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Orally Disintegrating Tablets and Related Tablet Formulations

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INTRODUCTION

Orally disintegrating tablets (ODTs) are solid single-unit dosage forms that are designed to be placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the aid of additional water. Despite a surge of orally disintegrating tablets in the market in the recent years, they potentially can be confused with other solid oral dosage forms that are consumed without additional water intake, including lozenges, buccal tablets, and chewable tablets. Lozenges and buccal tablets are intended to dissolve slowly in the mouth, whereas, orally disintegrating tablets must disperse or dissolve in the mouth quickly, within seconds. Chewable tablets are also different from orally disintegrating tablets because they require manual chewing action by the patients before they can be swallowed. The disintegration times are longer for the chewable tablets compared to the orally disintegrating tablets. For a tablet to be classified as an orally disintegrating tablet the disintegration time should be sufficiently rapid for the patient to not feel the need or compulsion to chew. Orodispersible tablets (1), rapidly disintegrating tablets (2), and fast-dissolving tablets (3) have been used as synonyms for orally disintegrating tablets. Examples of orally disintegrating tablets include over-the-counter drugs such as Claritin® RediTabs® (loratadine rapidly-disintegrating tablets) and Alavert™ (loratadine orally disintegrating tablets), and prescription drugs such as Maxalt-MLT™ (rizatriptan benzoate) and ZOFRAN® (ondansetron) Orally Disintegrating Tablets.

One of the greatest benefits of orally disintegrating tablets over conventional tablets is enhanced patient compliance and acceptance related to both feasibility and convenience of dosage administration (4). As many as 50% of the population have difficulty swallowing intact tablets and hard gelatin capsules (5). These include pediatric and

[1] The opinions expressed in this chapter do not necessarily reflect the views or policies of the U.S. Food and Drug Administration.

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geriatric populations who have difficulty swallowing large tablets. Patients who are bedridden, mentally retarded, uncooperative, nauseous, and those suffering from nervous or anatomical disorders of the larynx or esophagus, or on reduced liquid intake diets also cannot swallow conventional tablets. In such patients practitioners would expect much better compliance and therapeutic outcomes by administering orally disintegrating tablets instead of conventional tablets (6). Patient compliance can be enhanced by designing orally disintegrating tablets that have pleasant taste and texture because many people simply do not enjoy swallowing solid tablets. People who take medicines on an as-needed basis and active people who do not have convenient access to water could easily take them as well.

Orally disintegrating tablet drug delivery does, however, have certain limitations. Because orally disintegrating tablets require the users to produce their own saliva, those with very dry mouth may not benefit. Production of saliva depends not only on the drug product formulation but the ability and condition of the user. Also, the administration of orally disintegrating tablets to increase compliance in uncooperative patients, such as those being treated for mental illness, does not guarantee compliance. Patients have found various ways of hiding the medication such as sticking the Zydis tablet behind the teeth to avoid swallowing the medication (7). Nonetheless, orally disintegrating tablets offer practitioners an added tool in enhancing compliance in some patient populations (3).

The candidate drug categories for orally disintegrating tablets are diverse, such as cardiovascular drugs used for chronic conditions with large geriatric population as users, and drugs taken on as-needed bases, including analgesics, drugs to treat erectile dysfunction, and antihistamines. Patient interest and demand provide a substantial opportunity for the pharmaceutical industry to expand product lines and develop new marketing initiatives. However, in expanding product lines, manufacturers should consider the potential differences in bioavailability between the orally disintegrating tablets and traditional tablets. With traditional, or conventional, tablets, the contact times between the drug substance and oromucosal tissues are minimal, and most of the absorption takes place in the stomach and/or the intestines. However, drug released from orally disintegrating tablets also has the opportunity to be absorbed by local oromucosal tissues and pregastric regions, especially if the residence time in the mouth is prolonged. Oromucosal and pregastric absorption can potentially produce a rapid response, and partial avoidance of first-pass effects and gastrointestinal irritation (5). Therefore, formulation as a "bioequivalent" line extension of a conventional oral dosage form may be difficult for some drugs because of varying degrees of pregastric absorption which can have an impact on C_{max} (maximum plasma concentration), T_{max} (the time to reach C_{max}), and AUC (area under the curve of plasma concentration plotted over time). As an example, a different pharmacokinetic profile for an orally disintegrating tablet compared to a conventional oral dosage form was found with hydrochlorothiazide. Based on the biopharmaceutical classification system (BCS) hydrochlorothiazide is classified to be highly soluble and poorly permeable (BCS Class III) (8). Corveleyn and Remon compared pharmacokinetic parameter values (AUC, C_{max}, T_{max}, and half life) obtained from subjects who took the conventional hydrochlorothiazide tablet, freeze-dried orally disintegrating formulation A, or freeze-dried orally disintegrating formulation B (9). Formulation A contained maltodextrin, polyethylene glycol 6000, xanthan gum, and hydrochlorothiazide to make an aqueous suspension. Formulation B contained miglyol, maltodextrin, methocel LV, and hydrochlorothiazide to make an emulsion. The suspension or emulsion was poured into PVC blisters and the samples were freeze-dried. The dissolution rate for formulation A was faster than the other dosage forms both in water and in 0.1 N hydrochloric acid. At the end of 30 minutes complete dissolution occurred for formulation A, but only about 80%

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TABLE 1 Conventional Hydrochlorothiazide Tablets versus Orally Disintegrating Tablets–Average Pharmacokinetic Parameters Determined from 6 Healthy Volunteers

Formulation	AUC_{0-24h} (ng/hr/mL)	C_{max} (ng/mL)	T_{max} (min)	$T_{½}$ (h)
Formulation A[a]	1843.4 ± 476.2[d]	244.2 ± 44.3	142.5 ± 47.4	5.4 ± 1.8
Formulation B[b]	1072.8 ± 368.6	201.8 ± 38.5	135.0 ± 35.8	5.2 ± 2.2
Esidrex® 25[c]	1009.5 ± 399.8	200.1 ± 34.9	183.7 ± 40.7	5.8 ± 2.3

[a]Formulation A: Orally disintegrating tablets containing maltodextrin, polyethylene glycol 6000, xanthan gum, and hydrochlorothiazide.
[b]Formulation B: Orally disintegrating tablets containing miglyol, maltodextrin, methocel LV, and hydrochlorothiazide.
[c]Esidrex® 25 (Ciba, Basel, Switzerland): Conventional reference formulation.
[d]$p < 0.05$; AUC was significantly higher for Formulation A compared to the other two formulations.
Source: From Ref. 9 with permission from Elsevier.

dissolution occurred for the other formulations. As shown in Table 1, the AUC_{0-24h} value for formulation A was significantly higher than either the reference formulation or Formulation B. The C_{max} was also higher for formulation A, but not significantly. Differences in T_{max} and $T_{1/2}$ (half life, or the time for the plasma concentration to decrease by one half) were also not significant. Based on these observations it is apparent that the formulation of orally disintegrating tablets can significantly change the bioavailability of some drugs.

