A REVIEW ON PATENT RELATED TECHNOLOGIES OF ORALLY DISINTEGRATING TABLETS

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ABSTRACT

New drug-delivery technologies are often championed by contract manufacturing organizations. For new technologies that provide significant clinical as well as financial value, research and innovation in the contract manufacturing and pharmaceutical segments lead to the emergence of numerous competing versions of the technologies. Such a technology evolution has been evident for orally disintegrating tablets (ODTs). Designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve compliance, particularly in certain populations where swallowing conventional solid oral-dosage forms presents difficulties. The Zydis lyophilization technology provided the first approved ODT in the United States in 1996. The earliest US regulatory definition for an ODT reflected the lyophilized ODTs that prevailed at the time. An ODT was defined as “a solid-dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed on the tongue (1).” The emergence of multiple ODT technology platforms created some regulatory challenges due to increasing variance in the critical product attributes of ODTs, notably disintegration time and tablet size. It can be assumed that the regulatory challenge was most acute for generic product applications. Hypothetically, in an abbreviated new drug application, the disintegration time of a generic product could be 30–45 s, and the disintegration time of a reference product 0–10 s. Prolonged disintegration times may result in failure to meet the defining performance characteristics of the ODT dosage form, such that the product might require water for administration or chewing to facilitate swallowing.
Where the patient or caregiver’s expectation is for rapid dispersion in the mouth, larger units with slower disintegration times could result in confusion regarding the product quality and even present a choking hazard. Thus, in addition to product definition, patient safety is also a significant consideration.

**KEYWORDS:** orally disintegrating tablets, Hypothetically, Prolonged disintegration etc.

**INTRODUCTION**

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Over the past three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. Products of ODT technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding. New ODT technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphasia. This has encouraged both academia and industry to generate new orally disintegrating formulations and technological approaches in this field. The 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.

**Description**

**Drug selection for oral disintegrating tablet.**

The ideal characteristics of a drug for oral dispersible tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for ODT.
Advantages

- Easy to administer to the patient who cannot swallow such as pediatric, geriatric, bedridden, stroke victim and institutionalized patient (especially for mentally retarded and psychiatric patients)
- Pregastric absorption leading to increased bioavailability/rapid absorption of drugs from mouth, pharynx and esophagus as saliva passes down to stomach, also avoids hepatic metabolism.
- Convenient for administration to traveling patients and busy people who do not have accesses to water.
- Excellent mouths feel property 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.  

4. Desired criteria for ODTs

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.

Patient technologies related to orally disintegrating tablets

OraSolv and DuraSolv are CIMA’s core ODT tablet based technologies. The ingredients contained in the technology include polyols as fillers, disintegrant, which may include an effervescence couple, flavor, sweetener, and lubricant. The drug may be taste masked if required typically utilizing a fluid bed coating process. The tabletting process includes direct compression, and can accommodate a wide range of potency from less than 1 mg to as high as 500 mg. Tablets manufactured with OraSolv technology should contain an effervescence couple along with micro particles of drug within a rupture able coat. The tablets
manufactured are compressed at a low hardness that promotes fast disintegration. The dosage forms need to be packaged in foil–foil aluminum blisters with a dome shape that impact physical protection and impermeability to moisture. This constitutes the PakSolv Technology. Tablets manufactured with DuraSolv technology contain a non-directly compressible filler and a lubricant. They may or may not contain effervescence, and the drug need not be taste masked. DuraSolv tablets are compressed at higher hardness compared to OraSolv that allows for packaging in bottles or push through blisters. The advantages of tablet-based technology include low cost of goods, standard manufacturing technology, standard packaging format and materials, and low development costs and risks. Disadvantages include slightly longer disintegration time.

Lyoc Technology
Lyoc technology is owned by Cephalon Corporation. CIMA is a subsidiary of Cephalon, and currently manages the Lyoc R&D efforts. This was the first freeze drying-based technology introduced for ODTs. The process involves preparation of a liquid solution or suspension of the drug containing fillers, thickening agents, surfactants, non-volatile flavoring agents, and sweeteners. This homogenous liquid is then deposited in blister cavities and subjected to freeze drying. Advantages of Lyoc compared to other freeze dried dosage forms include absence of preservatives.

