



## A REVIEW ON NEW GENERATION ORODISPERSIBLE TABLETS AND ITS FUTURE PROSPECTIVE

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Received: 26 April 2010, Revised and Accepted: 17 Oct 2010

### ABSTRACT

Advancements in oral delivery of active ingredients include a number of technologies, many of which may be classified as oral disintegrating tablets (ODTs). A number of companies have marketed products using various nomenclatures including ODT as well as their own trademarked names. The new generation of orally disintegrating tablet (ODT) technologies is no longer limited by dosage strength, bitter active pharmaceutical ingredients (APIs), and narrow therapeutic applications. Today's emerging technologies can produce robust, versatile tablets with exceptional taste masking and controlled release, broadening the applications of this dosage form. Over the last decade, ODTs have grown steadily in demand and importance as a convenient, potentially safer alternative to conventional tablets and capsules. ODTs are solid dosage forms that disintegrate in the mouth in less than 60 seconds, and are thus swallowed without the need for water. Since their introduction to the market in the 1980s, ODTs have become one of the fastest-growing segments of the oral drug delivery industry, and their product pipeline is rapidly expanding. They are particularly beneficial to people who have difficulty taking conventional solid dosage forms, including children, the elderly, patients who have swallowing difficulties, the mentally ill, and the disabled. This review depicts the various formulation techniques, ingredients used, and overview of patented formulations.

**Keywords:** Oral disintegrating tablets, ODTs preparations, Patented technologies.

### INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS has made a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue.<sup>1</sup> Orodispersible tablets are also known as "Mouth dissolving tablets", "Orally disintegrating tablets", "Melt- in- mouth", "Fast dissolving drug delivery", " Rapimelts tablets", "Porous tablets", "Quick dissolving tablets" <sup>2</sup> etc. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia <sup>3-6</sup>, and Centre for Drug Evaluation and Research (CDER). US FDA defined ODT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue". European pharmacopoeia also adopted the term "orodispersible tablet" as a tablet that is to be placed in the mouth where it disperses, rapidly before swallowing despite various terminologies used.<sup>1</sup> Recently, ODT have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance especially in elderly and children. In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging.

Along with the rapid market growth of ODT products, the technologies, too, have advanced considerably over the years. The newest generation of ODTs can produce more robust, versatile tablets that overcome some of the limitations of earlier ODTs.<sup>7</sup> Companies such as Eurand can produce pleasant tasting tablets, overcoming the common problem of poor drug taste compromising the benefits of an ODT. In addition, some companies is developing controlled release ODTs, significantly broadening the applications of this dosage form. A key reason that companies choose an ODT over other delivery technologies is that it is a relatively easy and often less risky delivery option to develop. Since the route of administration remains the same, ODTs that are formulated as bioequivalent line extensions or generic versions of an existing oral dosage form have minimal clinical requirements to gain approval. Some of the common applications of ODTs are listed in table 1.

Table 1: Common reasons and conditions for using ODT <sup>7</sup>

Medication type	Indication
Fast – acting	Pain , fever, heartburn, diarrhoea, migraine, anxiety, insomnia
Compliance-critical	Parkinson's disease, Alzheimer's disease, psychosis, Schizophrenia, Hypertension, Cholesterol, Transplantation
Paediatric	Cough/cold/allergy, Pain, fever, ADHD

### Advantages of fast dissolving drug delivery system <sup>8,9,10,11</sup>

Fast dissolving technology offers:-

- Improved compliance/added convenience
- Ease administration for patients who are mentally ill, disabled and uncooperative
- No water needed
- Can be designed to leave minimal or no residue in mouth after administration and also to provide a pleasant mouth feel.
- No chewing needed ,
- Better taste obtained by taste masking
- Improved stability, low sensitivity to environmental condition
- Suitable for controlled/sustained release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging high speed machinery.
- Cost- effective, lower production, packaging and distribution costs compared to current commercially available products.
- The technology is versatile and suitable for the development of enhanced products for veterinary medicines, OTC, Rx medicines & line extensions.
- The new proprietary method allows the incorporation of microencapsulated drugs for enhanced bioavailability, flexibility of dosing & immediate and/or controlled release.
- For superior therapeutic benefit

### First-generation ODTs <sup>12,13,14,15</sup>

While first-generation ODT technologies produce tablets that dissolve rapidly in the mouth, provide convenience and ease of swallowing, and have had success in the market, some of them fall

short in terms of taste masking and the accommodating high doses and because most first-generation technologies can handle only low amounts of APIs, their therapeutic applications are limited and are used only in immediate-release applications. A table 2 list today's major ODT technologies.

