing. Also, for many geriatric and pediatric patients, oral administration might not be a preferred route. In this regards, oral disintegrating tablets (ODT) provide a useful alternative. When ODT comes in contact with saliva, these tablets disintegrate instantaneously (within 30 sec) resulting in the release of drug. Furthermore, since it undergoes pre-gastric absorption, it bypasses first pass metabolism, which can be beneficial for drugs with significant hepatic metabolism. This review article discusses the traditional and advanced technologies utilized in manufacturing of ODT, excipient selection and quality control test. The article also discusses its application in various disease conditions.

Keywords: Oral disintegrating tablets, dysphasia, swallowing problems, orodispersible tablets, oral films, lyophilization

Introduction

In past decade, formulation research and pharmaceutical industry has witnessed new advances in oral (Kong et al., 2016; Kwong, 2017; Sharma et al., 2016) and topical/transdermal field (Jain et al., 2016; Jain et al., 2017; Patel et al., 2016a; Patel et al., 2015). Among them, the major advances came in the field of oral drug delivery, which is traditionally considered as preferred route for delivery. This route of administration is considered as the most widely used route as it offers advantages like ease of administration, versatility, patient compliance and accurate dosing (Morishita and Peppas, 2006). The companies are therefore constantly focusing on various oral delivery systems that offer greater patient compliance, effective dosages and minimal chances of side effects. However the oral route might not be a preferred route in certain cases (Lindgren and Janzon, 1991).

- The difficulty in swallowing i.e. dysphasia is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups. 35% in the general population, 30-40% of elderly institutionalized patients and 18-22% of all persons in long term care facilities have this problem (Ekberg et al., 2002). Hence they might not comply with prescription, which results in non-compliance and ineffective therapy.
- Unpleasant taste is also one of the important formulation problems that are encountered with such oral product.
- In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult.
- Faster onset of action required for faster relief.

Hence considering the aforementioned scenarios, the solid dosage form that can be administered or swallowed as a liquid where in the bitter taste of drug is masked would be the ideal dosage form. One such approach is oral disintegrating tablets (ODT) or fast disintegrating/ dissolving tablets (FDDT). ODT provides patient with more conventional means of taking their medication, however, at the same time, it overcomes all the major problems of conventional solid dosage form as mentioned above. When they come in contact with tongue, these tablets disintegrate instantaneously which results in faster

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drug release which then dissolves or disperses in the saliva. According to the FDA Guidance 'ODTs [should] be considered oral preparations that dissolve/disintegrate rapidly in the oral cavity, with an *in vitro* disintegration time of approximately 30 seconds or less". Some of the commercially available ODT products are mentioned in Table 1 Adapted from (Cremer, 2003).

Table 1. Some commercially available ODT products in the market

Products	ODT Company/Partner
Benadryl Fastmelt	Yamanouchi/Pfizer
Claritin Reditabs	R.P. Scherer/Schering-Plough
Tempra FirsTabs	CIMA/Mead Johnson
Excedrin QuickTabs	Ethypharm/BMS
Maxalt MLT	R.P Scherer/Merck
Remeron SolTabs	CIMA/Organon
Riaminic SoftChews	CIMA/Novartis Consumer Health
Zofran ODT	R.P. Scherer/Glaxo Smithkline
Zyprexa Zydis	R.P. Scherer/Merck

ODT can be manufactured by a variety of technologies, including direct compression, wet granulation, and freeze drying. Some techniques use different disintegrating mechanisms, such as super-disintegrants and/or effervescent agents, which cause the tablets to disintegrate rapidly in the mouth.

Desired Criteria for ODT

General criteria for ODT are highlighted below (Lorenzp-Lamosa et al., 1997; Patel et al., 2006):

- Do not require water to swallow
- Be compatible with taste masking.
- Be portable without fragility concern.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allows the manufacturing of tablet using conventional processing and packaging equipment at low cost.

