Journal of Pharmaceutical Sciences xxx (2016) 1–11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

Review of Disintegrants and the Disintegration Phenomena

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ARTICLE INFO

Article history:
Received 19 October 2015
Revised 17 December 2015
Accepted 17 December 2015

Keywords:
disintegrants
swelling
strain recovery
formulation
imaging methods
solubility
water sorption
compaction
dissolution

ABSTRACT

Disintegrant is one of the most important components in a typical tablet dosage form. It is responsible for ensuring the break-up of the tablet matrix upon ingestion. Disintegrants act by different mechanisms, and a number of factors may affect their performance. It is important for formulators to understand how disintegrants function so as to be able to judiciously use disintegrants to develop optimized formulations. If the formulator is required to implement the quality by design paradigm while developing a tablet formulation, it would be important to determine the impact of component ranges and process variations on tablet performance and of particular importance, tablet disintegration. Thus, a better understanding of the mechanisms of disintegrants and the tablet disintegration processes can be critical to product design success. This review aims to provide an overview of tablet disintegrants and the disintegration processes with particular focus on the factors affecting the functionalities of disintegrants. An updated compendium of different techniques employed to evaluate disintegrant action and measure disintegration time is also provided. The objective of this review is to assemble the knowledge about disintegrants and the measurement of tablet disintegratability so that the information provided could be of help to tablet formulation development.

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Introduction

The orally administered compacted tablet is the most common and preferred solid unit dosage form for delivering medicaments to patients.[1] Advantages of tablets include the ability for accurate dosing, long shelf life, and cost-effective production.[2,3] Most tablets manufactured are for oral administration although some tablets may be prepared for other uses. Oral tablets may be designed as immediate or modified release dosage forms by the use of appropriate ingredients and manufacturing techniques. Tablet formulations generally consist of active pharmaceutical ingredients (APIs) together with a mix of other ingredients, collectively referred to as additives or excipients. Upon ingestion, the tablet should be capable of releasing the API in the manner it is designed for. Some tablets may also contain 2 or more APIs. Excipients play a vital role in the design of the tablet dosage form by determining its functionality and performance. Excipients are generally regarded as pharmaceutically "inactive" ingredients added with APIs during formulation but they often have important specific functions and should possess some important requisite features for their functionality. However, substances selected to be pharmaceutical excipients must be physiologically inert or inactive and when incorporated into the dosage form remain physically and chemically stable throughout the required shelf life of the dosage form. Excipients must not introduce microbiological contamination, be commercially available, and can be manufactured or processed according to the required pharmaceutical standards.[4]

Excipient types used in tablet formulations include disintegrants, fillers, binders, glidants, lubricants, antioxidants, ultraviolet absorbers, dissolution modifiers, absorbents, flavoring agents, colorants, wetting agents, and preservatives.[1,3] Not all the excipient types may be included in a formulation except when expressly needed. A good tablet formulation should not be the result of a random combination of excipients with API but by a systematic approach with rational excipient selection to provide the optimally balanced combination in the formulation design space aimed at providing the desired product performance, cost consideration, manufacturability, and patient acceptability.[3] A newer class of excipients called "co-processed" excipients is now increasingly being introduced. Co-processed excipients are made by combining 2 or more excipients in an optimized ratio or method to provide superior synergistic properties.[5] In formulation development, they

The authors declare no conflict of interests.

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http://dx.doi.org/10.1016/j.xphs.2015.12.019
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can reduce the number of ingredients needed and can improve production consistency.[1]

Despite being considered as physiologically inactive, excipients may have significant impact on the biopharmaceutical performance of the dosage form. Among the tablet excipients, disintegrants are often considered as the most important as they ensure the break-up of the dosage form into smaller fragments upon ingestion, to allow the onset of drug dissolution and eventual absorption.[6] Disintegrants are often associated with promoting moisture penetration into the tablet matrix to initiate the disintegration process (Fig. 1). The bioactive fraction in a tablet only becomes bioavailable after disintegration.[7] The disintegration process can mechanistically be subdivided into 2 stages—breakdown into coarse aggregates and subsequent deaggregation into fine primary particles. Some non-disintegrating tablets may also be produced for highly soluble APIs with excipients that would rapidly dissolve upon ingestion.[1,2]

A comprehensive understanding of the functionality of disintegrants and their mechanisms of action would be very important in the selection of disintegrants. Thus, the aim of this review is to provide the required overview of the disintegrant types and their mechanisms of action with an updated compendium of relevant studies undertaken.