Zydis Technology
Zydis technology is owned by RP Scherer, a subsidiary of Cardinal Health. This drug delivery system consists of freeze-dried tablets having active drug designed to rapidly disintegrate in the mouth. The freeze-dried tablet is made by lyophilizing a suspension or solution of drug containing various excipients such as polymer, polysaccharides, preservatives, pH adjusters, flavors, sweeteners, and colors, which is then filled in blisters. Freeze drying occurs in the blisters, which are then sealed and further packaged. Some of the advantages of the Zydis system include fast disintegration time. Some of the disadvantages include low throughput, high cost of goods, and limited taste masking.

Flashtab Technology
Flashtab tablet matrix consists of a swellable agent (modified starch or microcrystalline cellulose) and a super disintegrant (crospovidone or croscarmellose). The system may also contain, depending on the need, a highly water-soluble polyol with binding properties such as mannitol, sorbitol, maltitol, or xylitol, instead of the swellable agent as mentioned before.
The active is taste masked by direct coating. Tablets manufactured using this technology produce durable tablets in which the excipients are first granulated using wet or dry granulation process, then the coated drug is mixed with the excipient granules and compressed into tablets that can be handled and packaged using conventional processing equipment. Tablets for blister packaging can withstand the pressure used to push the tablet out of the lidding foil of the blister card. Tablets containing hygroscopic material can also be blister packaged, by using high-quality polyvinyl chloride or aluminum foils, which provide a higher degree of moisture protection than ordinary polyvinyl chloride or polypropylene foils.\textsuperscript{12}

**FlashDose Technology**

Fuisz technologies is the inventor of the FlashDose technology. It is now owned by Biovail. FlashDose tablets are manufactured utilizing SHEARFORM matrix in which material containing substantial amounts of fibrous polysaccharides, which are processed by simultaneous action of flash melting and centrifugal force, are compressed to form fine sugar fibers. FlashDose tablets containing a matrix of these sugar fibers disintegrates very rapidly upon contact with saliva, with disintegration times of a few seconds. The tablets produced by FlashDose are hydrophilic and highly porous, owing to relatively low compression during the pressing of the tablets. For taste masking, Fuisz uses its own patented, single-step, solvent-free process, termed ‘‘CEFORMTM technology,’’ which produces uniform microspheres with a very narrow particle size distribution. The resulting tablets produced by this process are soft, friable, and highly moisture sensitive. They require specialized packaging materials and processes to protect them from external humidity and mechanical abrasion.\textsuperscript{13}

**WOWT\textsuperscript{AB}**

WOWTAB tablets are developed by Yamanouchi Pharma Technologies. The main ingredients in the tablets include low- and high-moldable sugars. The low-moldable sugars promote quick dissolution and include mannitol, lactose, and glucose. High-moldable sugars promote good hardness upon compaction and include maltose, sorbitol, and maltitol. The active and other excipients are granulated with a solution containing both the sugars in a fluid bed granulator. The granules obtained are blended with lubricants and flavors and then compressed to form tablets. The tablets are then stored in a controlled humidity and temperature system for conditioning and then packaged in blisters or bottles. Taste masking
of the active may be achieved by the use of cyclodextrins. ODT Technologies in Development.  

Kryotab™
Biotron designs and develops freeze-dried tablets and micro particles using low-temperature and cryogenic processing technologies. The products developed may be used for different dosage forms such as oral, parenteral, pulmonary, and transdermal delivery. Kryotab technology’s two version used to develop different dosage form are Kryotab-MIM and Kryotab-CD. Unlike RP Scherer’s Zydis technology, in this technology, the unit doses are not initially formed from liquid dispersions, but from the tabletted article subjected to freeze drying. The water needed to be removed during freeze drying is introduced into the tablets in the form of ice particles and mixed along with excipients and active and subsequently compressed at low temperature. The porosity in the tablet is determined and controlled by the number and size of ice particles. Microencapsulated liquid or gelled binder is incorporated in the tabletted mixture to obtain rigid tablets with high tensile strength. During compression, the microcapsules disintegrate and release the binder, which improves the adhesion between the compressed drug and excipient particles.  

