Material properties for making fast dissolving tablets by a compression method

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Received 7th January 2008, Accepted 16th April 2008
First published as an Advance Article on the web 6th June 2008
DOI: 10.1039/b800209f

Fast dissolving tablets (FDTs) are prepared by several different methods including crystalline transition, phase transition, sublimation, spray drying, and direct compression. Of these approaches, a conventional tablet compression method is used most widely because of its low cost and ease of manufacturing. Research on FDTs prepared by the compression method has focused on decreasing the dissolution (or disintegration) time of the tablets in the mouth, while maintaining sufficiently high mechanical strength to withstand handling during manufacturing, packaging, and transportation. The key to developing a successful FDT formulation by the compression method is to select the right excipients and the right processing techniques. In general, FDTs are made of highly hydrophilic materials and possess highly porous structures for fast water absorption into the tablet matrix. The excipients that are currently used as well as those that are expected to be used for the future development of improved FDTs are described.

Introduction

During the past decade, the FDT (fast dissolving tablet) technology, which makes tablets dissolve or disintegrate in the mouth without additional water intake, has drawn a great deal of attention.[1] The technology is also referred to as fast disintegrating tablet, fast dispersing tablet, rapid dissolve tablet, rapid melt tablet, quick disintegrating tablet, and orally disintegrating tablet. The FDT formulation is defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".[2] The tablets disintegrate into smaller granules or melt in the mouth from a hard solid structure to a gel like structure, allowing easy swallowing by the patients. The disintegration time for those tablets varies from a few seconds to more than a minute.[1] Table 1 lists examples of commercially available products on the market. It also lists the information on the drug, technology, marketing company and company that developed the technology.

FDT is a desirable dosage form for patients with problems swallowing tablets or other solid dosage forms. It has advantages over oral solutions including better stability, more accurate dosing, and lower volume and weight. The dosage form can be swallowed as a soft paste or liquid, and suffocation is avoided because there is no physical obstruction when swallowed. With better acceptance of this dosage form, improved mechanical properties, fast disintegration time, and pleasant taste, use of FDTs can be extended to a more general patient population with daily medication regimens. From the pharmaceutical industry's point of view, FDTs can provide a new dosage form for drugs nearing the end of their patent life. Manufacturers can therefore extend market exclusivity by reformulating an existing product

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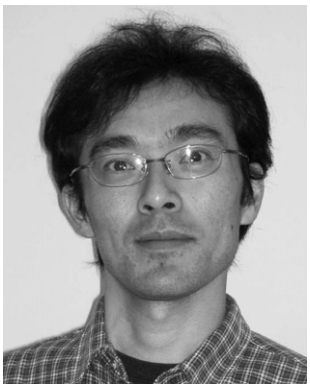

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Table 1 Examples of fast dissolving tablets currently available on the market

Drug product	Active ingredient	Indication	Marketing company	Technology	Technology Company
Alavert	Loratadine	Allergy	Wyeth	OraSolv/DuraSolv	Cima Lab
Aricept	Donepezil	Alzheimers	Eisai		
Benadryl Fast	Diphenhydramine pseudoephedrine	Allergy, cold, sinus	Johnson and Johnson	WOWTAB	Astellas Pharma (formerly Yamanouchi)
Claritin RediTabs	Loratadine	Allergy	Schering-Plough	Zydis	Cardinal Health
Prevacid SoluTab	Lansoprazole	Duodenal ulcer	TAP		
Remeron SolTab	Mirtazapine	Depression	Organon	Durasolv	Cima Lab
Maxalt-MLD	Rizatriptan benzoate	Migrane	Merck	Zydis	Cardinal Health
Zofran ODT	Ondansetron	Nausea	GlaxoSmithKline	Zydis	Cardinal Health
Zomig ZMT	Zolmitriptan	Migrane	AstraZeneca	OraSolv/DuraSolv	Cima Lab
Zyprexa Zydis	Olanzapine	Schizophrenia	Eli Lilly	Zydis	Cardinal Health

as an FDT.[3] Since the tablets disintegrate in the mouth, drugs can be absorbed in the buccal, pharyngeal, and gastric regions.[4] Thus, rapid drug therapy intervention and increased bioavailability of drugs might be possible.[4] Because pre-gastric drug absorption avoids first pass metabolism, the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.[3]

Administration of FDTs is different from conventional tablets, and the FDTs should have several unique properties to accommodate the rapid disintegration time.[5] They should dissolve or disintegrate in the mouth without water or with a very small amount of water as the disintegration fluid is the patient's saliva. The disintegrated tablet should become a soft paste or liquid suspension, which provides good mouth feel and enables smooth swallowing. "Fast dissolution" or "fast disintegration" typically requires dissolution or disintegration of a tablet within one minute.[5]

Taste masking is one of the most important areas in the preparation of the FDTs.[6] Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste is critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste masking techniques should be used.[6] An ideal taste masking technology should not impart grittiness and should produce good mouth feel. The amount of taste masking materials used in the dosage forms should be minimized to avoid excessive tablet size. The taste masking technology should also be compatible with other components and properties of the formulation.