First-generation ODTs are commonly characterized by high porosity, low density, and low hardness, making them brittle and difficult to handle. As a result, they often require blister packaging, which is less convenient for patients than bottles and entails high production costs. Freeze-dried ODTs are especially friable, making them difficult to package conventionally and raising questions about storage stability. Furthermore, it's difficult to use traditional flavours and sugars to mask poor-tasting APIs with first-generation ODTs, which restricts their application to non-bitter APIs. The common approach is to use flavouring and sweetening agents to overpower the taste rather than neutralize it. Today, there are only a few technologies on the market that provide effective taste-masking capabilities, which requires a physical barrier between the API and the taste buds. One such technique is coacervation (encapsulation). As the ODT market matures, pharmaceutical companies are seeking additional capabilities from these dosage forms. These include higher API loading, more effective taste masking, controlled-release capability, low friability, cost-effective development, and more packaging options.

**New generation of ODTs** <sup>12,13,14,15</sup>

New generation of ODTs available today, is one that can be combined with a proprietary process to improve taste masking, allow a modified-release profile, and enhance bio-availability. As a result, formulators can taste-mask even extremely poor-tasting drugs, use high doses of API, and expand the range of therapeutic applications.

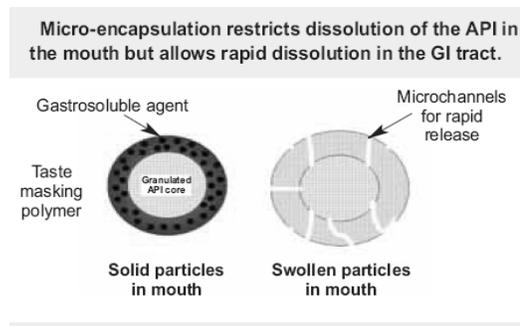
These ODTs comprises of rapidly dispersing microgranules, a direct-compression blend, and an external tablet lubrication method. The result is an ODT with excellent physical robustness, mouth-feel, and disintegration properties. The tablets dissolve in 15 to 30 seconds (depending on dosage strength) and produce a smooth, pleasant tasting mixture of API granules and carrier that is easy to swallow. The tablets are made on standard presses, accept printing on both sides, typically have a friability of less than 0.5 percent, and can be packaged in bottles or blister packs.

Combining micro-encapsulation with ODT technology effectively can mask bitter APIs and can be applied to soluble and poorly soluble substances, as well as to high-dose products. One technology is based on coacervation, a coating technique that encapsulates individual drug particles completely and provides superior taste masking. The coacervation process places a uniform coating of polymeric membranes of varying thicknesses and porosities directly onto dry crystals or granules, creating particles that are typically 150 to 300 microns. The membranes create an inert barrier between the API and the taste buds and a stabilization barrier between the API and the tablet excipients.

This coacervation technique has taste-masked a wide range of extremely poor-tasting drugs, including zolpidem (for insomnia), sumatriptan (for migraines), ranitidine (for gastro-esophageal reflux

disorder), and cetirizine (for allergic rhinitis). It has also been applied to theophylline, ibuprofen, acetaminophen, and pseudoephedrine, and products on the market that have incorporated the technique include Children's Chewable Advil, Rulid (roxithromycin), and the Benadryl line of products.

One of the biggest challenges for an ODT that uses taste-masking polymers is achieving bioequivalence with the conventional form (reference product).The polymers can impede API release in the gastrointestinal (GI) tract, delaying the onset of action. Using a micro-encapsulation technique restricts dissolution of the API in the mouth, but allows rapid dissolution in the GI tract, thus overcoming the bio-equivalence obstacle as given in figure 1.