FORMULATION CONSIDERATIONS OF ORALLY DISINTEGRATING TABLETS

Aside from the bioavailability issues that may affect how the manufacturer expands the product line, additional challenges of developing oral disintegrating tablets include achieving palatability and assuring practical hardness and friability without increasing the disintegration time. Achieving palatability may require taste masking of the active ingredients which may be bitter in taste. Taste masking can be achieved by coating the active ingredient particles with a polymer by spray drying, spray congealing, or coacervation (5). For example, Khan et al. (10) were able to formulate rapidly-disintegrating tablets for bitter tasting ondansetron hydrochloride by using aminoalkyl methacrylate copolymer (Eudragit® EPO, Roehm GMBH, Darmstadt, Germany). For taste masking purposes they formed a drug–polymer complex by precipitation. Saturated solutions of ondansetron hydrochloride and Eudragit EPO in ethanol were prepared. The solution was injected into 0.1 N sodium chloride under stirring. The resulting foamy matrix on top was separated and dried under vacuum. The dried matrix was then pulverized and stored for use. In vitro drug release was evaluated by dissolving the drug-polymer complex (equivalent to 10 mg of ondansetron hydrochloride) in 10 mL of simulated salivary fluid (SSF, pH 6.2), and shaken for 60 seconds. Several different drug polymer ratios were tested and when the polymer concentration was greater than or equal to 20% the dissolution of the drug in SSF was not detectable. Several different formulations were made and bitterness was not detected by the test subjects even in unflavored tablets.

Taste masking is also achieved by the addition of sweeteners and flavoring agents. Kayumba et al. (11), were able to develop quinine sulfate pellets for taste masking purposes in pediatric dosing. In this study the quinine sulfate pellets were produced by mixing the active ingredient with microcrystalline cellulose. The blend was wetted with water then subjected to extrusion–spheronization. Eudragit EPO, which is a cationic

copolymer consisting of butylmethacrylate-(2-dimethylaminoethyl) methacrylate-methyl methacrylate (1:2:1), was chosen because it dissolves readily in low pH in the presence of gastric fluid (pH 1.0–1.5) but can prevent the release of drug in saliva where the pH is higher (pH 6.8–7.4).

An example of successful taste masking is Mirtazapine SolTab® which uses OraSolv® (CIMA Labs, Minneapolis, Minnesota, U.S.A.) technology (12). In REMERON SolTab® the active ingredient, mirtazapine, is coated. The coated pellets are held together by water-soluble ingredients. When the patient takes REMERON SolTab® the water soluble ingredients and flavors disperse and dissolve in the mouth while the coated pellets remain intact until the pellets reach the stomach where they dissolve. Despite the available technologies taste masking may not be successful if the loading of the bitter drug is high or if the residence time of the tablet in the mouth is prolonged. A formulation scientist must also make careful selection of excipients and their particle sizes to avoid grittiness.

TECHNOLOGIES FOR MANUFACTURING ORALLY DISINTEGRATING TABLETS

Technologies for manufacturing orally disintegrating tablets include the freeze-drying method, cotton candy technology, and compressed tablets. Some examples of orally disintegrating tablet technology and products are listed in Table 2. The Zydis® (R.P. Scherer, Troy, Michigan, U.S.A.) technology is used to make freeze-dried wafers which dissolve nearly instantly in the mouth and leave no gritty residue. Compressed tablets usually dissolve slower than the freeze-dried wafers and may leave a gritty mouth feel if insoluble excipients are used. However, the compressed tablets technology is less expensive and may be more suitable for loading large amounts of active ingredients.

TABLE 2 Examples of Orally Disintegrating Tablets Technology Platforms

Platform	Patent holder	Principle	Example product (manufacturer)
Zydis®	Cardinal health	Liquid dispersion of active ingredients and excipients are lyophilized in preformed blister packs	Caritin Reditabs® (Schering Plough) MAXALT-MLT™ (Merck)
Flash Dose®	Fuisz technology	Directly compressed tablet; combines active ingredient with an amorphous floss of saccharides or polysaccharides, and other excipients	Ultram® ODT (Biovail)
DuraSolv®	CIMA Labs	Directly compressed tablet; contains soluble fillers	NuLev®(Schwarz Pharma)
OraSolv®	CIMA Labs	Directly compressed tablet; contains effervescing excipients	REMERON SolTab® (Organon USA Inc.)
WOWTAB®	Yamanuchi	Compressed tablets; uses fluid bed granulator to coprocess sugar-based materials (mannitol, lactose, maltose et al.) to optimize compactibility with solubility	Benadryl Fastmelt (Pfizer)

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Freeze-Drying Technology

The first entrance of freeze-drying or lyophilization technology into the field was the Zydis delivery system developed by R.P. Scherer. It is a mixture of gelatin, sugar(s), active ingredient, and other components poured into the depression of a blister pack. Water is sublimed away during lyophilization leaving a highly porous, relatively soft solid. The resulting wafers dissolve or disperse on the tongue rapidly in about three to five seconds. Some of the limitations of the freeze-dried wafers are drug solubility and a drug loading limitation of about 60 mg for water-soluble drugs (5). The wafers are also moisture sensitive and very fragile, requiring special packaging. Maxalt-MLT™ (rizatriptan benzoate orally disintegrating tablets) manufactured by Merck & Co., Inc. is an example of lyophilized tablets. The tablets are individually packaged in unit blister packs with peel off backing which are placed inside aluminum pouches for added protection. The pouches are placed inside a carrying case. Patients are instructed not to remove the blister pack from the pouch until ready to consume the tablets.