Advantages of ODT

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations, while also offering the advantages over both traditional dosage forms. It provides the convenience of a tablet formulation, while also allowing the ease of swallowing provided by a liquid formulation. The major advantages of ODT are highlighted below:

- Allows high drug loading.
- No water needed
- No chewing needed
- Better taste
- Improved stability
- Suitable for controlled/sustained release actives
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery
- Cost- effective

ODT can also significantly increase the oral bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those cases (Velmurugan and Vinushitha, 2010). As ODT undergo pre-gastric absorption, it bypasses first pass metabolism, which can be beneficial for drugs with significant hepatic metabolism.

Key Ingredients of ODT formulation

Important ingredients that are used in the formulation of ODT should allow instant release of the drug and consequently faster dissolution. Therefore, selection of excipients is critical for ODT formulations (Hirani et al., 2009). Excipients balance the properties of the actives in fast-dissolving tablet and demand a thorough understanding of the chemistry of these excipients to prevent interaction with the actives.

Binders keep the composition of these ODT together during the compression stage. The selection of a binder or combination of binders is essential to maintain the integrity as well as stability of the tablet. The temperature of the excipient should be preferably around 30–35°C for faster melting properties (Irfan et al., 2016). Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in ODT formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used.

Emulsifying agents are also used in ODT formulations. 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% to about 15% by weight of the final composition (Yadav et al., 2012). Lubricants can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants reduce grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Diluents are significant in the formulation of fast-melting tablets. Besides adding bulk, diluent improve the textural characteristics and can enhance the disintegration in the mouth. The recommended diluent for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol and starch hydrolysate for higher aqueous solubility and good sensory perception. Lactitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10% to about 90% by weight of the final composition.

Flavors and taste-masking agents make the products more palatable and pleasing for patients. It helps in overcoming bitterness and undesirable tastes of some drugs. Both natural and synthetic flavors can be used to improve the organoleptic characteristic of fast-melting tablets. 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. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition (Siddiqui et al., 2011).

Table 2. Some Patented Technologies for Fast Dissolving Tablets

Technology	Company's Name	Technology base
Zydis	R.P. Scherer, Inc.	Freeze Dried
FlashDose	Fuisz Technology, Ltd	Moulding
WowTab	Yamanouchi Pharma	Direct compression
Durasolv	CIMA Labs	Direct compression
Orasolv	CIMA Labs	Direct compression
FlashTab	Ethypharm	Direct compression

Various Approaches for Manufacturing of ODT

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation. Various technologies used in the manufacture of ODT. With the emphasis in Quality by Design (QbD) approach, it is important to understand the principle behind these technologies and there are some published reports emphasizing on the use of statistical control and QbD in formulation development (Jain et al., 2015b; Patel et al., 2016b; Shah et al., 2014). The following section will therefore discuss conventional and advance technologies utilized for manufacturing of ODT. Table 2 enlists patented technologies for fast dissolving tablets.

Freeze-drying

Freeze-drying (lyophilization) is a process in which water is sublimated from the product after freezing. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are kept in refrigerator for further freeze-drying. After freeze-drying, the aluminum foil backing is applied on a blister-sealing machine (Dobetti, 2001).

This technique is useful for thermal sensitive drugs. Freeze-dried forms offer more-rapid dissolution times than other available solid products. Furthermore, this technique creates an amorphous porous structure of the drug that can dissolve rapidly. The resulting tablets are usually very light and have highly porous structures that further assist rapid dissolution or disintegration. The use of freeze-drying, however, is strongly limited by the time and handling required for processing, the limited amount of materials processed for each batch, and the high cost of the equipment and processing. Other major disadvantages of the final dosage forms include the lack of physical resistance in standard blister packs and their limited ability to accommodate adequate concentrations of active. Some of the technologies utilizing this process are discussed below:

Zydis (R.P. Scherer, Inc.)