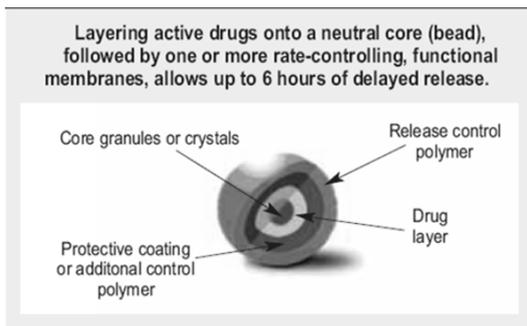


**Fig. 1: Micro-encapsulation restricts dissolution of API in mouth but allows rapid dissolution in the GI Tract**

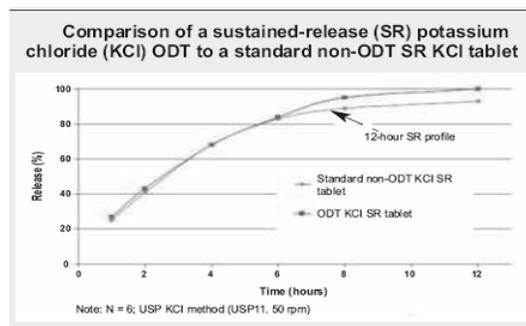
Controlled release Combining ODTs with specialized functional polymers and coating processes can lead to ODTs with sustained-, modified-, and customized-release profiles. It is even possible to combine release profiles in a single dose. Typical of these approaches are micro-encapsulation and multiparticulate coating technologies, which allow formulators to create modified-release polymer layers around API particles. These particles are flexible enough for compression without breakage or loss of the modified-release properties and small enough to provide good mouth-feel. Adjusting the coating parameters (thickness, composition, porosity, pH modifying agents, and number of layers) changes the desired plasma profile.

Some technologies provides sustained release by layering active drugs onto a neutral core (bead), followed by one or more rate-controlling, functional membranes

Allowing up to 6 hours of delayed release as given in figure 2, these layered beads can be less than 500 microns in very robust ODTs. figure 3 compares a sustained-release potassium chloride (KCl) ODT that maintains its rate of release as long as 12 hours to a standard non-ODT sustained- release KCl tablet. Incorporating bead populations with different release profiles into the dosage form enables formulators to optimize the in vivo release profile. For example, the ODT could release the API as either a burst or sustain the release with a lag time of at least 4 hours.



**Fig. 2: Layers active drugs onto a neutral core and rate controlling membranes**



**Fig. 3: Comparison of different ODT sustained release tablet**

### Pharmacokinetics

After absorption, drug attains therapeutic level and therefore elicits pharmacological action, and thus both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution, while FDTs rapidly disintegrate in oral cavity and thus dissolution is fast. Due to disintegration of FDTs in mouth absorption starts at mouth then pharynx and oesophagus. Some factors like age, GI pH, blood flow through GI are taken into consideration, because elderly people has to be considered as separate unique medicare population.

In geriatric patients decreases in body mass and total body water result in decreased volume of distribution of water soluble drugs and increased volume of distribution (Vd) of lipid soluble drugs. Decrease in liver volume, regional blood flow to liver reduces the bio-transformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of drugs is increased.

### Approaches for fast dissolving tablet

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 Fast dissolving tablets include

#### Freeze drying or lyophilisation

A process in which water is sublimated from the product after freezing. Lyophilisation is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation. Lyophilisation results in preparations, which are highly porous, with a very high specific surface area, and which dissolve rapidly and show improved absorption and bioavailability. Jaccard and Leyder used lyophilisation to create an oral pharmaceutical preparation that not only dissolves rapidly but also improved the bioavailability of several drugs such as spirinolactone and trolendomycin. Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug on the basis of which US Patent 6,010,719 was granted. Tablets prepared by lyophilisation, are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions.<sup>16-19</sup>

#### Molding

Tablet produced by molding are solid dispersion. Molded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is generally made from water soluble sugars. The active ingredient in most cases is absorbed through the mucosal lining of the mouth. The manufacturing process of molding tablets involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mold plates to form a wetted mass (compressing molding). The solvent is then removed by air drying. Thus the process is similar to what is used in the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

Molded forms are also prepared using a heat-molding process that involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at -30°C under vacuum. Another process used is called no-vacuum lyophilisation, which involves the evaporation of a solvent from a drug solution or suspension at standard pressure. Pebley et al., evaporated a frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth,

or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol, or maltodextrin), and a solvent in a tablet shaped mould. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.<sup>16,13,20</sup>

#### Spray drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. Allen *et al.* have reported applying this process to the production of fast dissolving tablets. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatine as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 second in an aqueous medium.<sup>6,21,22</sup>

#### Sublimation

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. In studies conducted by Heinemann and Rothe<sup>23</sup>, Knitsch *et al.*<sup>24</sup>, and Roser and Blair,<sup>25</sup> inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane) were compressed along with other excipients into a tablet. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

Koizumi *et al.*<sup>26</sup> applied sublimation technology to manufacture tablets that rapidly dissolve in saliva. Mannitol is used as a matrix former, and camphor was used as a sublimating agent. The tablets dissolved in 10-20 seconds and displayed satisfactory handling properties. Makino *et al.*<sup>27</sup> reported a method using water as pore-forming material. A mixture of drug and a carbohydrate (e.g. erythritol, glucose, sucrose, xylitol). The water was then removed, yielding highly porous tablets with satisfactory mechanical strength and a high dissolution rate.

#### Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. This technique can now be applied to fast dissolving tablets because of the availability of improved tablet excipients, especially Tablet disintegrants and sugar-based excipients. Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction superdisintegrants and a better understanding of their properties have increased the popularity of this technology. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.<sup>1,6,21</sup>

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of first dissolving tablets. Bi *et al.* and Watanbe *et al.* used microcrystalline cellulose (MCC) and low

substituted hydroxypropyl cellulose (HPC) to manufacture rapidly disintegrating tablets. The ratios of MCC to HPC varied from 8:2 to 9:1. Ito and Sugihan investigated applying agar powder as a disintegrants because the powder absorbs water and swells considerably without forming a gel at physiological temperatures.

Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by the overall cost of the product.

Another approach to fast dissolving tablets by direct compression is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, maltitol, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol), which display high aqueous solubility and sweetness, and hence, impart taste masking and a pleasing mouthfeel.

#### 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 making their bitter taste.<sup>28</sup>

#### Patented technologies for fast dissolving tablets

Each technology has a different mechanism, and each fast-dissolving/disintegrating dosage form varies regarding the following

- Mechanical strength of final product;
- Drug and dosage form stability;
- Mouth feel;
- Taste;
- Rate of dissolution of drug formulation in saliva;
- Swallowability;
- Rate of absorption from the saliva solution; and
- Overall bioavailability.

#### Zydis Technology:-

Using concept of Gregory *et al.* Scherer has patented the Zydis technology. Zydis, the best known of the fast-dissolving/disintegrating tablet preparations, and was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatine. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation. Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience. The amount of drug that could be incorporated should generally be less than 60 mg for soluble drugs. The particle size of the insoluble drugs should be less than 50mm and not more than 200mm to prevent sedimentation during processing. There are some disadvantages to the Zydis technology. The process of freeze-drying

is a relatively expensive manufacturing process. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidity. It readily absorbs water, and is very sensitive to degradation at humidity greater than 65%.<sup>17,29</sup>

#### OraSolv technology

The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the OraSolv formulation is two-fold. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavours; both coating the drug powder and effervescence are means of taste masking in OraSolv. This technology is frequently used to develop over-the-counter formulations. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. 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. Lyophilisation and high degrees of compression, as utilized in OraSolv's primary competitors, may disrupt such a taste masking approach. The OraSolv technology is utilized in six marketed products. These formulations can accommodate single or multiple active ingredients and tablets containing more than 1.0 g of drug have been developed. Their disintegration time is less than 30s.<sup>17,30</sup>

#### DuraSolv technology

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. DuraSolv tablets are prepared by using conventional tableting equipment and have good rigidity (friability less than 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials.<sup>29</sup> 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. Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. 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.<sup>28</sup>

#### Flash dose technology

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, Flash Dose. The Flash Dose technology 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 Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self-binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing and are of two types.

- Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.
- Dual floss consists of a first shearform carrier material (termed "base floss", contains a carrier and at least one sugar alcohol generally sorbitol), and a second shearform binder matrix ("binder floss", contains a carrier and xylitol).

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.<sup>30</sup>

#### **Wowtab technology**

The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "Wit out Water". It has just recently been introduced into the U.S. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharides (good binding property). The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydys 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. The Wowtab product dissolves quickly in 15 seconds or less.<sup>17,31</sup>

#### **Flashtab technology**

Prographarm laboratory has patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tableting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.<sup>13</sup>

#### **OraQuick technology**

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.<sup>10</sup>

#### **Quick -Dis technology**

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the

film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within 30 seconds and 95% within 1 minute.<sup>13,17</sup>

#### **Nanocrystal technology**

For fast dissolving tablets, Elan's proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. 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.<sup>32</sup>

**NanoCrystal™** Fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix
- Product differentiation based upon a combination of proprietary and patent-protected technology elements
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations
- Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters)
- Wide range of doses (up to 200mg of API per unit)
- Use of conventional, compendial inactive components
- Employment of non-moisture sensitive inactives

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.

#### **Orodis® technology**

There are several technologies to consider for orally disintegrating tablets. Orodis® is compressed technology, beside a fast disintegration time in the mouth (15 to 30 seconds) it has many advantages against other technologies.