Cotton Candy Technology

Another technology for manufacturing orally disintegrating tablets is the cotton candy process, also known as the candy-floss process, which involves centrifugation to produce a floss-like crystalline structure. In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shearfoam process. The matrix is cured and milled to make a flowable, compactible, and highly soluble filler. Because of the formation of porous three-dimensional structures with the active ingredients encased in the pores, the resulting surface area is high. Therefore, dispersion and dissolution occur quickly when the product is placed in the mouth. This technology is patented as FlashDose® by Fuisz Technology (Chantilly, Virginia, U.S.A.) (13,14). FlashDose is characterized as having a bulk density of ranging from about 150 mg/mL to about 1300 mg/mL and porosity ranging from about 10% to about 90% of the dosage form volume. Therefore, there is much opportunity to manipulate the density in such a manner to not only make orally disintegrating tablets, but also chewable tablets.

Tablet Compression Technology

The tablet compression method generally relies on conventional manufacturing technology. Orally disintegrating tablets can be formed by either direct compression, wet granulation or by a wet compression method. Formulations can be optimized using traditional polynomial regression or an artificial neural network. Artificial neural networks (ANN) are commonly used for pattern recognition, such as in voice recognition, financial predictions, weather forecasting, insurance statistics, transportation, and even in pharmaceutical development in recent years (15–17). ANNs can be especially useful in dealing with complex relationships between input and output data, as in the case with formulation development involving multiple variables. The reader is referred to Chapters 3 and 4 in this volume for more details.

In the wet compression method, water is added to a powder blend and the mixture is kneaded until a homogenous wet powder mass is formed. The mass is then extruded through a sieve. Wet granules are then compressed into tablets. Using this method, Sunada and Bi (2) were able to develop rapidly disintegrating lactose tablets with disintegration times of less than 15 seconds. The rapidly disintegrating tablets were composed of α-lactose monohydrate of various particle sizes as follows: Lactose 450 M

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with average particle size of 13.2 μm, Lactose 200 M with average particle size of 23.9 μm, and Lactose 80 M with average particle size of 61.4 μm. Moisture content of the tablets was also varied from 4.70% to 18.80%. Using an ANN model it was determined that increases in moisture content increased the tensile strength of the tablets. The authors postulated that when lactose particles were wetted, the particles became coated with a layer of lactose solution. Then, during the drying process, the lactose solution forms solid bridges between particles by recrystallization. Thus, increased tensile strength resulted from increases in the extent of such bonding. Similarly, smaller particle sizes of lactose yielded tablets with greater tensile strengths, most likely from increased numbers of bonds formed. Compression of larger particle was thought to produce a greater number of cracks and pores. Disintegration times followed the patterns for tensile strength. Increased tensile strength was accompanied by an increase in disintegration time.

The wet compression method may not be suitable for active materials that are physically or chemically unstable in the presence of water. The direct or dry compression method is generally preferred because it is simpler, easier to automate, and avoids direct contact of water with the active material. As with wet compression, it is often capable of producing orally disintegrating tablets with sufficient physical robustness to allow physical handling and packaging. As demonstrated in Figure 1, an increase in compression pressure led to an increase in tensile strength of mannitol tablets and mannitol/freeze-dried sucrose tablets (18). However, a decrease in tensile strength led to higher porosity and faster oral disintegration times. In order to achieve fast disintegration, highly porous tablets are desired for fast wicking of water into the tablet structure. However, the lower compression force that produces porous tablets can compromise the tablet strength, leading to excessive friability. Because of these conflicting parameters it is important for the formulator to find a proper balance between compression force, tablet porosity, and physical robustness.

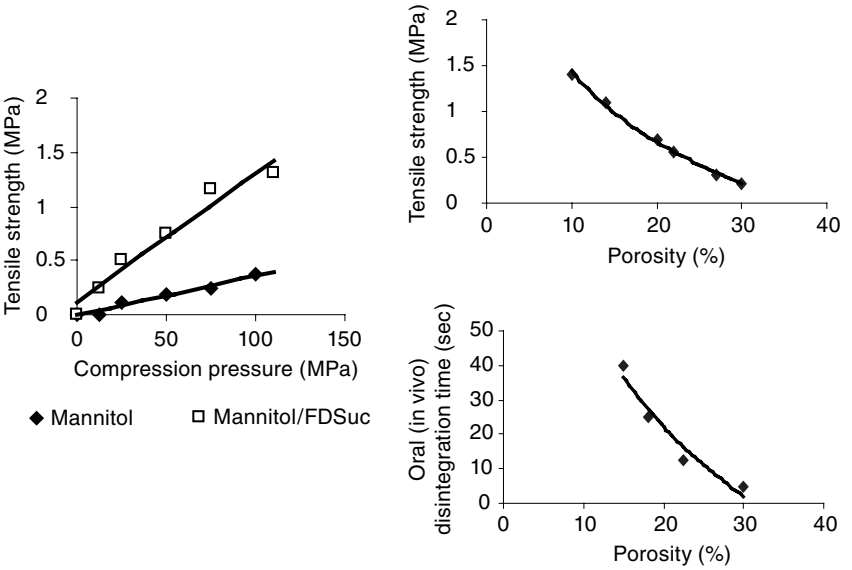

FIGURE 1 Relationship between compression pressure, porosity, and disintegration time for an experimental orally disintegrating tablet. *Abbreviation*: FDSuc, Freeze-dried sucrose. *Source*: Redrawn from Ref. 18.