Disintegrants

Disintegrants bring about tablet matrix break-up in an aqueous medium and are commonly classified further in literature as disintegrants and superdisintegrants.[6] "Normal" disintegrants include starch- and cellulose-based excipients such as corn starch, partially pregelatinized starch, microcrystalline cellulose, and low-substituted hydroxypropyl cellulose. Some clays (e.g., Veegum HV), gums (e.g., agar, guar, tragacanth, alginate), resins (e.g., polacrilin potassium), and finely divided solids (e.g., colloidal silicon dioxide, magnesium aluminum silicate) have also been employed as disintegrants. Chemical modification of starch, cellulose, and povidone brought about the development of more efficient disintegrants, capable of good disintegration action at much lower concentrations in the tablet formulations and are referred to as superdisintegrants. Superdisintegrants include sodium starch glycolate, croscarmellose sodium, and crospovidone.[8,9] In general, disintegrants are hydrophilic but insoluble in water or gastrointestinal juices.[6] Nonetheless, effervescent additives could also be considered as disintegrants even though they are soluble, thus an exception to the insolubility general rule. Effervescents are formed by combining a soluble organic acid with inorganic carbonate or bicarbonate and the volumetric air expansion helps in disintegration of the effervescent tablets when wetted. Another material class, inorganic carbonates, may also be considered as secondary disintegrants as they can facilitate tablet disintegration by reacting with the acidic juices in the stomach to generate carbon dioxide.

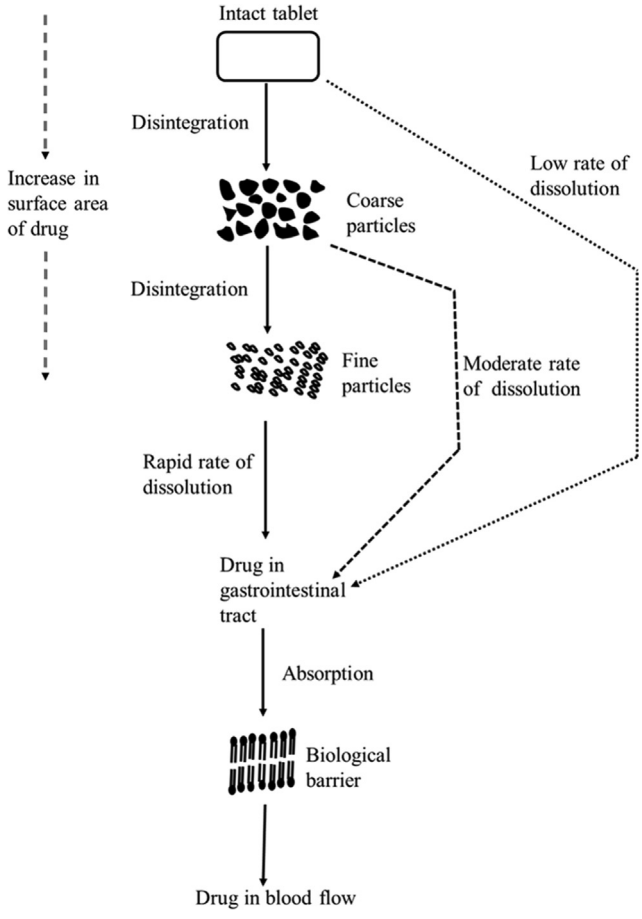

Figure 1. Fate of a disintegrating tablet upon wetting. Adapted from Alderborn[2] and Kottke and Rudnic.[1]

Different theories have been proposed for mechanisms of disintegrant action but a complete understanding of how all disintegrants act may still be deficient.[8,10] Disintegrant actions proposed include swelling, wicking (capillary action), strain recovery, interruption of particle-particle bonds, and heat of interaction.[6] Attempts had been made to propose a universal disintegration mechanism but it was later realized that the different types of disintegrants may function differently. In many cases, it was realized that a synergistic combination of mechanisms had acted together.[9,11]