An excellent example of ODT formulation obtained by freeze-drying technology is R.P. Scherer's (Basking Ridge, NJ) Zydis formulations. It consists of a drug physically trapped in a water-soluble matrix, which is freeze-dried to produce a product that dissolves rapidly when placed in the mouth. The matrix consists of a water-soluble mixture of saccharide and polymer, formulated to provide rapid

dispersion properties and to allow sufficient physical strength to withstand handling during use. The ideal drug candidate for Zydis would be chemically stable and water insoluble, and have a small particle size (preferably lower than 50 microM) (Manyikana et al., 2016). Water-soluble drugs might form eutectic mixtures and not freeze adequately; consequently, the dose is usually limited to 60 mg. Larger drug-particle sizes might present sedimentation problems during manufacturing. The tablet dissolves in the mouth within seconds after placement on the tongue. Thirteen products are currently available using Zydis technology.In the U.S., they include: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. On the worldwide market, other Zydis formulations are available for oxazepam, lorazepam, loperamide, and enalapril (Seager, 1998).

Lyoc (Farmalyoc; Laboratoire L. Lefon, Maisons-Alfort, France)

Lyoc is a porous, solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus. Lyoc's unusual properties result from the preparation method - freezing a thickened (paste like) emulsion containing the active as bulk or in coated microparticles. The final product, which accommodates high drug dosing, disintegrates rapidly but possesses poor mechanical resistance.

Quicksolv (Janssen Pharmaceutica, Beerse, Belgium)

Quicksolv is a porous solid form obtained by freezing an aqueous dispersion or solution of the active-containing matrix, then drying the matrix by removing the water using an excess of alcohol (solvent extraction). The final form disintegrates very rapidly but is limited to low drug content and can be used only with those actives that are insoluble in the extraction solvent.

Moulding

Moulded tablets usually are prepared from water soluble ingredients by compressing a powder mixture previously moistened with solvent (usually ethanol or water) into mould plates to form a wetted mass (compression moulding). Recently, moulded forms also have been prepared directly from a molten matrix in which the drug is dissolved or dispersed (heat moulding) or by evaporating the solvent from a drug solution or suspension at standard pressure (no-vacuum lyophilization).

Tablets produced by moulding are solid dispersions. It can dissolve totally in the molten carrier to form a solid solution, or dissolve partially in the molten carrier while the remaining particles stay undissolved and dispersed in the matrix. The characteristics of the tablets (such as disintegration time, drug dissolution rate, and mouth feel) will depend on the type of the dispersion or dissolution (Prateek et al., 2012). In general, the dispersion matrix is made from water-soluble sugars, which can improve disintegration and offer improved taste. However, moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablets often occurs during tablet handling and when blister pockets are opened. To overcome this limitation, hardness agents can be included in the formulation, but it can reduce the rate of tablet solubility. Compared with freeze-drying, the manufacturing process of moulding techniques is simpler and efficient at an industrial scale. However, they cannot achieve disintegration times comparable with those of lyophilized forms. Some of the technologies utilizing this process are discussed below:

FLASHDOSE (Fuisz Technologies, Ltd.)

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, FlashDose. The matrix is formed from saccharides or polysaccharides processed into an amorphous floss by the simultaneous action of flash melting and centrifugal force. It is then partially recrystallized (or cured) to provide a compound with good flowability and compressibility for tabletting. The FlashDose technology thus utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue (Prateek et al., 2012).

Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as CEFORM and serves as an alternative method of taste masking.

Takeda (Osaka, Japan)

They have developed compression-moulded mixtures containing a drug and a combination of starches and sugars with surfaces that have been wetted with a suitable amount of water (Prateek et al., 2012). The wetted mass is compression moulded and dried, and porous tablets (with sufficient mechanical strength to resist destruction during further manufacturing) are obtained. The FMT, the weight of which can reach 1-2 g, has a sufficiently rapid

disintegration time in the mouth (30-50 s according to examples reported in the patent application).