In an ideal situation, a drug's properties will not significantly affect tablet properties. However, many drug properties can affect tablet performance. For example, the solubility, crystal morphology, particle size and bulk density of a drug can affect tablet characteristics, such as strength and disintegration.[7] The FDT technology should therefore be versatile enough to accommodate a wide range of drug physicochemical properties.[5] Because the FDT formulation is designed to have a quick dissolution/disintegration time, tablet porosity is usually maximized to promote water absorption by the tablets. A strategy to increase tablet hardness without sacrificing tablet porosity or requiring special packaging to handle fragile tablets should be provided. Moreover, FDTs should have low sensitivity to humidity. This problem can be especially challenging, because many highly water-soluble excipients are used in formulations to enhance fast dissolving/disintegrating properties as well as to create good mouth feel. Some of those highly soluble excipients are susceptible to moisture uptake and will often deliquesce at high humidity. A good package design or other strategy can be employed to protect the tablets from various environmental conditions including moisture.[1]

Preparation of FDTs by the compression method

The critical properties of FDTs are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. One of the more common strategies to achieve rapid disintegration is to maintain a highly porous tablet structure, which will ensure fast water absorption into the matrix. To this end, tablet excipients should have high "wetability" to improve water penetration into a tablet's matrix. The porosity, however, is inversely related to compression pressure, which is in turn related to the strength of a tablet. Thus, it is important to find the optimum porosity that allows both fast water absorption and high mechanical strength. Moreover, low compression pressure causes FDTs to become too fragile for packaging in conventional blisters or bottles. A formulation and/or processing strategy is necessary to increase tablet mechanical strength without compromising porosity or necessitating special packaging.

Many methods of preparing FDTs have been described to date,[1] including lyophilization,[4,8] molding,[9] and the compression of wet powders to construct highly porous structures.[10] These methods, while effective, are time consuming and technically difficult, often requiring special processing equipment. As a result, these methods are not easily adapted by pharmaceutical companies. Additionally, although tablets produced by these methods disintegrate instantly, they are usually very weak and friable. The mechanical strength of the tablets may not be enough to withstand packaging, transportation, and patient handling. As an example of wet compression, wet granules of α-lactose monohydrate were compressed and formed into wet tablets. The tablets were then dried at 60 °C and kept in a desiccator for 12 h at room temperature.[10,11] The resulting tablets showed a disintegration time of less than 30 s and a hardness of 0.5 MPa. However, evaporation took place before compression, and there were also other issues related to compression, such as stickiness and adhesiveness due to the high moisture content of the granules.[12]

Tablets obtained by the conventional compression method are less friable, but disintegrate more slowly.[6] The compression

method, with or without wet granulation, is a convenient and cost-effective way to prepare tablets with sufficient structural integrity. Many attempts have been made to decrease the disintegration time of tablets exhibiting sufficient mechanical strength. Even though there have been many patents covering the development of FDTs, only a small number of publications describing this dosage form are available.[13–15]

Using conventional tablet compression for preparing FDTs is attractive because of the low manufacturing cost and ease of technology transfer. However, tablet presses were originally designed to make conventional tablets with high mechanical strength. When making conventional tablets, maintaining high tablet porosity is not a primary concern, and high compression force is applied to achieve high tablet strength. Many strategies have been investigated to adapt the traditional tablet press to FDT manufacture, and achieve both high porosity and adequate tablet strength.

Basic requirements of FDT excipients

Since FDTs are designed to disintegrate or dissolve in the oral cavity, the dosage form should have a decent taste with a smooth paste or solution after disintegration so that patients do not have an unfavorable sensation. If excipients have good water solubility, they will facilitate disintegration and dissolution. Pharmaceutical grade saccharides (or sugars) such as mannitol, sucrose, lactose, glucose, and xylitol have been used frequently in making FDTs. The molecular structures of typical sugars are shown in Fig. 1. Mannitol is one of the most common excipients for this dosage form because it is water-soluble and