For example, a study was conducted to evaluate the effects of tablet composition and compression pressure on disintegration time and friability using an ANN model (19). In a formulation containing various amounts of calcium silicate and compactible sugar (DiPac®), the relative amounts of the two excipients were varied. Calcium silicate was chosen as a model insoluble filler because of its desiccant-like property and compactible sugar was chosen as a model soluble filler because of its sweet taste which would be useful in orally disintegrating tablets. In general, low compression force and high amounts of disintegrants yielded faster disintegration. As shown in the contour graph in Figure 2, when a low compression pressure of 20 MPa and a high disintegrant level of 15% were kept constant, 50–60% calcium silicate and 60–100% compactible sugar were necessary to achieve fast disintegration and lower friability. The USP <1216> friability test allows for 1.0% loss of weight for conventional tablets (20), but many orally disintegrating tablets may not be able to meet the requirement. Special packaging, such as blister packs, may be used to help compensate for the limitations of their higher friability. In any case, orally disintegrating tablets should be at least sufficiently robust so that patients would have intact tablets that are elegant in appearance before they place them in their mouths.

In an example of the use of statistical experimental design, Schiermeier and Schmidt (21) described an optimized ibuprofen (enteric coated particles) direct compression formulation derived from a central composite design. The optimized variables were mannitol (34%), crospovidone (13%), and compression force (7 kN). The coated ibuprofen particles made up 50% of the total mass. The predicted 38.5 N tablet crushing strength and 16.9 seconds wetting time agreed well with the experimental results of 40.3 N and 17 seconds, respectively. Wetting time, defined as the time for complete wetting when the tablet is immersed in 10 mL water at room temperature, was used in lieu of disintegration time measurement as it was considered to mimic the action of saliva on the tablet (21).

Though direct compression offers many advantages in the manufacture of orally disintegrating tablets, wet granulation may offer additional opportunities. For example, Adelbury et al. (22) described the granulation of acetaminophen (37.4%) with D-mannitol using a hydrophilic waxy binder (PEG-6-stearate). One formulation included 2% AcDiSol (croscarmellose sodium) intragranularly. Two methods of granulation were tried: wet granulation with an emulsion of the binder, and melt granulation). Final formulations consisted of the granules dry blended with crocarmellose sodium, aspartame and magnesium stearate. Both methods were found able to produce tablets with hardness of 47.9 ± 2.5 N and disintegration times of 40 ± 2 seconds, but the melt granulation gave better hardness results, while wet granulation gave better disintegration results. It was concluded that the waxy binder enhanced compactibility without

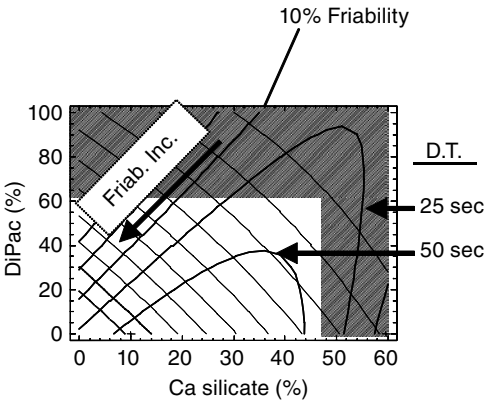

FIGURE 2 An experimental direct compression formulation containing various ratios of DiPac (*compactible sugar*) and calcium silicate. 15% super disintegrant and 20 MPa of compression force was used. D.T: Disintegration time (*seconds*) Friab. Inc.: Increasing friability. *Source*: Redrawn from Ref. 19.

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exceeding the disintegration time limits of < 3 minutes established by the EP (1) for orodisperse tablets.

CHOICE OF EXCIPIENTS

The excipients listed for a number of orally disintegrating products are provided in Table 3. Orally disintegrating tablets typically are composed of sweet fillers and flavoring agents. Freeze-dried tablets also generally contain gelatin that provides a melting sensation in the mouth. Compressed tablets typically are formulated with highly water-soluble fillers and relatively high levels of disintegrants. Insoluble fillers such as microcrystalline cellulose are sometimes used in these formulations but the formulator must make sure that their particle sizes are small and that their levels in the formulation are not excessive to avoid grittiness or any other unpleasant mouth-feel. Like conventional tablets, compressed orally disintegrating tablets need glidants (e.g., colloidal silicon dioxide) to help the particles flow and lubricants (e.g., magnesium stearate) to prevent sticking of the materials to the punches and facilitate ejection from dies.

TABLE 3 Inactive Ingredients Listed for Orally Disintegrating Tablets

Drug product	Technology platform	Listed inactive ingredients
MAXALT-MLT™ (rizatriptan benzoate orally disintegrating tablets)	Zydis®	Gelatin, mannitol, glycine, aspartame, and peppermint flavor
Caritin® RediTabs® (loratadine rapidly-disintegrating tablets)	Zydis®	Citric acid, gelatin, mannitol, mint flavor
Carinex® RediTabs® (desloratadine orally disintegrating tablets)	Zydis®	Microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate, butylated methacrylate copolymer, crospovidone, aspartame, citric acid, sodium biocarbonate colloidal silicon dioxide, ferric oxide red and tutti frutti flavoring
Ultram® ODT (Tramadol hydrochloride orally disintegrating tablets)	Flash Dose®	Aspartame, copovidone, crospovidone, ethylcellulose, magnesium stearate, mannitol, mint flavor, and silicon dioxide
Alavert™ (loratadine orally disintegrating tablets)	DuraSolv®	Artificial and natural flavor, aspartame, citric acid, colloidal silicon dioxide, corn syrup solids, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, modified food starch, and sodium bicarbonate
REMERONSolTab® (mirtazapine orally disintegrating tablets)	OraSolv®	Aspartame, citric acid, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orage flavor, polymethacrylate, povidone, sodium bicarbonate, starch, and sucrose
Children's Benadryl® Allergy & Cold Fastmelt (diphenhydraine citrate and pseudoephedrine HCl)	Wowtab®	Aspartame, citric acid, D&C red no. 7 calcium lake, ethylcellulose, flavor, lactitol, magnesium stearate, mannitol, polyethylene, soy protein isolate, and stearic acid

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DISINTEGRATING AGENTS

Disintegrants are very important components of compressed orally disintegrating tablets because they often are primarily responsible for the fast disintegration in the mouth (23). Orally disintegrating tablets can contain either a super disintegrant or an effervescent system as a disintegrating agent. Sometimes a combination of different disintegrating agents is used for better disintegration. An effervescent system (e.g., sodium bicarbonate and citric acid combination) generally provides a highly effective disintegrating system. The release of carbon dioxide when the effervescent agents come in contact with water helps to collapse the tablet matrix. To minimize any possible unpleasantness owing to a fizzing sensation in the mouth, formulators may choose to minimize the levels of effervescent ingredients used in the formulation.