- Hard tablets, not fragile- easy to handle
- No specific packing required, can be packaged in push - through blisters
- Smooth mouthfeel
- Pleasant taste- incorporation of taste masking agents and flavours
- All the materials meets USP and EP standards
- Conventional manufacturing equipment - not difficult to transfer to final production site.
- Cost effective

#### **Melt Ease™ technology**

Newer technology developed by nutrition formulators, which allows tablet dissolution in less than five sec (average 400mg tablet) this is the best mechanism available to ensure compliance and increase sales in two important markets, children and the elderly for many nutritional supplements at a very marginal development cost effect in specific formulations, including taste masking and sustained release on certain ingredients.<sup>13</sup>

Table 2: List of products categorized by technology

<b>ZYDIS PRODUCTS:</b>
<b>Claritin Reditab</b> micronized loratadine (10 mg), citric acid, gelatine, mannitol, mint flavour.
<b>Feldene Melt</b> piroxicam (10 or 20 mg), gelatine, mannitol, aspartame, citric anhydrous.
<b>Maxalt-MLT</b> rizatriptan (5 or 10 mg), gelatine, mannitol, aspartame, peppermint flavour.
<b>Pepcid RPD</b> famotidine (20 or 40 mg), gelatine, mannitol, aspartame.
<b>Zyprexa Zydis</b> olanzapine (5, 10, 15 or 20 mg), gelatine, mannitol, aspartame, methylparaben sodium, propylparaben sodium.
<b>Zofran ODT</b> ondansetron (4 or 8 mg), aspartame, gelatine, mannitol, methylparaben sodium, propylparaben sodium, strawberry flavour.
<b>Dimetapp Quick Dissolve Children's Cold and Allergy Tablets (OTC)</b>
<b>ORASOLV PRODUCTS:</b>
<b>Remeron Soltab</b> mirtazepine (15, 30, or 45 mg), aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavour.
<b>Temptra FirstTabs</b> acetaminophen (80 or 160 mg), inactive ingredients including mannitol (currently available in Canada).
<b>Triaminic Softchew (OTC)</b>
<b>DURASOLV PRODUCTS:</b>
<b>NuLev</b> hyoscyamine sulfate (0.125 mg), aspartame, colloidal silicon dioxide, crospovidone, mint flavouring, magnesium stearate, mannitol, microcrystalline cellulose
<b>Zomig ZMT</b> zolmitriptan (2.5 mg), mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid, anhydrous, colloidal silicon dioxide, magnesium stearate, orange flavour
<b>WOWTAB PRODUCTS:</b>
Benadryl Allergy & Sinus Fastmelt (OTC)
Children's Benadryl Allergy & Cold Fastmelt (OTC)

#### A promising future <sup>10, 13, 33-35</sup>

Oral delivery 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 having the highest patient compliance. The tablet is the most widely utilised oral dose format. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the ODT. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. A number of ODT are commercially available for human use using technologies developed by pharmaceutical companies such as Cardinal Healthcare, Janssen Pharmaceutical, Bioavail, and Eurand, Yamanouchi. However, these technologies use either expensive processing technology producing fragile tablets that require costly specialised packaging or use conventional tableting procedures which give longer than desired disintegration & still require specialised packaging. Dr Zeibun Ramtoola and her team at the Royal College of Surgeons in Ireland have addressed the above shortcomings by developing a novel, cost effective one step ODT manufacturing process using conventional tableting technology for the production of robust tablets suitable for conventional packaging. This proprietary technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. "supergenerics" for veterinary or human application.

The oral drug delivery market was estimated to be worth \$35bn in 2006 & forecast to reach \$52bn by 2010 with a CAGR of 10%. Of this, the ODT, taste masked & micro emulsion formulation segments constitute a 22% share with an expected CAGR of 17% to 2010. There is a clear opportunity for new enhanced oral products arising within this market segment. ODT technologies entered the market in the 1980s, they have grown steadily in demand and importance, and their product pipeline is rapidly expanding. In 2004, ODT products generated revenues of well over \$2 billion, an increase of 20% over 2003, according to a 2005 report by Technology Catalysts International. With multiple new consumer health and prescription product launches in recent years, the ODT market was predicted to easily reach \$3 billion in 2006, including brands and generics. The market continues to grow 20% each year, with a growing penetration of generic ODTs.

#### CONCLUSION

Future challenges for many ODT manufacturers include reducing costs by finding ways to manufacture with conventional equipment,

using versatile packaging, and improving mechanical strength and taste-masking capabilities. ODT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in traveling, patients who are may not have access to water. Such products provide opportunity for the product line extension in the market place and extension of patent term of innovator. Due to this wide significance of ODT, this drug delivery system may lead to better patient compliance and ultimate clinical output. Future might witness many more classes of drugs developed in the form of ODT.

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