Novartis Consumer Health (Basel, Switzerland)

They also have filed a patent application for tablets prepared by dispensing the drug solution or suspension into moulds, evaporating the solvent from the units (usually achieved by heating, pressure reduction, or microwave radiation), and then optionally sealing the dried units directly in the mould. The patent application reported only examples of low dose and low-weight forms, although higher amounts are claimed.

Nippon Shinyaku (Kyoto, Japan)

They use compression-moulds and dry a kneaded mixture containing the drug and a water-soluble sugar. This process is claimed to impart sufficient physicochemical stability to the tablet, good appearance, and an oral cavity dissolution time of less than 30 s.

Conventional Manufacturing Techniques

Direct Compression

Direct compression is the most commonly utilized technique for oral tablets and can also be used fairly well to manufacture ODT. It is cost effective, utilizes conventional equipment, commonly available excipients, and has limited number of process steps. Moreover, high doses can be accommodated in ODT, the final weight of which can easily exceed that of other production methods. Direct compression tablet's disintegration and solubilization are based on the single or combined action of disintegrants, water-soluble excipients, and effervescent agents. The disintegration time is, in general, satisfactory, although the disintegrating efficacy is strongly affected (and limited) by tablet size and hardness. Large and/or hard tablets can have a disintegration time greater than that usually required for ODT.

This technique significantly relies on the efficiency of disintegrating agent. The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate. The addition of other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties.

Two commonly used disintegants in direct compression methods are (Yadav et al., 2012):

(a) Super-disintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. Super-disintegrants can be classified into natural and synthetic super disintegrant.

- *Natural Super-disintegrants*: Isapghula Husk mucilage, Lepidium sativum seed mucilage, Fanugreek seed mucilage and Gellan Gum.
- *Synthetic Super-disintegrants:* Sodium starch glycolate, Crosspovidone and Modified Cellulose (Croscarmellose sodium).

Most commonly used super-disintegrants are sodium starch glycolate and croscarmellose sodium. Both exhibit similar average particle sizes; however, sodium starch glycolate has a narrower distribution, which contributes to the good flow properties. When examined under a scanning electron microscope, sodium starch glycolate particles are spherical. Crospovidone particles appear granular and highly porous, although crospovidone B particles appear less porous. This porous particle morphology facilitates rapid wicking of liquid into both particle and tablet and contributes to the compactability of the material. Croscarmellose sodium particles have a fibrous structure.

(b) Sugar Based Excipients:

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.

Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

(a) Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

(b) Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

Some of the technologies utilizing this process are discussed below:

FLASHTAB (Prographarm Group)

Ethypharm (Paris, France) recently launched Flashtab for multiparticulate actives (coated crystals and uncoated or coated microgranules) (Prateek et al., 2012). The simultaneous presence of a disintegrant with a high swelling (or disintegrating) force, defined as "disintegrating agent," and a substance with low swelling force (starch, cellulose, and direct-compression sugar), defined as "swelling agent," was claimed as the key factor for the rapid disintegration of a tablet, also offering satisfactory physical resistance.

ORASOLV (Cima Labs, Inc.)

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The Orasolv technology from Cima Labs (Eden Prairie, MN) produces ODT, which is a slightly effervescent containing multi-particulate forms. The taste-masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste-masking in OraSolv. However, the major disadvantage of the OraSolv formulations is its mechanical strength. It can only be lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing.

The OraSolv technology is utilized in six marketed products: four Triaminic Softchew formulations, Tempra FirsTabs, and Remeron SolTab. Other examples of effervescent application include a glycine-based low-dosage aspirin tablet produced by Top Laboratories (Greenwich, CT) and a product from Lab Pharm Res (Laval, Quebec, Canada) comprising one or more effervescent and disintegrating compounds for a synergic action of disintegration and dissolution. The main drawback of using effervescent excipients is their inability to prevent moisture absorption. Manufacturing requires a controlled environment at low relative humidity (RH) and protection of the final tablets with moisture-impermeable blisters. As a consequence, the cost of FMTs is higher than the cost of standard tablets made by direct compression, despite the lower cost profile compared with other, more sophisticated technologies.