In conventional tablets, super disintegrants, such as croscarmellose sodium, sodium starch glycolate, and crospovidone are generally effective at lower concentrations than the traditional disintegrant, starch, and may be used at 2–5%. Although higher levels of super disintegrants do not necessarily produce faster disintegration in conventional tablets, as much as 15% of super disintegrants may be beneficial in orally disintegrating tablets. Super disintegrants are strongly hygroscopic materials that aid in wicking water from the saliva into the internal structure of the tablets. An advantage of using super disintegrants over the effervescent system is that they are less vulnerable than effervescent systems to the detrimental effect of moisture. Nevertheless, the hygroscopicity of super disintegrants is such that both their functionality and tablet stability can be compromised by excessive exposure to high humidity. Of the three widely used super disintegrants, croscarmellose sodium seems to be less effected by high moisture level in regards to functionality, but all disintegrants and disintegrant systems are vulnerable to the detrimental effects of humidity (19). High levels of disintegrants, high levels of soluble fillers, heat generated from the tablet presses, and atmospheric moisture can easily induce or promote stickiness at the punches which may pose a challenge to the formulation scientist.

In an attempt to find a distintegrant having high compactibility and disintegration ability suitable for an orally disintegrating direct compression tablet formulation, Bi et al. (24) studied the ratios of microcrystalline cellulose (MCC) and low-substituted Hydroxypropylcellulose (L-HPC). Ethenzamide and ascorbic acid were selected as models for poorly and easily water soluble drugs, respectively. In general, they found shortest disintegration times when the MCC/L-HPC ratio was in the range of 8:2 to 9:1.

Ozeki et al. (25) compared several disintegrants in a 200-mg rapidly disintegrating oral formulation. The drug load was aspirin granulated with 5% acid-treated yeast cell wall (AYC granules). Prior data had suggested that AYC functions as both a binder and as a disintegrant. The mixture of granules and 10% disintegrant were compressed at 100 MPa in a universal testing machine with external lubrication. Compared with croscarmellose, L-HPC, and calcium carboxymethyl cellulose, carboxymethyl cellulose produced tablets exhibiting the fastest water uptake rate and lowest in vivo disintegration time (mean = 20.1 second) while generating what was judged an acceptable hardness of at least 3 kgf.

SWEETENERS

Sugars, sugar alcohols, and other artificial sweeteners are preferred fillers in orally disintegrating tablets. Sugars and sugar-based excipients provide good mouth feel because

they are water soluble. Together with other flavoring agents and artificial sweeteners such as aspartame, they help to mask the taste of active ingredients, many of which are bitter even in small doses. Some examples of sugars and sugar-based excipients used in orally disintegrating tablets are amorphous sucrose, dextrose, maltitol, mannitol, and xylitol. Sugar alcohols such as maltitol, mannitol, and xylitol have the added advantage of containing fewer calories compared to sucrose and do not promote tooth decay. Mannitol and xylitol have negative heats of solution, thereby imparting a cooling sensation in the mouth.

Sugimoto et al. (26) studied orally disintegrating tablets containing amorphous sucrose prepared by the crystalline transition method (CTM) and found that a level of 10–20% amorphous sucrose in the tablet was suitable. The method requires storage of the tablet under certain conditions of relative humidity and temperature, during which there is a conversion of amorphous to crystalline sucrose, accompanied by an increase in tablet hardness and an alteration in porosity and disintegration time. In the 10–20% amorphous sucrose range, tablets of "a little less" than the desired 1 MPa tensile strength or greater were produced yielding in vivo disintegration times in the approximate rage of 10–50 seconds.

Common artificial sweeteners in orally disintegrating tablets are acesulfame potassium, aspartame, and saccharin sodium. Acesulfame potassium and aspartame are about 200 times sweeter than sucrose and saccharin sodium is about 300 times sweeter than sucrose (27). Although they impart similar sweet taste in the mouth their physical characteristics, including particle size, flow, and mechanical properties vary widely (28). Because these artificial sweeteners have sweetening intensities much higher than that of sucrose, they can be used in smaller quantities. However, sucrose generally has superior flow properties and exhibits lower brittleness. When used in moderate quantities, sucrose may help reduce the likelihood of capping or lamination of tablets containing brittle drug substances. Acesulfame potassium particles are generally smaller than sucrose particle but have similar flow characteristics and their compacts have mechanical properties (brittle fracture index and bonding indices) similar to sucrose compacts. Therefore, with its sweetening intensity of 200 relative to sucrose, acesulfame potassium can be used in place of sucrose in order to achieve smaller tablet sizes. Aspartame has similar sweetening intensity as acesulfame but its particles have needlelike shape leading to poor flowability. Aspartame compacts also exhibit high brittleness, but if used in small amounts aspartame may contribute to good tablet strength because of its high bonding index. Saccharin, with its irregular particle shape and high brittle fracture index of the compact, also exhibits poor flowability and a propensity to capping and lamination when present in high quantities. However, it may be useful in small quantities where it does not impact the overall flowability, uniformity, and strength of the tablets.

Sucralose is a relatively new sweetener approved by the FDA in 1998. It has a similar chemical structure as sucrose with three hydroxyl groups substituted by chlorines. Its sweetness intensity is 300–1000 times that of sucrose. One of the advantages of sucralose is that it is stable in high heat. Therefore, it may used in products requiring sterilization, pasteurization, and baking (27).