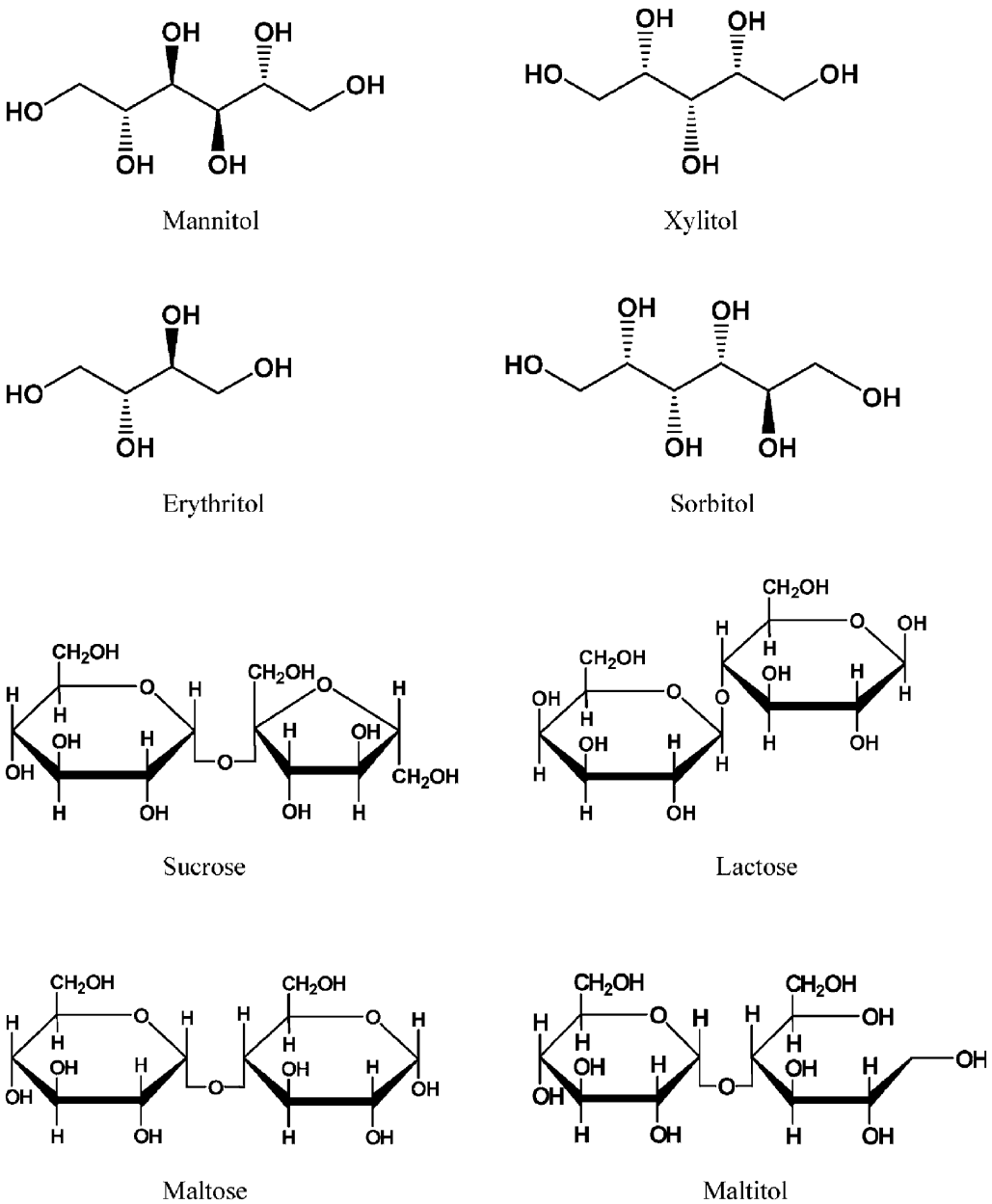

Fig. 1 Molecular structures of typical pharmaceutical sugars.

non-hygroscopic. It also produces a unique cooling sensation in the mouth and has a pleasant taste when chewed or dissolved.[16] Sugars can be used as diluents, binders, and/or taste-improving agents hence they are not categorized with respect to a single, specific function. Moreover, it is common practice to use a sugar for multiple purposes. For example, sucrose can act as a dry binder in the amorphous state by undergoing a phase transition, and also as a liquid binder during wet granulation.

The particle size of the excipients in a FDT must be considered. The smaller the particle size, the better the patients' compliance as larger particles make for a "gritty" feel in the mouth. Smaller particles result in a smooth tablet surface, which will also improve cosmetic properties. However, smaller size may impart poor material properties including poor flowability, high segregation, moisture sensitivity, and/or low porosity in a tablet. It is therefore important for the pharmaceutical scientist to balance the properties of the materials to achieve optimal patient compliance, efficacy, stability, and processability.

Saccharides (sugars) with different compression characteristics

There are a lot of pharmaceutical excipients that have been used in the development of FDTs that are currently on the market. Few pharmaceutical excipients, however, achieve both fast disintegration and high mechanical strength, and pharmaceutical scientists have struggled to balance the two opposing properties. Pharmaceutical excipients can be categorized so as to facilitate formulation design. For example, pharmaceutical saccharides (sugars) have been divided into two groups based on their physicochemical properties.[17,18] One group consists of low compressibility saccharides that exhibit rapid disintegration in the mouth when made into tablets. These saccharides include mannitol, lactose, glucose, sucrose, xylitol, and erythritol. The other group consists of highly compressible saccharides that yield high mechanical strength. The sugars in this category are maltose, sorbitol, maltitol, and trehalose (Table 2). Combinations of sugars from each group can be optimized to develop successful FDTs.

When coating and granulating a mixture containing a low compressibility saccharide and a high compressibility saccharide, compressibility of the former can be improved so that adequate mechanical strength is obtained while maintaining rapid disintegration. For example, when mannitol was granulated with maltose solution as a binder in a fluidized-bed, mannitol's low compressibility was improved. After compression, an adequate hardness of 5.9 kp, and a low friability of 0.65 % were observed while maintaining a fast disintegration time of 20 s.[17] This formulation approach produced a viable FDT with adequate mechanical strength and quick disintegration in the mouth.