DURASOLV (Cima Labs, Inc.)

DuraSolv is Cima's second-generation fast-dissolving/ disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. The newest DuraSolv formulation, NuLev, is actually dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such DuraSolv formulations from stock bottles to ensure they are not exposed to high levels of moisture or humidity. Excess handling of tablets can introduce enough moisture to initiate dissolution of the tablet matrix.

One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Furthermore, taste masking effect is also compromised due to high compaction. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound. DuraSolv is currently available in two products: NuLev and Zomig ZMT.

WOWTAB (Yamanouchi Pharma Technologies, Inc.)

The WOWTAB fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. It has just recently been introduced into the U.S. The WOWTAB technology utilizes sugar and sugar-like (e.g., mannitol) excipients. The Wowtab manufactured by Yamanouchi (Tokyo, Japan) is an intrabuccally dissolved compressed moulding comprising granules made with saccharides having low and high mouldability, respectively. The Wowtab reportedly can accommodate high doses of multiparticulate watersoluble or insoluble drugs, dissolves rapidly, and has an adequate hardness. Due to its significant hardness, the WOWTAB formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The taste masking technology utilized in the WOWTAB is proprietary, but claims to offer superior mouthfeel due to the patented SMOOTHMELT action.

Spray-Drying

Highly porous and fine powders can be produced by spray drying process, as the processing solvent is evaporated rapidly during spray drying. For fast dissolving tablets, they developed formulation by using mannitol as bulking agent, hydrolysed and non-hydrolysed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (ex. citric acid) and/or alkali material (e.g. $NaHCO_3$) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds) (Slowson and Slowson, 1985).

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.

Recent Advanced Technologies

Ziplets technology

It is evident that the main challenge in developing an ODT is

to achieve both good physical resistance and disintegration properties. Generally, direct-compression approach is preferred because it is cost effective and utilizes commonly available equipment and materials. On this basis, Eurand (Pessano con Bornago, Italy) recently developed the Ziplets technology, which can be used with water insoluble compounds as both bulk actives and as coated microparticles. It was found that the addition of a suitable amount of a water-insoluble inorganic excipient combined with one or more effective disintegrants imparted an excellent physical resistance to the ODT and simultaneously maintained optimal disintegration, even at low compression forces and tablet hardnesses. It demonstrated satisfactory properties (such as hardness, friability, and disintegration time) can be obtained at a high dose (450 mg) and weight (850 mg). In fact, handling problems during manufacturing (breakage of the tablet edges or formation of powder, which adversely affects the blistering phase) are avoided because of mechanical resistance. The risk of tablet breakage during the opening of the blister pack is eliminated. The use of water-insoluble inorganic excipients also offers better enhancement of disintegration characteristics than most commonly used water-soluble sugars or salts (Shukla et al., 2009).

Oral films and wafers

Oral films and wafers are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes. They are developed to provide rapid disintegration on the tongue without the need for water. They have the advantage of a large specific surface area for disintegration. One or a combination of the following processes like hot-melt extrusion, solid dispersion extrusion, rolling and solvent casting are used to manufacture these films. A major limitation of these dosage forms is low drug loading capacity and limited taste masking option.

Nanocrystal Technology

For fast dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Higher dissolution rate is achieved by decreasing particle size increasing the surface area (Jain et al., 2015a). This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique (Hirani et al., 2009).

NanoCrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible

Evaluation of ODT

The following tests are performed to evaluate the quality of the ODT formulations. Most of these tests are similar to the tests performed for conventional tablets.

General Appearance

The general appearance of a tablet includes tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

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

Tablet thickness

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

Uniformity of weight

In general, twenty tablets were taken and their weight is determined individually and collectively on a digital weighing balance. The average weight of one tablet is determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Tablet hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. Hardness of the tablet of each formulation is determined using Monsato Hardness tester.

Friability

It is measurement of mechanical strength of tablets. Roche fribaiator was used to determine the friability by following procedure. A preweighed tablet was placed in the fribaiator.