MEASUREMENT OF TASTE

The success of orally disintegrating tablets relies heavily on the taste and texture of the product, as well as the disintegration time (29). The texture or mouth-feel of a

product can easily be predicted by the formulation based on the amount of soluble excipients and the amount and particle sizes of the insoluble excipients. However, predicting the taste masking of bitter drugs is more challenging. Taste recognition occurs at three levels: the receptor level, the circuit level, and the perceptual level (30). At the receptor level are the taste buds that detect different tastes such as bitter, sour, salt, sweet, umani, and trigeminal. Umani refers to the glutamate taste, such as monosodium glutamate. Trigeminal refers to the burning sensation produced by spices and peppers. At the circuit level is the neural transmission of the sensation to the brain. At the perceptual level is the thalamus of the brain where the sensation is recognized as a certain taste. While a human taste trial for orally disintegrating tablets is necessary to confirm acceptability before marketing the drug product, manufacturers may conduct an in vitro test as a routine screening tool for ease and cost-savings. In a study conducted by Murray et al. (30), an electronic device called e-tongue (Alpha M.O.S., Toulouse, France) was utilized to measure the reduction of bitterness of active ingredients by changing the sodium chloride concentration in the formulation. The e-tongue is composed of probes mimicking the taste buds, transducer for neural transmission, and computer for the human brain. Measurements are performed potentiometrically with readings taken against a $Ag/AgCl_2$ reference electrode. Then the signals are quantified and digitized, and the data are analyzed by software. The reduction of bitterness of the active ingredients, quinine hydrochloride and magnesium sulfate, with increase in salt content, was measured against a known bitter agent, urea. With a salt concentration of 0.50 M, reductions of bitterness for urea, quinine hydrochloride, and magnesium sulfate were 76.83%, 54.37%, and 24.34%. The results were comparable to the trained taste panel results, but the variances in e-tongue testing were much lower than the variance observed in human testing. Although the in vitro test cannot replace human taste testing, such technology may provide a useful screening tool where routine testing in humans is expensive or unsafe.

MEASUREMENT OF DISINTEGRATION TIME

Current compendial disintegration test methods are limited in their ability to assess orally disintegration tablets because of the rapid disintegration of ODTs and the strong agitation and large volume of medium employed in the compendial test method. Several novel approaches have been developed that may be more suitable for research and development (R&D) and quality control (QC). For example, Morita et al. (31) described a method involving a disintegrating bath and a CCD camera. The camera was interfaced to a PC running motion capture and image analysis software. With the ability to detect morphological changes during disintegration, the authors suggest that their method would have utility both in formulation development and quality control. El-Arini et al. (32) described the use of a texture analyzer (TA) in which the flat-ended cylindrical probe penetrates into the disintegrating tablet while it is immersed in water. The results are plots of distance moved by the probe under a small set force as a function of time. From these disintegration profiles, the start and stop times of disintegration may be determined.

A simpler method based on the use of a linear variable displacement transformer (LVDT) that also provides a digital output of disintegration time and tablet thickness has been reported (33). By examining the change in the tablet thickness over time it was possible to determine subtle differences in disintegration efficiency between several model tablets. As shown in Figure 3 the tablet containing Primojel® (Fonterra™ Ltd., Auckland, New Zealand) with a higher moisture content of 21.5% exhibited similar

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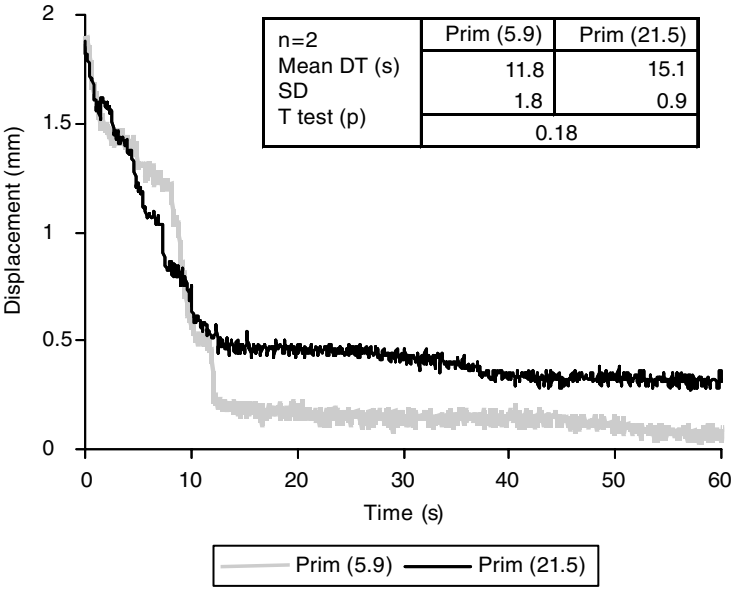

FIGURE 3 Disintegration profile of an experimental tablet containing a super disintegrant, Primogel, with 5.9% or 21.5% moisture content. *Source*: From Ref. 33.

disintegration rate as the tablet containing Primojel with lower moisture content of 5.9%. However, Primojel with lower moisture content appeared to yield a more complete dispersion of residual particles.

More recently, Abdelbary et al. (34) describe another device that measures the penetration distance (versus time) of a probe travel (under a fixed load of 50 g) into a tablet that is submerged in disintegration medium. They described their approach as more closely mimicking the situation in a subject's mouth than some earlier methods by (*i*) putting the test tablet on a moveable platform, thereby eliminating the use of adhesive attachment tape required by some earlier methods and exposing both sides of the tablet, and (*ii*) allowing detached particles to be gradually eliminated. A diagrammatic representation of the output for Spasfon® (Himont Pharmaceuticals, Ltd., Lahore, Pakistan) and Flash Tab® (Ethypharm, Houdan, France) is provided in Figure 4. The beginning of the plateau area represents the disintegration time. The effects of medium and temperature on the disintegration times of orally disintegrating tablets, Spasfon®, Flash Tab®, and Wowtab® were evaluated. Compared to distilled water, artificial saliva generally provided faster

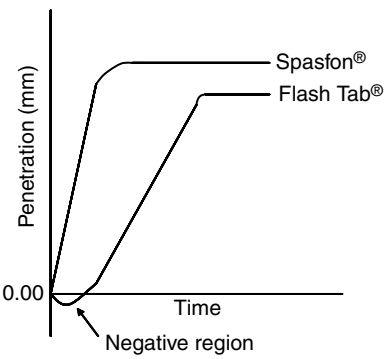

FIGURE 4 Diagrammic representation of disintegration as measured by probe penetration. *Abbreviations*: Spasfon®, lyophilized oil in water emulsion; Flash Tab®, formulation including disintegrating agents. *Source*: Redrawn from Ref. 34.