One suggested factor affecting a saccharide's compressibility was related to surface free energy as measured by the Owens–Wendt plot.[17] The high compressibility saccharides had the surface free energy of a very high-polar component relative to the low compressibility sugars. Moreover, IR measurements showed many hydroxyl groups on the surface of the high compressibility particles. It is assumed that the surface free energy of the highly polar components is due to the hydroxyl groups on the particle surface and that this hydrophilic substituent affects the cohesive properties of each particle to improve compressibility. The surface free energy of the polar components of the saccharides affects their compressibility.[17] Another mechanism for increasing hardness is suggested to be a crystalline transition, which will be discussed more in the following section. After granulation, amorphous maltose exists on the surface of the mannitol particles. During the conditioning process, the amorphous maltose adsorbs moisture resulting in crystallization of the maltose. The resulting particles stick to each other more strongly, which results in increased tablet mechanical strength.[17]

Pharmaceutical sugars are widely used in making tablets. They are safe, easy to handle, and have a sweet taste. However, their compressibility or dissolution properties are not generally sufficient to make FDTs and the development of novel sugars (*i.e.*, sugar derivatives), which have both high compressibility and dissolution, is desired.

Crystalline transition method

The crystalline transition method (CTM) makes use of the phase transition of pharmaceutical excipients, especially sugars, from the amorphous to crystalline state to improve tablet mechanical strength while maintaining porosity. Amorphous forms of sugars have higher compressibility than crystalline forms,[19,20] so they can contribute to high tablet porosity. However, amorphous sugars have a tendency to absorb more moisture than crystalline ones, which means that the tablets containing amorphous sugars are more sensitive to moisture. An amorphous state is metastable and will tend to convert to a thermodynamically stable crystalline state over time. The amorphous state can be easily prepared by freeze-drying or spray drying. For example, a FDT was

Table 2 Compression characteristics of various saccharides with their disintegration time and melting points (modified from Mizumoto *et al.*[17])

	Saccharides	Hardness/kp	Disintegration time (*in vivo*/s)	Melting point/°C
Low compressibilty	Mannitol	0	<10	166
	Lactose	0	<10	202 (anhydrous) 214 (monohydrate)
	Erythritol	0	<10	122
	Xylitol	0	<10	93–95
	Glucose	0.2	<10	146 (α-D-) 150 (β-D-)
	Sucrose	0.5	<10	186
High compressibility	Sorbitol	2.2	>30	95
	Maltitol	2.5	>30	150
	Trehalose	3.4	>30	97
	Maltose	6.8	>30	102 (monohydrate)

prepared by compressing a mixture of mannitol and amorphous sucrose.[21] Mannitol and sucrose were used as a diluent and a binder, respectively. A blend of the two was compressed at varying compaction pressure and exposed to various conditions of temperature and humidity to induce phase transition.[21] The storage temperature and humidity affected the rate of crystalline transition and it was shown that the faster the crystalline transition, the faster the rate of increase in tablet tensile strength.[21–23] Higher storage temperatures or higher relative humidity led to a faster moisture uptake and also crystallization of the amorphous material resulting in a faster increase in the tablet mechanical strength.[21–23]

The mechanism of the CTM can be understood by using the moisture sorption model of amorphous sucrose.[24] Amorphous sucrose is hygroscopic and can absorb ambient moisture, leading to the formation of hydrated amorphous material. The absorbed water can act as a plasticizer and also influence free volume due to breakage of hydrogen bonds between the molecules in the solid. This can lower the glass transition temperature (T_g) to, or below, the operation temperature changing it from a glassy to a rubbery state.[25] The hydrated amorphous material with increased physical reactivity may not hold a relatively large amount of moisture. Therefore, the loss of moisture might induce crystallization of the amorphous sucrose with the release of the absorbed water. The hydrated amorphous sucrose in an FDT can be converted into the crystalline form and the crystalline sucrose forms new internal contact points in the tablet (Fig. 2).[21,22]

When FDTs are prepared by CTM, a level of 10–20 % amorphous sucrose in the tablet is suggested.[21,23] The tensile strength increases with an increasing percentage of amorphous sucrose due to its good compactability. However, the higher amorphous content causes a longer disintegration time in the mouth. Furthermore, it affected the structure of the tablets: the tablets with higher initial porosity shrank, whereas the tablets with lower porosity expanded due to the recrystallization of the sucrose.[23] The tensile strength of the tablet remarkably increased during storage, although the porosity of the tablet seemed hardly changed.