OraQuick™
KV Pharmaceutical’s two proprietary taste masking technologies, FlavorTech_ and MicroMask_, are utilized for developing OraQuick tablets. MicroMask provides taste masking by incorporating a drug into matrix microspheres. The first step involved in formulating the tablet include dissolving the sugar (sucrose, mannitol, sorbitol, xylose, dextrose, fructose, or mannose), and protein (albumin or gelatin) in a suitable solvent, such as water, ethanol, isopropyl alcohol, and ethanol–water mixture. The porosity of the product is determined by the quantity of solvent used in the formulation. The solution of the matrix is then spray dried, yielding highly porous granules. The matrix granules are mixed with other excipients such as binder, lubricant, sweeteners, flavors, coloring agent, fillers, disintegrants, surfactants, etc. The drug can be added at this stage in the form of taste-masked granules, otherwise added first in the matrix granule. The granules or powder obtained is then compressed at low compression force to form tablets that are soft and friable but highly porous. After the tablets are compressed, they are subjected to a sintering step. Tablets are sintered in an oven, typically at temperature of about 50_C to 100_C for few minutes to several hours or at 90_C for about 10 min. During this step, the compressed tablets containing
binder (polyethylene glycol) in the earlier step melts and binds particles to form stronger tablet.\textsuperscript{16}

**Quick-Dis\textsuperscript{TM}**

Lavipharm Laboratories is the inventor of Quick-Dis technology. Quick-Dis technology refers to thin, easily dispensed, flexible, and rapidly dissolving films for the local or systemic delivery orally.\textsuperscript{[17]} Quick-Dis disintegrates rapidly upon wetting when placed under the tongue. This drug delivery of Lavipharm has the capability of being printable, non-tacky in nature while dry, with a low-residual water content, easy to process. The film thickness ranges from 1 to 10 mils, and surface area can be 1–20 cm\textsuperscript{2} for any geometry. Lavipharm manufactures its oral films by a solvent-casting process, using water as the preferred solvent followed by a drying step. The coating thickness range is typically from 5 to 20 mils with aerated oven drying. The films can also be processed alternatively using cold- or hot-melt extrusion technique.\textsuperscript{17}

**Advatab\textsuperscript{TM}**

Eurand is the owner of Advatab drug delivery system. Eurand is known for its Microcaps technology, which involve taste-masking drug particles using microencapsulation process based on coacervation/phase separation technique. Eurand applied Microcaps technology to design ODTs (Advatab), which contains taste-masked active ingredients. The primary ingredients in the dosage form include sugar alcohols and saccharide with particle size less than 30 mm along with disintegrant and lubricant.

The lubricant used in the formulation is added as an external lubricant compared to conventional formulations, which contain an internal lubricant. The company claims that this allows the tablets to be stronger compared to conventional tablets as internal lubricants are hypothesized to decrease binding of the drug particles. The dosage forms are manufactured using conventional tabletting and packaging equipments. The tablets, which can handle high drug loading and coated particles, can be packed in both bottles and pushed through blisters.\textsuperscript{18}

**Qdis\textsuperscript{TM}**

Phoqus owns the Qdis technology. The dosage forms comprises of ODTs containing agglomerates greater than 50 mm in size that comprises at least 10\% or more of superdisintegrants without drug. The agglomerates are blended with excipients, and drug particle size ranging in size from 50 to 300 mm. The resulting soft tablets are coated using an
electrostatic dry-powder deposition technology. This coating strengthens the tablet while still providing rapid disintegration.\textsuperscript{19}

**Frosta\textsuperscript{TM}**

Akina owns Frosta technology. The technology incorporates manufacture of highly plastic granules using a plastic material, a material enhancing water penetration, and a wet binder. These granules can then be compressed into tablets at low pressure, thus enabling fast disintegration upon administration.\textsuperscript{20}

**Cotton candy technology**

This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. The cotton candy process also known as the candy floss process. A mouth dissolving tablet is formed using candy floss or shear form matrix. It involves the formation of matrix of polysaccharides or saccharine by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallised to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients, excipients and subsequently compressed to ODT. This process can accommodate larger drug doses and offer improved mechanical strength. However, high process temperature limits the use of this process.\textsuperscript{21\&22}

**Nanocrystal technology**

NanoCrystal\textsuperscript{TM} Fast dissolving technology provides for: Pharmacokinetic benefits of orally administered nanoparticles (\textless 2 microns) in the form of a rapidly disintegrating tablet matrix. Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded As Safe) ingredients, filled into blisters, and lyophilized. This method avoids manufacturing process such as granulation, blending and tabletting which is more advantages for highly potent and hazardous drugs. For fast dissolving tablets, Elans 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 dissolution rate.\textsuperscript{23}

**Shear form technology**

In this technology, a shearform matrix, ‘Floss’ is prepared. Feedstock prepared with a sugar carrier is subjected to flash heat processing. In this process, sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which causes the temperature of the mass
to rise and hence an internal flow condition is created, permitting part of it to move with respect of the mass.