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disintegration. The temperature of the media (room temperature versus 37°C) did not appear to effect the disintegration time in any predictable manner. However, when the acetaminophen orally disintegrating tablets were evaluated, the disintegration rates were faster when the temperature of the medium was 37°C compared to when room temperature medium was used. In the same study, the in vitro disintegration times were compared to the in vivo disintegration times. For the in vivo study, 14 healthy volunteers were used. They were instructed to initially rinse their mouths with distilled water. The timer was started when the tablet was placed on the tongue and stopped after the last noticeable particle was disintegrated. Volunteers were allowed to move the tablet against the upper palate with the tongue, but biting, side-to-side movement, or swallowing of saliva was not permitted. Measurements were taken in three replicates. A good correlation of the in-vitro disintegration times and the in vivo disintegration times was found.

While disintegration testers with specialized probes can be very helpful during research and development, it may sometimes be desirable to use more widely available and standardized equipment for routine in vitro testing. In such cases, formulators may be able to use the compendial disintegration apparatus as described in USP <701> with slight modification in determining disintegration times. The current USP <701> provides disintegration requirements for uncoated tablets, plain-coated tablets, enteric coated tablets, buccal tablets, sublingual tablets, hard gelatin capsules, and soft gelatin capsules (35). However, the USP does not specify requirements for the orally disintegrating tablets because the USP <701> is designed to be a limits test where the disintegration times are assumed to be potentially long. For orally disintegrating tablets, the disintegration times of tablets can be individually quantified. However, the USP disintegration test is an in vitro test using about 900 mL of medium and vigorously oscillating basket, providing conditions very unlike in vivo environment. Therefore, the USP test may be more suitable for quality control purposes rather than for research and development.

Currently, there is no clear consensus in regards to how fast the orally disintegrating tablets should disintegrate in a person's mouth or in vitro. However, the preference is, the faster the better. As described by Yoo et al. (13) in their U.S. Patent for FlashDose®, "it is to provide a rapidly dispersing dosage form that can disperse in less than about five minutes, preferably less than about ninety seconds, more preferably in less than about thirty seconds and most preferably in less than about ten or fifteen seconds." The European Pharmacopeia calls orally disintegrating tablets the orodisperse tablets, which is defined as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed." The European Pharmacopeia allows a disintegration time of 3 minutes for the orodisperse tablets (1). However, other regulatory bodies may require shorter disintegration times. For example, the USP monograph for Ondansetron Orally Disintegrating Tablets the in vitro disintegration time requirement is "not more than 10 seconds (36)." While some manufacturers of orally disintegrating tablets may be inclined to use the upper limit of 3 minutes as a guidance for ease of manufacturing, in general, any orally disintegrating tablet that does not exhibit sufficiently fast in-vivo disintegration and pleasing mouth-feel would not fare well in the competitive market.

Fang et al. (37) evaluated several over-the-counter medications labeled to be fast disintegrating or dissolving, as listed in Table 4. They compared the mean in vivo disintegration times of these products to an in vitro disintegration test. The desktop disintegration test as proposed by the authors is a fast and simple test using a 1 mL plastic syringe to deliver water to the tablets. The orally disintegrating tablet is placed on a flat surface and 1 mL of water is slowly delivered to the tablet using a plastic syringe within about 5–10 seconds. At the end of 30 seconds in contact with water, the tablet is checked

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TABLE 4 Over-The-Counter Drug Products Labeled to be Fast Disintegrating or Dissolving

Product Name	Labeling	Direction for consumer
Claritin RediTabs	Orally disintegrating tablets	Place 1 tablet on tongue; tablet disintegrates, with or without water
Alavert	Orally disintegrating tablets	Tablet melts in mouth. Can be taken with or without water
Children's Benadryl Fastmelt®	Dissolving tablets	<There is no special direction on labeling for taking this medicine other than the suggested dose>
Triaminic Softchews	Softchew Tablets	Let Softchew dissolve in mouth or chew Softchew tablet before swallowing, whichever is preferred

Source: From Ref. 37.

by manual palpation for completeness of disintegration. Completion of tablet disintegration is indicated by collapsing of the tablet matrix with no palpable core. As presented in Table 5 both Claritin RediTabs and Alavert passed the 30 second desktop disintegration and exhibited relatively fast in-vivo disintegration times of less than one minute. Children's Benadryl Fastmelt and Triaminic Softchews did not pass the desktop disintegration and the mean in-vivo disintegration times were also prolonged. Upon examination of the labeling the ones that passed the desktop disintegration test were labeled "orally disintegrating tablets," whereas, ones that did not pass the test were labeled "dissolving tablets" and "Softchew Tablets." Interestingly, the Triaminic Softchews which were comparatively large tablets, failed to disintegrate within 30 seconds using the desktop testing method, even when the volume of water was doubled from 1 mL to 2 mL. The tablets were probably labeled as Softchew because of their large size which would encourage the chewing action by patients. As shown in Table 4, patients are instructed to either dissolve or chew the Softchew tablets, whichever is preferred. Because the volume of saliva that a patient can produce is highly variable between patients and is partially dependent on the taste, texture, and size of the tablets, it makes good sense to keep the size of the orally disintegrating tablets small.

The over-the-counter drug market is highly competitive and products without high consumer satisfaction would not survive. Products specifically labeled orally disintegrating tablets appear to require very fast disintegration times in the presence of minimal amount of water for them to gain market success. Therefore, to ensure

TABLE 5 In Vitro Desktop Disintegration Versus In Vivo Disintegration Times of Over-the-Counter Drug Products

Product name	Desktop disintegration in 30 seconds	Mean in-vivo disintegration time
Claritin RediTabs (loratadine 10 mg)	Pass	20 seconds
Alavert (loratadine 10 mg)	Pass	59 seconds
Children's Benadryl Fastmelt (Diphenhydramine Citrate 19 mg)	Fail	2 minutes 29 seconds
Triaminic Softchews (Acetaminophen 160 mg, Dextromethorphan HBr 5 mg)	Fail	1 minute 52 seconds

Source: From Ref. 37.