Conditioning of tablets at a certain temperature and humidity was also investigated, and involved different kinds of pharmaceutical polymers, such as polyvinylpyrrolidone (PVP), or other excipients.[26–29] For example, highly water-soluble polymers absorb moisture and form new contact points as the amorphous sugars described above do, although crystal transition seems a rare occurrence in the case of polymers.[26] Similar to the CTM, the mechanical strength of the tablets can be increased significantly with humidity conditioning. This increase might be due to the formation of liquid bridges in the presence of moisture, and then formation of solid bridges after drying.[29,30] As shown in Fig. 3, as water molecules from the atmosphere are adsorbed onto the surface of the particles (A), the water molecules form a liquid film with the vapor pressure over the adsorbed moisture layer equal to P_2 (B). The adsorbed moisture layer will dissolve the particles and the dissolution in the adsorbed moisture will lead to a decrease in the vapor pressure P_2 (C). The decrease in P_2 is effectively offset by the increase in the temperature of the film and the particles caused by the heat released on condensation of the water vapor. The moisture sorption happens spontaneously and the thickness of the condensate film grows as long as $P_1 > P_2$. The solid continues to dissolve until saturating the film, maintaining the vapor pressure over the adsorbed moisture layer (P_2). After drying, a solid bridge occurs and increases the bonding between the particles (D).[30]

Phase transition method (PTM)

Saccharides and sugar alcohols can be categorized not only by compressibility but also by melting point. Based on the melting

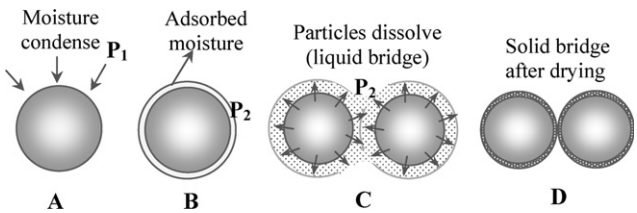

Fig. 3 Schematic view of moisture sorption by water-soluble particles explaining the increase in mechanical strength in FDTs before and after moisture conditioning (modified from ref. 30).

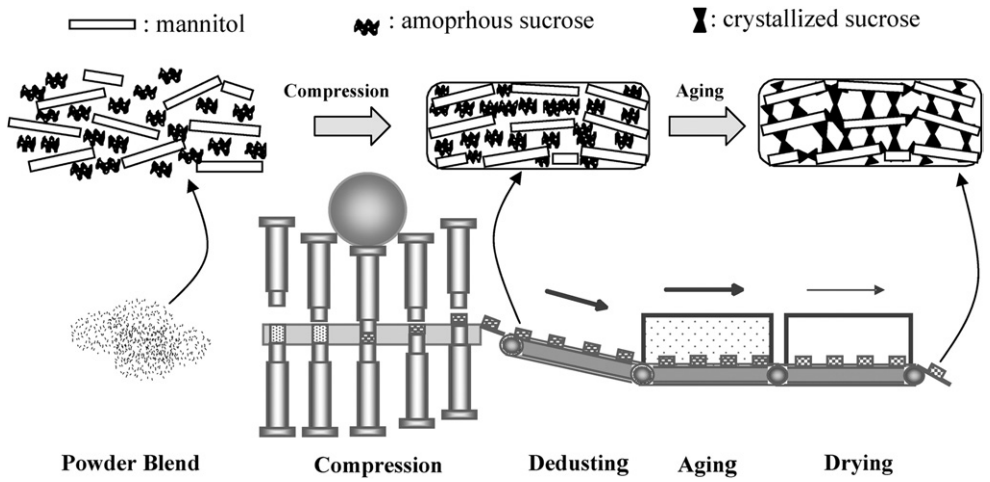

Fig. 2 Schematic illustration of the manufacturing process of FDTs prepared by the crystalline transition method using mannitol and amorphous sucrose (modified from ref. 21 and 55).

points (Table 2), they were divided into two groups and investigated using conventional granulation and compression apparatus.[31] Erythritol is the high melting (122 °C) and xylitol the low melting (93∼95 °C) sugar alcohol. Erythritol and xylitol were used as a diluent and a binder, respectively for fluid bed granulation. After compression, the resulting tablets were placed in a drying oven and heated at a temperature close to the melting point of xylitol (approximately 93 °C). Conditions were maintained for a certain period of time and the tablets then allowed to cool to room temperature (Fig. 4). The hardness of the processed tablets was found to increase with increasing xylitol content.

Tablet hardness and disintegration time were primarily affected by the heating process, but also by the content of saccharides or sugar alcohols.[31] Heating was found to increase pore size within the tablets. It was suggested that the diffusion of xylitol in the tablets caused increased tablet hardness with increasing pore size. Xylitol melted, diffused, and solidified again in the heated tablets resulting in a greater bonding surface area between the powder particles and increased hardness. Tablets containing about 5% xylitol showed hardness of 4 kp and an oral disintegration time of < 30 s.[32] It was also suggested that increasing tablet hardness by heating and storage was not dependent on the crystal state of the sugar alcohols, but related to the formation of inter-particle bonds or the increased bonding surface area induced by the melting of xylitol particles and their subsequent solidification upon cooling.[31] Other pharmaceutical materials, such as polyethylene glycol, and wax, have been also applied to the PTM.[33,34]

Sublimation methods

The low porosity of compressed tablets may reduce water penetration into the tablet matrix resulting in slow disintegration or dissolution because these processes only occur at the surface. However, when volatile solids are compressed into tablets using a conventional method, they can be removed by sublimation to produce highly porous structures (Fig. 5). Typical materials used for this purpose include camphor, menthol, thymol, urea, ammonium carbonate, and ammonium bicarbonate.[35–37] For example, camphor can be incorporated into FDTs and then sublimated in a vacuum oven resulting in highly porous tablets with a porosity of up to 40%.[38]

The sublimation method is useful for making highly porous tablets, but vacuum treatment is a time consuming and costly process. Use of other materials, which could be sublimed under more general conditions (*e.g.*, room temperature and/or normal pressure), would be of greater utility.