Mechanisms of Disintegrant Action

Swelling

The most accepted mechanism for tablet disintegration is by disintegrant swelling.[8,12] Swelling is associated with dimensional amplification where particles enlarge omni-directionally to push apart the adjoining components, thereby initiating the break-up of the tablet matrix (Fig. 2a).[13] Most popular disintegrants swell to some extent and swelling phenomena have been well reported.[1] The swelling ability of a disintegrant depends on several factors and some of the most commonly cited factors are chemical structure and degree of crosslinking.[6] Porosity of the compact is also a very important contributor to the performance of swelling disintegrants. A porous tablet matrix with large void spaces could muffle the swelling action of disintegrants and impede their efficiency in tablet disintegration. Conversely, low porosity compacts prepared by using very high compression forces could hinder liquid entry and prolong the disintegration time or result in failure to disintegrate. Thus, tablets should be prepared at the optimal porosity to provide adequate mechanical integrity without compromising disintegratability.

A correlation was found between the rate of disintegration force development and the disintegration time but not between the extent of disintegrant swelling and the maximum disintegration force. Thus, the rate of disintegration force development is important for rapid matrix disintegration.[14,15] The concentration of disintegrant in a formulation is also important. Clearly, not all swelling materials can be disintegrants. A swelling substance that becomes gelatinized after swelling will form a gel plug and not bring about tablet disintegration. Hence, strongly swelling gums such as agar, karaya, and tragacanth are not effective disintegrants.[1] Ferrero