This is followed by its exit through the spinning head that flings the floss under centrifugal force and draws into long and thin floss fibres, which are usually amorphous in nature. the floss so produced is further chopped and recrystallised to provide a uniform flow, thus facilitate blending. Then the recrystallised matrix, active drug and other excipients are blended together and finally compressed into tablets. Active drug and other excipients may be blended with the floss before recrystallising it. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to rapid solubilisation of sugars in presence of saliva.23

**Pharmaburst technology**

Pharmaburst technology is patented by SPI pharma. Pharmaburst technology uses off the shelf coprocessed excipients to create an ODT that, depending on the type of active ingredients and loading, dissolves within 30- 40 seconds. The quantity of pharmaburst required in a formulation depends on the active ingredients in the tablet. The process involves a dry blend of a drug, flavor and lubricant that are compressed into a tablet on a standard tablet press with stock tooling. The Manufacture process can be carried out under normal temperature and humidity conditions. The tablets can be packaged in blister packs or bottle.24

**Challenges in Formulating ODTS**

**Palatability**

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient’s oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.25&26

**Mechanical strength**

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi dose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.27,28&28
Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.\textsuperscript{30}

Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films.\textsuperscript{31,32}

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.\textsuperscript{32}

Table 1 Patent technology and drug used\textsuperscript{33,34}

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<thead>
<tr>
<th>Technology</th>
<th>Process involved</th>
<th>Drug used</th>
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<tr>
<td>Zydus</td>
<td>Lyophilization</td>
<td>Loratidine</td>
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<td>Lyoc</td>
<td>Freeze drying</td>
<td>Phluroglucinol hydrate</td>
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<td>Quicksolv</td>
<td>Lyophilization</td>
<td>Cisapride</td>
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<td>Flash-tab</td>
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<td>Paracetamol</td>
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<td>Wow-tab</td>
<td>Compressed mould tablet</td>
<td>Famotidine</td>
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<td>Flashdose</td>
<td>Cotton candy process</td>
<td>Tramadol</td>
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<td>Durasolv</td>
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<td>Baclofen</td>
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<td>Taste masking</td>
<td>Hyocaminesulphate</td>
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<td>Adatab</td>
<td>Direct compression</td>
<td>Cetrizine</td>
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Industrial Applications

Industrial applications include the following:

- To develop an orally disintegrating dosage forms and to work with existing disintegrants
- To further improvise upon the existing technology of ODTs
- To optimize the blend of disintegrants or excipients to achieve ODTs
- To select and develop proper packaging material and system for enhanced stability of the product and also develop cost-effective product
• To arrive at various taste-masking agents and prepare palatable dosage forms thereby increasing patient compliance
• To develop disintegrants from different polymers which are used as coating materials by certain modifications and use them for formulating ODTs

**Future Prospects**
Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms. The target population has expanded to those who want convenient dosing anywhere, anytime, without water. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand. By paying close attention to advances in technologies, pharmaceutical companies can take advantage of ODTs for product line extensions or for first-to-market products. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for ODTs in the days to come.

**CONCLUSION**
As discussed in this article, drugs can be administered into humans by various drug delivery systems. A large number of companies are in the ODT drug delivery market, which is evident from the number of products launched as ODT and patents approved. Amongst other drug delivery companies, those in the ODT market possess tremendous potential of extending the drug product life cycle, reducing the attrition rate during the drug development stage, and extending the profitability of existing products. Owing to its flexible nature, molecules of a wide variety of doses and chemical characteristics can be incorporated into an ODT. As pharmaceutical companies are now starting to recognize the need for more technological advances to meet the new challenges in the future, ODT continues to have a significant impact and contribution in meeting those demands and challenges.

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