Disintegrants

A disintegrant helps the tablet to break up into smaller pieces upon contact with aqueous solution. Fast disintegration of a tablet matrix in the oral cavity facilitates swallowing and increases the surface area of the tablet particles, which enhances the rate of absorption of the active ingredient to achieve the desired therapeutic effect.[39] Every marketed tablet has a certain level of disintegrant and it is important to investigate which and how much disintegrant is necessary for a given tablet formulation.

Disintegration starts when a small amount of water or saliva contacts the dosage form (wetting) and penetrates the tablet matrix by capillary action. Therefore, the material properties of pharmaceutical excipients and also the matrix structure including pore size and distribution need to be considered for successful formulation development. Since most disintegrants swell to some extent, swelling pressure is generally considered the main factor for tablet disintegration. Disintegrants or super-disintegrants with efficient disintegrating properties at relatively low levels can be used in the formulation of FDTs. They are generally added at a level of 1–10% (w/w%).[40,41] One of the most desirable properties of disintegrants is rapid swelling without an accompanying viscosity increase (no gel formation), because high viscosity on the surface of the tablet will hinder water penetration into the tablet matrix to slow disintegration.

There are a lot of disintegrants and super-disintegrants on the market and most of them can be considered for use in FDTs. Typical examples include crospovidone (crosslinked PVP), croscarmellose (crosslinked cellulose), sodium starch glycolate

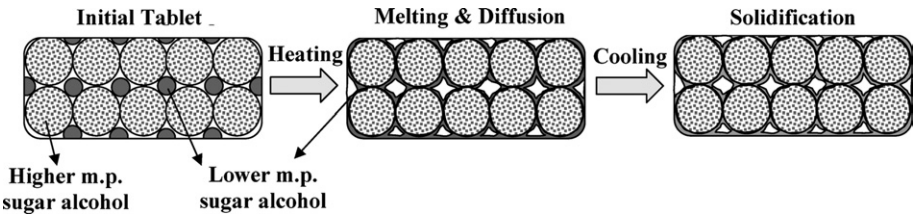

Fig. 4 Schematic illustration of a fast disintegration tablet prepared by the phase transition method using a higher melting (erythritol) and a lower melting (xylitol) sugar alcohol (modified from ref. 31).

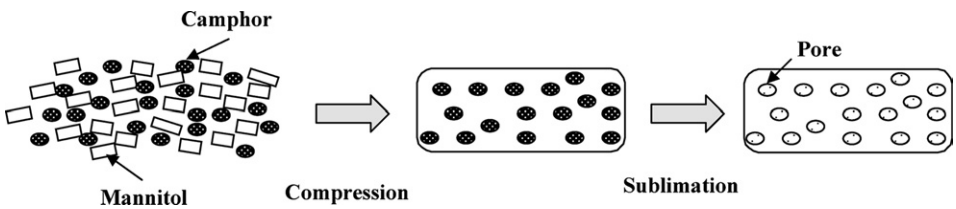

Fig. 5 Schematic view of the preparation of a porous tablet using sublimation of camphor (modified from ref. 38).

(crosslinked starch), and low-substituted hydroxypropylcellulose.[40,41] Crospovidone is a synthetic and water insoluble crosslinked homopolymer with the chemical structure of *N*-vinyl-2-pyrrolidone (Fig. 6). A unique one-step polymerization process known as "popcorn" polymerization is used to synthesize crospovidone polymers. Crosslinking chemically "entangles" the polymer chains and is a major determinant of the product's properties. This process results in a porous structure with densely crosslinked polymers and a morphology that rapidly wicks liquids into the particle to enhance swelling and disintegration. Crospovidone polymers are non-ionic so their disintegration properties are independent of pH changes in the gastrointestinal tract. Moreover, they do not form gels. Each grade has a different particle size distribution and density, and variable swelling behavior that plays an important role in its disintegrant properties.[41] Different grades of Kollidon and Polyplasdone are crospovidone products of BASF and ISP, respectively (Table 3). Ac-Di-Sol® (Croscarmellose sodium) is an internally crosslinked sodium carboxyemthylcellulose. Primojel® is a sodium starch glycolate produced by crosslinking and carboxymethylation of potato starch. Both exhibit good water uptake with high capillary action and rapid swelling. The high swelling capacity together with high water penetration leads to fast tablet disintegration. Disintegrants are usually water insoluble materials that swell on contact with moisture, therefore the addition of excess disintegrant can lead to grittiness after tablet disintegration. The appropriate disintegrant and disintegrant quantity should be carefully investigated for a given FDT formulation.