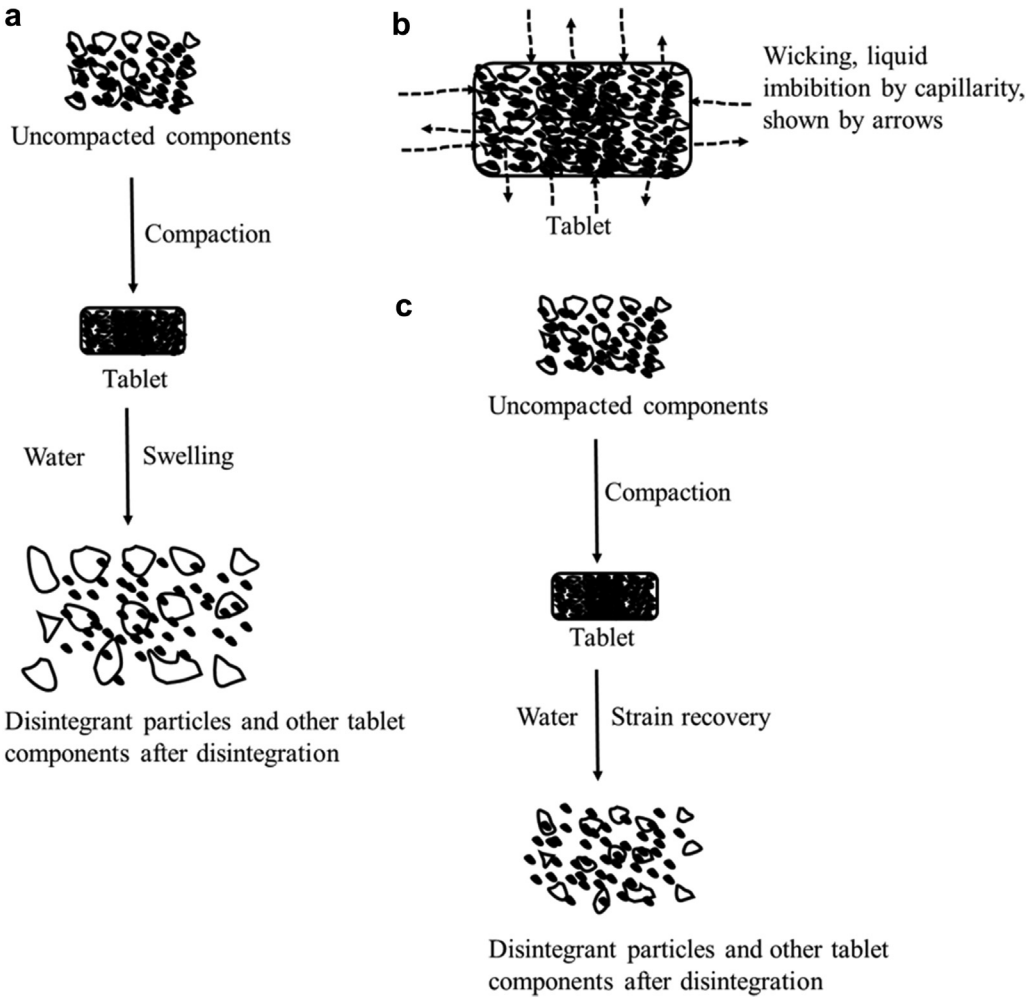

Figure 2. Schematic diagram of (a) swelling, (b) wicking, and (c) strain recovery mechanisms.

et al.[16] proposed that consolidation mechanism is important for controlling the compact microstructure that can define the swelling disintegrant responses. The swelling capacity of some disintegrants is pH dependent. Sedimentation volumes of cross-linked starch and cellulose were affected by acidic pH, whereas crospovidone and pregelatinized starch were unaffected.[17] In another study, Chen et al.[18] reported that the disintegration rate of tablets containing sodium starch glycolate or croscarmellose sodium decreased in acidic media but that of tablets containing crospovidone were unaffected.

Wicking

Wicking may be defined as a process of liquid entry by capillarity into the microstructured crevices within the compact to displace the air.[19,20] A schematic of the wicking mechanism is depicted in Figure 2b. Apart from disintegrants, other tablet components may also confer hydrophilicity to the matrix and can contribute to liquid penetration. In that sense, wicking cannot be considered as a primary disintegration mechanism. However, most researchers agree that water imbibition into the compact is a prerequisite to disintegrant activation.[6] If wicking is a critical attribute, then the micro-pore structure within the compact will be of prime importance. The penetration rate will depend on the balance between capillary and opposite viscous forces.[21] Capillary flow can be described by the Washburn's equation[14]:

$$L^2 = \left(\frac{\gamma\cos\theta}{2\eta}\right)rt$$

where L is liquid penetration length into the capillary, γ is the surface tension, θ is the solid-liquid contact angle, r is the pore size, t is the time, and η is the liquid viscosity. Tortuosity factor, k, is included in the above equation to account for liquid penetration into the powder bed and is expressed as below.

$$L^2 = \left(\frac{\gamma\cos\theta}{2\eta k^2}\right)$$

The value of k is unity for parallel capillaries whereas for a network comprising tortuous capillaries of different hydrodynamic diameters, the proposed value of k may be up to 2.5.[22] Thus, the resultant equation shows that larger pore sizes would accommodate more liquid uptake, which may translate to faster disintegration. Conversely, higher packing density decreases the pore sizes and the volume of liquid penetration. It can be hypothesized that the coarser particles should yield larger pores. In a study by Rudnic et al.,[23] disintegration efficiency was increased when coarser particle size disintegrants were used.

Khan and Rhodes[24] examined the water sorption properties of major tablet disintegrants and concluded that the high efficiency of some disintegrants is due to their high rates of water uptake. On the

other hand, Gissinger and Stamm[25] reported that the formation of porous capillary network alone cannot adequately explain the disintegration process and other factors (e.g., swelling force) are also important. Microcrystalline cellulose is often used in tablet formulations both as filler and disintegrant, and the mechanism of its disintegrant action is proposed to be a combination of wicking and disruption of particle-particle bonds.[6,26] Bele and Derle[27] concluded that the main mechanism of disintegrant action of polacrilin potassium is by wicking.