Fribaiator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabalator for at least 4 minutes. At the end of test tablets were dusied and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

%Friability = loss in weight / Initial weight x 100 equation (1)

Disintegration test

The definition of fast-melting (or disintegrating) tablet appeared in a compendial publication for the first time in 1998. So far, neither the US Pharmacopeia nor the European Pharmacopoeia had defined a specific disintegration test for the ODT. The results obtained using the compendia test for dispersible tablets only approximate the actual disintegration time in the mouth. Although the compendial test for dispersible tablets can be applied to ODT with certain limitations, it is still necessary to define a suitable method to better discriminate between the disintegration times of ODT and to better correlate in vitro and in vivo data. The texture analysis apparatus is used to measure the start and end time points of tablet disintegration. A constant penetration force is applied to tablets via a cylindrical flat-ended probe. The tablet, under constant force, is immersed in a defined volume of distilled water, and the time is plotted against the distance the probe travelled into the tablet. Typical time-distance profiles, generated by the texture-analysis software, enable the calculation of the starting and ending disintegration time.

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to get an idea about the stability of the formulation. Ten tablets from each formulation are kept in a desiccator over calcium chloride at 37˚C for 24 h. The tablets are weighed and exposed to 75% RH, at room temperature for two weeks. Required humidity can be achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as control is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded to know the moisture uptake.

In vitro dispersion time

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

Dissolution test

Dissolution methods for ODT are practically identical to the approach taken for conventional tablets. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments yielding irreproducible dissolution profiles. The USP 2 Paddle apparatus which is the most suitable and common choice for orally-disintegrating tablets in which a paddle with a speed of 50 rpm commonly used. The dissolution of ODT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a complete profile (Hirani et al., 2009; Velmurugan and Vinushitha, 2010).

Application

Fast-dissolving antidepressant

In a recent study two-thirds of depressed patients prefer antidepressant ODT to its conventional tablet formulation. And crucially, 50% of patients were more likely to comply with a fast dissolving antidepressant formulation (Wade et al., 2012).

Remeron SolTab is the only fast dissolving antidepressant available in the market and has a unique mechanism of action, which differs from the SSRI (Selective serotonin reuptake inhibitors) class of antidepressants. Remeron SolTab combines mirtazapine, the active ingredient of Remeron- that acts on both serotonergic and noradrenergic systems - with a fast dissolving drug delivery system allowing intake without water and offering a pleasant orange taste. Results from the global survey involving almost 4,000 patients using Remeron SolTab in 20 countries confirm that such a formulation is both preferred by patients and improves patients' compliance to treatment. Similar results have been found recently in a large Swiss observational study involving over 1000 patients.

The survey - conducted on-line - asked depressed patients what they thought about the fast dissolving Remeron SolTab compared to conventional mirtazapine tablets. Preliminary responses to date show that more than 86% of patients are positive about Remeron SolTab; and 50% say they are more compliant now that they are using Remeron SolTab. More than 63% said they prefer this new formulation. The survey will continue to recruit patients with the ultimate aim of obtaining responses from 4,500 patients by the end of 2005.

Cancer

One of the major side effects of chemotherapy is vomiting. Odanseteron is generally used to overcome this side effect. A study was conducted by formulating odansetron ODT and checking is safety and efficacy. A total of 427 cancer patients receiving cyclophosphamide chemotherapy participated in this multicenter, double-masked, double-

dummy, parallel-group, randomized study comparing the antiemetic efficacy and safety of an 8-mg conventional ondansetron tablet (OT, n = 212) taken twice daily with an 8-mg orally disintegrating ondansetron tablet (ODT, n = 215) taken twice daily for 3 days (Davidson et al., 1999). Complete or major control of emesis (0 to 2 emetic episodes) between days 1 and 3 was seen in 80% of OT and 78% of ODT patients. The 90% confidence interval for the differences between treatments was -8.6% to 4.4% (de-fined interval of equivalence, +15%), showing that the formulations were equivalent. In the secondary efficacy analysis, no significant differences were observed in the rates of complete control of emesis (no episodes of emesis) over 3 days (63% and 64% of the respective groups) and on day 1 (84% and 81%, respectively) and in the complete control of nausea over 3 days (37% and 43%, respectively) and on day 1 (59% and 61% of patients, respectively).