The particle size distribution of Kollidon CL and Polyplasdone XL is similar (Table 3). However, bulk and tapped densities of the both are significantly different due to the smoother surface of Kollidon CL or the porous structure of Polyplasdone XL.[41] Kollidons CL-F and CL-SF have lower bulk densities than that of Polyplasdone XL because of their smaller particle sizes. Promojel has the highest bulk and tapped densities and Ac-Di-Sol is in between Kollidon CL and Primojel.[41]

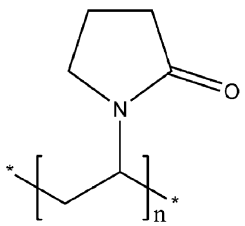

Fig. 6 Chemical structure of *N*-vinyl-2-pyrrolidone.

Selection of the right disintegrant depends on the formulation application and preparation procedure. For example, when FDTs are prepared using lactose as a diluent, *in vivo* disintegration time is dependent on the type of disintegrant.[42] The tested disintegrants in the study were Ac-Di-Sol, L-HPC (low-substituted hydroxylpropylcellulose), ECG-505 (carmellose calcium), Polyplasdone XL-10 (crospovidone), and carmellose (NS-300). NS-300 imparted the fastest disintegration of the five evaluated, and the disintegration time was not affected by tablet hardness at the levels considered. Moreover, tablets containing glycine showed faster disintegration than those without glycine, mainly due to the fine wetting nature of this amino acid. This result is reported for some amino acids which act as disintegration accelerators.[42] In another example of famotidine FDTs, crosscarmellose sodium was superior to crospovidone, Indion 414, and sodium starch glycolate.[43] Crospovidone can work as an efficient disintegrant with fast swelling properties.[41] When mannitol and crospovidone were formulated by a direct compression method, the effects of the amount of mannitol and crospovidone as well as the compression force on the characteristics of the tablet were investigated.[44] An optimum tablet formulation, containing 34% mannitol and 13% crospovidone, was recommended and provided a short wetting time of 17 s and a sufficient crushing strength of 40 N.[44]

Some amino acids, such as L-lysine HCl, L-alanine, glycine, and L-tyrosine, can be formulated as disintegration accelerators in FDTs.[45] The tablet wetting time of a FDT is fastest with L-lysine HCl, followed by L-alanine, glycine, and L-tyrosine. The difference is due to the physical properties of the amino acids, since each amino acid has different polar and dispersion surface free energy. The polar free energy is the dominant surface free energy in L-lysine HCl. However, dispersion free energy is the dominant parameter for L-tyrosine. More polar amino acids have a stronger affinity to water so wetting is faster. A linear trend is observed between tablet wetting time and the polar component of the amino acids. When the polar component of the amino acid is large or the dispersion component has a small value, faster wetting of the tablet is observed.[45]

FDTs were prepared by direct compression using microcrystalline cellulose (MCC) and low-substituted hydroxypropyl cellulose (L-HPC) as disintegrants.[46,47] It was found that the ratios of the two disintegrants MCC : L-HPC in the range of 8 : 2 to 9 : 1 showed the shortest disintegration times. On the other hand, poly(acrylic acid) superporous hydrogel (SPH) microparticles were reported to be a super-disintegrant having a unique porous structure and they were added as a wicking agent to decrease disintegration time.[48]

Table 3 Overview of typical disintegrants with their characteristics and swelling pressures[41]

Disintegrants	Particle size/μm	Swelling pressure/kPa	Bulk density/g ml^{-1}	Tapped density/g ml^{-1}	Company
Kollidon CL	110–130	171	0.33	0.43	BASF
Kollidon CL-F	20–40	29	0.21	0.28	BASF
Kollidon CL-SF	10–30	22	0.14	0.21	BASF
Kollidon CL-M	3–10	68	0.20	0.27	BASF
Polyplasdone XL	100–130	110	0.28	0.36	ISP
Polyplasdone XL-10	30–50	94	0.33	0.48	ISP
Ac-Di-Sol	49	271	0.46	0.72	FMC
Primojel	41	158	0.76	0.92	DMV

There are many commercially available disintegrants. Disintegrants are water insoluble polymers that remain as granules in the mouth. Thus, their mouth feel is worse than that of water-soluble excipients, such as sugars. A new class of disintegrants, which can swell and then subsequently dissolve, will lead to significant advances in not only FDT formulations, but also all pharmaceutical tablet formulations.

Effervescent materials

Effervescence is a reaction between a soluble acid and an alkali metal carbonate to form carbon dioxide (CO_2). It is spontaneous when water is added to the materials, and a small amount of water is enough to start the reaction. The process is a chain reaction with water being one of the reaction products, as per the following:

$$R\text{–}COOH + NaHCO_3 + H_2O \rightarrow R\text{–}COONa + H_2CO_3 + H_2O \rightarrow$$

$$R\text{–}COONa + H_2O + CO_2 + H_2O \rightarrow R\text{–}COONa + CO_2 + 2H_2O$$

Effervescence reactions also take place with moisture from the atmosphere during storage. Therefore, special packaging to protect products incorporating effervescent components from moisture is utilized. Another constraint to this approach is that only drugs that are chemically stable under both acid and alkali conditions could be used.