Strain Recovery

During tablet manufacturing, tablet constituents are subjected to a high compaction pressure, of the mega Pascal (MPa) range, within the constrained space available in the die between the punches. During compaction, particles deform and interparticulate bonds are forged. Strain recovery is the reversible viscoelastic process of deformation.[28] According to this theory, when compacted disintegrants come in contact with the aqueous media, mechanical activation of disintegrant polymer chains help to partially recover their original shapes. Disintegration medium could also plasticize the disintegrant polymers and assist polymer chains to adopt the most energetically favorable positions. The pressure generated during this kinetic process could result in tablet disintegration.[6] Under this condition, the shape recovery process will be unidirectional and in the opposite direction of exerted compaction force.[13] The relaxation and recovery of the stressed particles give rise to rapid movement and volume expansion, causing the breakage of bonds and, if extensive, break-up of the compact matrix. The schematic of strain recovery mechanism is depicted in Figure 2c. Hess[29] reported the recovery of croscarmellose sodium particle shape on exposure to moisture. Improvements in swelling efficiency of starch particles (after compression) were observed in some cases.[1] On the other hand, Lowenthal[30] concluded that regaining the original shape of starch grain after compression is not considered as the mechanism of disintegrant action for this disintegrant. Desai et al.[31] and Quodbach et al.[13] studied the strain recovery mechanism in greater detail and concluded that the superdisintegrant crospovidone works mainly by this mechanism. In comparison with swelling and wicking, this mechanism is less studied. Hence, it would be interesting to see how researchers will study this phenomenon further and under different conditions.

Interruption of Particle-Particle Bonds

Interruption of particle-particle bonds can be considered as one of the most important contributors to matrix break-up. Although a full understanding is still deficient, past studies have provided some information about this mechanism. Three different bonding mechanisms have been suggested to be involved when tablets are made: solid bridges, mechanical interlocking, and intermolecular forces active over various distances.[32] Among these 3 bonding types, intermolecular forces are considered to be the prevailing bonding type in compact formation.[32,33] One of the proposed tablet disintegration mechanisms is the interruption of these binding bonds when a tablet comes in contact with disintegration medium or gastrointestinal liquid.[6,34] It has been suggested that tablets containing microcrystalline cellulose disintegrate by the disruption of intermolecular bonds holding the cellulose fibers together by the imbibed water.[34] Different techniques have been explored to quantify the intermolecular bonds involved in tablet matrix interruption. Luangtana-anan et al.[35] found a correlation between the disintegration time and the intermolecular forces present in the tablets. In the study, contact angles of different materials with different media were determined to calculate the Hamaker constants. These constants represented intermolecular forces for that particular material and disintegration medium. Disintegration time increased correspondingly with the value of Hamaker constant. However, the disintegration time of magnesium carbonate tablets did not fit the hypothesis. It was postulated that another supportive disintegration mechanism may be present. Also, this technique could not differentiate the swelling component from disruption by breakage of intermolecular forces, if both are responsible for tablet disintegration. Ferrari et al.[33] investigated the interruption of particle-particle bonds in compacts by various disintegration media by correlating disintegration time with liquid uptake and disintegration force development. However, the study was limited to specific materials with known bonding characteristics. Additionally, the techniques described did not include the study of possible kinetic energy and thermal changes that occur during the interruption of particle-particle bonds and wetting of tablet constituents. Hence, it can be suggested that the interruption of particle-particle bonds is the result of the active mechanisms discussed above and therefore this phenomenon should be seen more as the overall resultant outcome of these active mechanisms.

Heat of Interaction

Exothermic (heat generation) or endothermic (heat absorption) interactions are manifested by materials on interaction with water. Exothermic properties are observed when disintegrants interact with the aqueous media.[34] The heat generated can cause localized stress associated with the expansion of air retained in the compact and this can theoretically aid compact disintegration. Luangtana-anan et al.[35] examined the enthalpy changes for different disintegrants. However, some researchers suggested that the amount of heat generated by wetting is rather small and may not be sufficiently significant to cause effective expansion of the entrapped air in the compact to bring about its break-up.[36] Lowenthal[34] also opined that if heat generation was an important mechanism of tablet disintegration, then break-up would have occurred during compaction or ejection as significant heat was produced during the compression cycle. Caramella et al.[37] observed that the increased temperature of the aqueous medium did not necessarily enhance the disintegration process in some tablet formulations. Moreover, endothermic properties are exhibited by some of the disintegrants.[36] Thus, it is necessary to study heat of interaction mechanism to ascertain the extent of its influence and if a thermodynamic model could be developed to explain its role in the tablet disintegration process. To date, current literature and research work have not substantially proven this mechanism of action.