The taste of ODT was acceptable to the majority of patients (89%) who received it. OT and ODT were both well tolerated. Thus 8 mg ODT twice daily represents a palatable, well-tolerated, and effective antiemetic treatment for the control of cyclophosphamide-induced emesis and nausea and provides equivalent treatment to OT 8 mg twice daily.

Migraine

Zomig Rapimelt™ (Zolmitriptan), a tiny, orange-flavored tablet that melts on the tongue in less than 10 seconds provides patients with both prompt and long-lasting migraine relief. Belonging to the triptan class of migraine medications, Zomig Rapimelt™ offers patients the convenience of taking it *anytime* and *anywhere*.

In a recent study of 471 migraine sufferers, 70 per cent preferred to treat their migraine with an orally dispersible tablet rather than with the traditional pill (Dowson et al., 2002). According to the study, authored by Dr. Allan Purdy, neurologist at the Queen Elizabeth Health Sciences Center in Halifax, Nova Scotia, Zomig Rapimelt™ provides a convenient alternative to the conventional tablet (Dowson et al., 2002). This may allow earlier treatment of migraine attacks whenever or wherever they occur.

The primary endpoint of the randomized, double-blind study was headache response in patients with IHS-defined (International Headache Society) migraine. From an efficacy standpoint, the fast-melting tablet provided rapid and consistent relief within a wide array of migraine types. Zomig Rapimelt™ was found to be highly effective and well-tolerated. Improvement in headache pain was seen in as little as 30 minutes, and significant patients experienced headache relief in two hours. The efficacy of Zomig Rapimelt™ was similar to that of conventional tablet formulations. In addition, because of its pleasant tasting orange flavour, Zomig Rapimelt™ encourages compliance**.** Study results showed that 92 per cent of patients found the fast-melting tablet easy to manage and 80 per cent liked its taste.

Allergies and asthama

Allegra ODT is used for treating seasonal allergy symptoms such as sneezing, runny nose, itchy throat, or itchy, watery eyes. It is also used to treat hives and skin itching. This medicine is an antihistamine and works by blocking a substance in the body called histamine.

Central nervous system

ULTRAM® ODT (tramadol hydrochloride) Orally Disintegrating Tablets is a centrally acting analgesic in an orally disintegrating formulation using a tablet formulation base. The chemical name for tramadol hydrochloride is (±) cis -2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

An orally swallowed immediate release tablet of tramadol has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving an orally swallowed immediate release tablet of tramadol. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of an orally swallowed immediate release tablet of tramadol in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg daily.

Summary

According to results from a recent survey, seven of ten medical professionals believe that a fast dissolving antidepressant tablet will improve patient compliance, and 50% say that a fast dissolving antidepressant therapy would be useful in half, most or all of their depressed patients. Other research shows that 57% of depressed patients prefer Remeron SolTab to the conventional tablet, and 43% say they would be more likely to take a medication in the form of a fast-dissolving tablet.

Though the target populations for these new ODT dosage forms have generally been pediatric, geriatric, and bedridden or developmentally disabled patients, patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates for ODT. In the near future, other patient populations will also be

targeted. A novel application for ODT is in veterinary medicine, for example, to avoid pilling a cat. With ODT dosage forms increasingly available, it will be likely that prescribers will recommend such products for their noncompliant patients. The ease of administration of a fast-dissolving/disintegrating tablet, along with its pleasant taste, may encourage a patient to adhere to a daily medication regimen. Although an ODT may not solve all compliance issues, it may be enough of an advance to be of therapeutic significance.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper

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