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good-marketability of the products, manufacturers should conduct taste testing and patient acceptability testing of the orally disintegrating tablets.

OTHER TABLET FORMULATIONS

Other non-conventional solid dosage forms that are placed in the mouth include buccal tablets that are placed in the buccal pouch of the mouth, sublingual tablets that are placed beneath the tongue, lozenges that are slowly dissolved or disintegrated in the mouth. For USP description of these dosages forms are shown in Table 6 (1,38) Additional information may be found in Chapter 12 in volume 2 of this series. Chewable tablets and effervescent tablets are also non-conventional solid dosage forms that share many characteristics with the orally disintegrating tablets and are further described below.

Chewable Tablets

The USP defines chewable tablets as, "… [tablets] that may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste." As mentioned in the introduction, chewable tablets differ from orally disintegrating tablets because they are intended to be chewed in the mouth prior to swallowing, rather than dissolve or disperse quickly in the saliva. However, they share many characteristics with orally disintegrating tablets. They are manufactured in

TABLE 6 Compendial Descriptions of Orally Disintegrating Tablets and Related Tablet Formulations

Tablet type	Compendial source USP or EP	Description
Orodispersible tablets	EP	Uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed; disintegrates within 3 minutes
Oral lyophilisates	EP	Solid preparations intended either to be placed in the mouth or to be dipersed (or dissolved) in water before administration; obtained by freeze drying; disintegrates within 3 minutes in 200 mL water
Buccal tablets	USP	Intended to be inserted in the buccal pouch; active ingredient is absorbed directly through the oral mucosa
Sublingual tablets	USP	Intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa
Soluble, effervescent tablets	USP	Intended to be dissolved or dispersed in water before administration; prepared by compression and contain, in addition to active ingredients, mixtures of acids and sodium bicarbonate, which release carbon dioxide when dissolved in water
Chewable tablets	USP	Formulated and manufactured so that they may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste

Source: From Ref. 1 and 38.

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similar ways as orally disintegrating tablets, mainly by direct compression of powders and pellets using various types of sugar and fillers. They are generally formulated as immediate release dosage forms and are intended for convenience, compliance, and patient acceptance. They can be taken without additional water, but need to be easily crushed in the mouth. Whereas, orally disintegrating tablets generally need to be small in size, chewable tablets may be larger and may be more accommodating for loading high amounts of active ingredients. Therefore, chewable dosage forms have become popular for delivering bulky ingredients like vitamins, minerals, antacids, and dietary supplements. Bitter tasting and bulky active ingredients like acetaminophen can also be formulated in chewable tablets. Like orally disintegrating tablets, taste-masking and ensuring good texture can be a challenge. Bitter tasting active ingredients are coated or pelletized with waxy polymers. Hot melt pelletization can be applied to bitter active ingredients to coat the active particles with melting binder such as polyethylene glycol. Different grades of polyethylene (e.g., PEG 2000, 3000, 6000, 8000, 10000, and 20000, from lowest to highest viscosity) yield pellets of different physical properties, such as granule size, intragranular porosity, and uniformity (39). Another method of taste masking bitter ingredients is to add taste masking agents to powder. Suzuki et al. (40) describes the use of hard fats and sweetening agents to formulate chewable acetaminophen tablets with suppressed bitterness, good taste and mouth feel. They found that Witocan®, hard fats used to make chocolates, made a satisfactory matrix for acetaminophen chewable tablets. Lecithin (Bencoat BMI-40) and saccharin were also added to the formulation.

Effervescent Tablets

According to the European Pharmacopeia, effervescent tablets are defined as "uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates, which react rapidly in the presence of water to release carbon dioxide." A commonly used acid in effervescent tablets is citric acid because of its citrus taste. Other less commonly used alternatives are malic, tartaric, adipic, and fumaric acids. Sodium bicarbonate is the most commonly used base, but potassium bicarbonate, sodium carbonate, and potassium carbonate are also used. As discussed earlier, some orally disintegrating tablets may have effervescent characteristics to aid in disintegration. However, unlike the orally disintegrating tablets, those labeled as effervescent tablets are generally intended to be placed in the water for dispersion prior to oral administration. Therefore, effervescent tablets can be much larger than orally disintegrating tablets or chewable tablets. They need special packaging like the orally disintegrating tablets in order to protect the tablets from humidity and handling. The manufacture of effervescent tablets is similar to that of conventional tablets, but special care must be exercised to protect the formulation from humidity. The formulations are also similar to compressed orally disintegrating tablets. A notable difference is that unlike other types of tablets effervescent tablets require the use of water-soluble lubricants in the formulation or prelubricated punches. Hydrophobic lubricants such as magnesium stearate are replaced with water-soluble lubricants like polyethylene glycol with molecular weight of 6000 or greater and sodium benzoate (27,41).

SUMMARY

Orally disintegrating tablets afford many opportunities yet challenges to the pharmaceutical industries. They provide therapeutic benefits to patients who cannot take or do

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not prefer conventional tablets. Existing technologies such as the compressed tablet method, freeze-dried method, and cotton-candy process provide various options for manufacturing orally disintegrating tablets. However, the real challenges in manufacturing the orally disintegrating tablets are feasibility and marketability. Freeze-dried method and wet compression are not desirable for water-labile active ingredients. Highly bitter active ingredients would pose a greater challenge, and many require pre-coating of the active ingredients. Active ingredients that need higher drug loading may be easier to make into compressed tablets than lyophilized tablets, but formulators need to be careful not to make the tablets too big. Otherwise they would be more appropriately called chewable tablets. Also, bioavailability studies may need to be conducted to determine if the pharmacokinetic parameters of individual drugs are different for the orally disintegrating tablets compared to the conventional tablets. Tools such as artificial neural network can help the formulator develop orally disintegrating tablets with desirable strength and release characteristics. The development of orally disintegrating tablets as a delivery system has presented challenges that spawned interesting new technologies. Ongoing research and development can be expected to improve on orally disintegrating tablets technology and broaden its applicability to drug therapy.

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