Disintegrants for Pharmaceutical Tablets

Starch and Its Derivatives

Starch and its derivatives are multifunctional tablet formulation excipients and are recognized to be the earliest tablet disintegrant used.[4,6] Starch is a carbohydrate consisting mainly of soluble amylose and insoluble amylopectin (Fig. 3a). Amylose is a linear α1-4 linked polymer chain of glucose subunits. Amylopectin composed of larger, branched polymer chains of α-glucose units with α1-4 linkages and α1-6 linkages.[6,38,39] Amylose and amylopectin consist of semicrystalline and intercrystalline amorphous areas in alternating layers and these layers are known as granule growth rings.[40] The exact structure of starch is somewhat varied. The proportions of the 2 types of polysaccharides vary according to the botanical source of the starch, for example, amylose content of tapioca starch is reported to be 17%-21%, potato starch 22%-25%, and corn starch 22%-30%.[39] Swelling is the accepted mechanism of action for starch-based disintegrants. The degree of swelling of the individual grains of corn, potato, tapioca, and waxy corn starches was

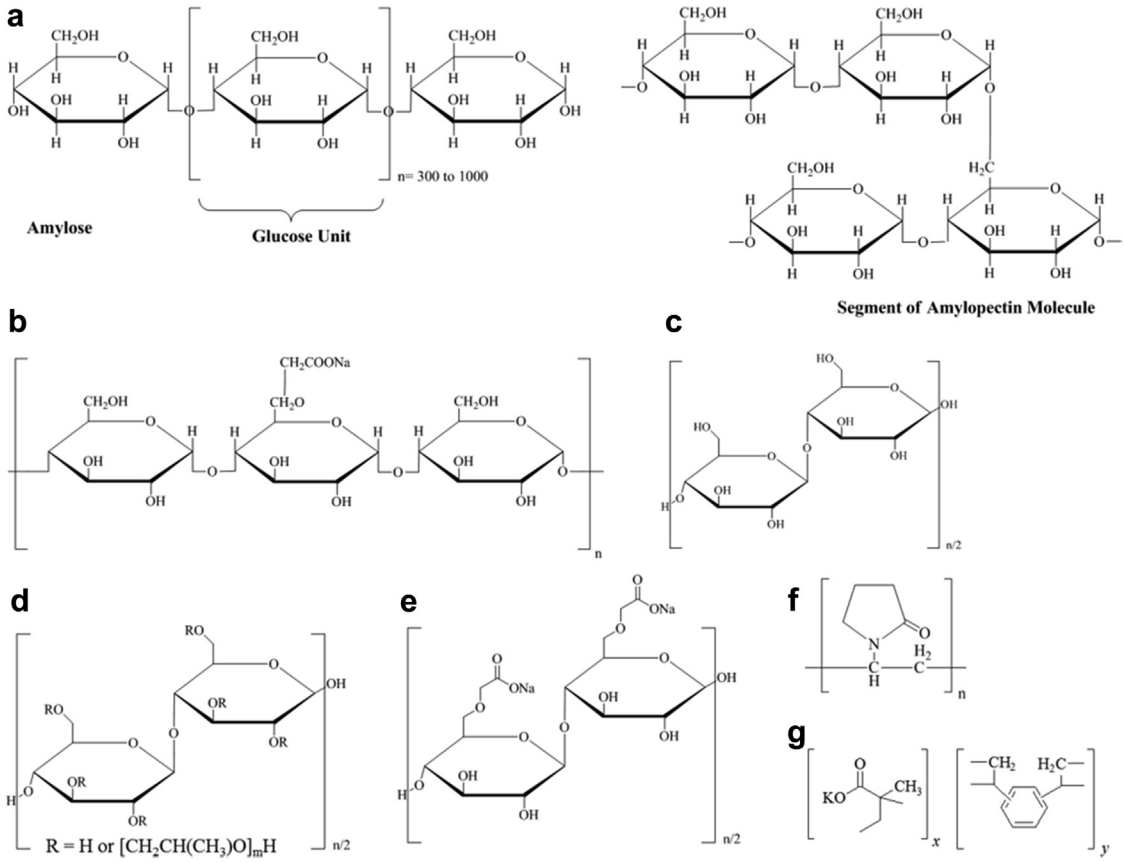

Figure 3. Structural formulas of (a) amylose and amylopectin, (b) sodium starch glycolate, (c) microcrystalline cellulose, (d) low-substituted hydroxypropyl cellulose, (e) croscarmellose sodium, (f) crospovidone, and (g) polacrilin potassium.