When incorporated into FDTs, tablets will disintegrate quickly due to the effervescent carbon dioxide. Therefore, the effervescent couples can be regarded as a disintegrant in the FDT formulation. The carbon dioxide generated in the tablet can also improve the overall taste. OraSolv® technology is a good example of a product with effervescent excipients.[49,50]

Acidic components used in FDTs include food acids (citric acid, tartaric acid, and malic acid), acid anhydrides such as succinic anhydride, and acid salts (NaH_2PO_4, $Na_2H_2P_2O_7$). Among the various acids, citric acid is the most frequently used. Carbonate sources include bicarbonate and carbonate forms. Examples are sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. However, bicarbonates are more reactive.

Other ingredients

A smooth tablet surface and good surface texture are desirable for patients. To improve tablet surface texture, a new type of FDT formulation was investigated using excipients with a spherical shape and fine pharmaceutical excipients. Microcrystalline cellulose (Avicel PH-M series) is a spherical excipient with a very small particle size (7–32 μm), as compared with conventional microcrystalline cellulose (Avicel PH-102®, 100 μm). When tablets were prepared by direct compression using spherical microcrystalline cellulose (Avicel PH-M-06, size 7 μm), and low-substituted hydroxypropylcellulose (L-HPC) in a ratio of 9 : 1, they had sufficient mechanical strength with rapid disintegration (within 15 s) and good patient compliance. L-HPC was used as a disintegrant at a low compression force. Moreover, flowability can be improved through the use of spherically shaped particles.[51]

Some waxy materials have a low melting point and moderate hydrophilic lipophilic balance (HLB) value. Superpolystate® (PEG-6-stearate) is an example with a melting point of 33–37 °C and an HLB value of 9. It acts as a binder, increasing the mechanical properties of tablets while facilitating disintegration.[12] Due to a low melting point, it melts in the mouth leaving no residue or grittiness on the tongue. However, careful attention should be given to the amount used as a high concentrations of the waxy binder caused compression problems including sticking to the machine punches.[12] Moreover, when hardness and disintegration time were compared between wet and melt granulations, the methods were found to produce different results. Wet granulation was ultimately recommended as the manufacturing method, and croscarmellose sodium was added to facilitate tablet disintegration. Sodium sulfate hydrate ($Na_2SO_4 \cdot 10H_2O$) has a unique property in that the salt dissolves into its own lattice water at 37 °C, while being stable at lower temperatures.[52] Tablets produced from this material, however, were not preferred due to their salty taste.

Processes to improve material properties

Direct compression using a co-ground mixture of mannitol and crospovidone (9 : 1 ratio) was shown to improve tablet hardness, which could not be obtained by a simple addition of their individual ground mixtures.[53] The co-ground mixture was prepared with a vibration rod mill. It was suggested that crospovidone acted as a grinding assistant for mannitol in the co-grinding process, thus enhancing the hardness of tablets by increasing the contact area among powder particles. It decreased the particle size and increased the specific area of the co-ground mixture.[53]

Suspensions of mannitol (85%) and microcrystalline cellulose (10%) with various types of disintegrants (Ac-Di-Sol, sodium starch glycolate, or Kollidon CL, 5%) were spray dried to obtain a solid mass of excipients.[54] The dried excipients were mixed with a drug to prepare FDTs. Spray dried excipients showed a low angle of repose, thus having free flowing properties for direct compression. Scanning electron microscopy observation also confirmed that spray drying gave spherical particles with porous structures, which provided good flow properties. Wetting of Kollidon CL tablets was faster than for the other two. Moreover, when comparing tablets prepared with spray dried particles to those made by direct compression, the tablets made by the latter method took longer to disintegrate.

Almost all of these approaches require a balance between tablet hardness and dissolution. Only a limited number of materials can be used for pharmaceutical applications. For this reason, many scientists have tried various combinations of existing materials as well as new manufacturing processes. Since it is always preferred to use a single material than a mixture, development of novel materials ideal for FDT formulations is necessary more than ever.

New materials for future FDTs

As described above, FDTs have two opposing properties that must be balanced for optimum product performance: sufficient hardness for handling and rapid dissolution in the mouth with a limited amount of saliva. Conventional tablets have high

mechanical strength and stand up to rough handling because they are manufactured with high compression force and the resulting tablets have extremely low porosity. The rapid penetration of saliva into a tablet is essential for a FDT. FDTs should therefore be as porous as possible, but the tablet strength tends to decrease with increasing porosity. In general, highly elastic materials (*e.g.*, polymers) are advantageous for making hard tablets. However, they require more time to dissolve and form a viscous layer at the tablet surface, which prevents further saliva from penetrating into the tablet. Many attempts have been made to resolve this conflict, and several FDTs have been successfully launched as commercial products. However, even the commercial products have issues of low hardness or excessive disintegrating time, or both. The development of new materials, which are highly elastic and highly soluble with low viscosity, is desired. The requirement of low viscosity dictates that the materials be non-polymeric or be of relatively low molecular weight.

Many attempts have been made to mask undesirable material properties by manipulating the manufacturing process. However, complicated processes, such as crystalline transition, phase transition, and spray drying, could raise production costs hence simpler manufacturing processes are preferred. The ideal materials have high plasticity, high water-solubility, and mix readily with the active ingredient(s). Continued efforts are necessary to develop ideal materials for FDTs.

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