precisely measured by Hellman et al.[41] After storing these starches under different humidities, swelling for corn, potato, tapioca, and waxy corn starches at 100% relative humidity (RH) was 9.1%, 12.7%, 28.4%, and 22.7%, respectively. Considering the starch grain as a 3-dimensional molecular network, researchers postulated that hydration at the junction points of such network could expand the structure and the extent of hydration at these junctions would collectively determine the extent of swelling. The versatility of starch and its derivatives as excipients is that based on their derivatizations, they can be used as disintegrants, binders, diluents, glidants, and thickening agents in tablet formulations.[38]

Native starches do not necessarily have ideal properties for some of their reported functionalities. For example, a large amount of native starch (10%-15%) may be required for it to act as an efficient tablet disintegrant. Starch also does not possess good compressibility. Physical and chemical modifications have been attempted to improve the properties of native starches.[6] Heating the starch grains will rupture the grain structures by the gelatinization process. These processed starches are called pregelatinized starches. Based on the temperature and exposure time, starches will be pregelatinized to different degrees. Pregelatinization has significant impact on the physical attributes of the preprocessed starch as an excipient. Partial pregelatinization improves the flowability and compressibility of starch while still retaining some disintegrant property. Full pregelatinization makes the excipient soluble in cold water and it can be used as a binder but is no longer effective as a disintegrant.[6,42] Sodium starch glycolate is the sodium salt of cross-linked carboxymethylated starch (Fig. 3b), which shows improved moisture absorption, resulting in massive volumetric increase.[43,44] Sodium starch glycolate is classified as a superdisintegrant by this very strong swelling characteristics and being spherical in shape, it can improve flow.[14] Concentrations of sodium starch glycolate used in tablet formulations may range from 2% to 8%.[45]

Cellulose and Its Derivatives

Celluloses comprise β1-4-linked glucose subunits and are more crystalline than starches. Native celluloses consist of alternating regions of compact microcrystalline and less dense amorphous regions. Acid hydrolysis of cellulose degrades the polymeric chains by breaking down the amorphous regions but leaves the microcrystalline portions relatively intact, making the widely used tablet excipient, microcrystalline cellulose. The chemical structure of microcrystalline cellulose is shown in Figure 3c. After acid hydrolysis, the insoluble cellulose residue is filtered, washed, and dried, often spray dried after re-suspension to form dry, porous microcrystalline cellulose.[6,46] Microcrystalline cellulose is used as a disintegrant, diluent, or binder in tablet formulations and is capable of undergoing plastic deformation at relatively low yield pressure, which helps in the preparation of compacts at low compression forces.[47] The widely accepted mechanism for microcrystalline cellulose action in consolidation is hydrogen bonding created between adjacent particles when compacted. However, Al-khattawi et al.[47] demonstrated that the hydrogen bonding is not solely responsible for the densification of microcrystalline cellulose. This work had relied on atomic force microscopy and Fourier transformed infrared spectroscopy to study microcrystalline cellulose densification. A conglomerated hypothesis was proposed that considered mechanical interlocking, amorphous region, shape surface topography, and roughness as important parameters responsible

for microcrystalline cellulose densification. As a disintegrant, cylindrical-shaped microcrystalline cellulose particles act by providing the capillarity to draw in liquid into compacts for the separation of bonded particles.[26] However, the disintegration efficiency of microcrystalline cellulose is not high and a concentration up to 20% of microcrystalline cellulose may be necessary to promote effective tablet disintegration. Low-substituted hydroxypropyl cellulose is a modified hydrophilic, water insoluble cellulose (low substituted form of cellulose ether; Fig. 3d) and can be used as a tablet disintegrant in the range of 2%-10%.[6] Another modified cellulose excipient is croscarmellose sodium, which is a cross-linked carboxymethyl cellulose sodium (Fig. 3e).[6,14,48] Croscarmellose sodium particles are long and narrow (fibrous) with curves and twists. Swelling, wicking, and strain recovery mechanisms are proposed for this superdisintegrant.[6] It may be used in concentrations of 2%-5% in tablet formulations.[48]

Crospovidone

Crospovidone is a water insoluble synthetic cross-linked polyvinylpyrrolidone (Fig. 3f) manufactured by the proliferous polymerization of vinylpyrrolidone.[49,50] This polymer is also known as a "popcorn" polymer as it possesses a "popped" structure. There are 2 accepted methods to manufacture crospovidone. In one method, the crosslinking agent is formed *in situ* whereas it is added in the other method.[49] The coarser crospovidone grades disintegrate tablets faster.[9] The amounts of crospovidone used in tablet formulations varied in literature reports. Generally, crospovidone is used in the range of 2%-5% in tablets prepared by direct compression and wet granulation methods.[6,50] Researchers first proposed differing mechanisms of disintegrant action and there was no consensus. Wicking followed by secondary swelling was proposed by Kornblum and Stoopak.[51] Many researchers had suggested wicking.[52-58] Others proposed good swelling efficiency or high swelling pressure as the disintegration mechanism.[36,59,60] Later, strain recovery was also proposed and validated as the disintegration mechanism of crospovidone.[6,13,31]

Resin and Its Derivatives

Ion exchange resins have also been employed as tablet disintegrants. These insoluble cross-linked copolymers are formed by a main polymer matrix, mostly styrene cross-linked with divinylbenzene, with a functional ion-active portion. Detailed description about ion exchange resins can be found in the review by Guo et al.[61] The most common ion exchange resin used as a disintegrant is polacrilin potassium (Fig. 3g). It is manufactured by copolymerizing methacrylic acid with divinylbenzene, followed by neutralizing the product with potassium hydroxide.[62] Polacrilin potassium is highly hydrophilic with good swelling property, which is important for its disintegrant action.[6] Wicking and strain recovery are also reported as possible mechanisms for this cation exchange resin.[27,63] Commonly, it is used at concentrations of 2%-10% in tablet formulations, although 2% had been reported to be sufficient.[62] A systematic characterization of different brands of polacrilin potassium was carried out by Bele and Derle.[64] When incorporated in a tablet formulation as a disintegrant, it is reported to improve plasma drug concentration of diclofenac potassium when compared with crospovidone.[65] It was proposed that *in vitro* permeation and *in vivo* bioavailability of anionic drugs such as diclofenac potassium could be improved by a cation exchange resin through the Donnan membrane phenomenon where the multifunctional excipient improves bioavailability apart from acting as a disintegrant. By also acting as a cation exchange resin, the drug has to be gradually exchanged for cations and allows for a reduced dissolution rate. This behavior has been investigated in the development of controlled release or taste-masked dosage forms. Polacrilin potassium had been reported to interact with drugs and possibly enhance particular degradation pathways such as ester hydrolysis.[6] Some anion exchange resins were also investigated for their capacity to be disintegrants. These included cross-linked copolymers of divinylbenzene and styrene with quaternary methyl amine functional groups. Anion exchange resins performed well as disintegrant for basic drugs so as to avoid ionic binding between resin and drug.[66]

Factors Affecting the Performance of Disintegrants

Factors affecting the performance of a disintegrant include its particle size, methods of disintegrant incorporation especially for wet granulation, applied compression force, moisture content, and reworking.[67] Changes in the particle size of a disintegrant can affect its performance as a tablet disintegrant. Disintegration time decreased with increase in particle size of starch when the formulation was compressed without a lubricant.[68] However, with a lubricant, disintegration time decreased with decrease in particle size of the disintegrant as lubricant coverage decreased with increase in surface area, resulting in faster disintegration with finer disintegrant particles. Rudnic et al.[23] concluded that the increase in crospovidone particle size improved disintegration and dissolution of tablets. The method of disintegrant addition was also reported to be important, especially for tablets prepared from wet granulated granules.[1,69] It was reported that the disintegrants incorporated in both extra- and intragranular fractions achieved the best overall disintegration performance.[4] In a separate study by Khattab et al.,[70] both disintegration and dissolution were fastest for tablets prepared with extra- and intragranular disintegrants in comparison with formulations with disintegrants added either in the extra- or intragranular phases. However, Gordon et al.[71] showed that the disintegrant promoted dissolution of the poorly soluble drug better when incorporated intragranularly. He et al.[72] reported that disintegrant incorporated intragranularly decreased the dispersibility of a poorly wettable drug because of the formation of dense granules while extragranular disintegrants provided the best dispersibility. However, van Kamp et al.[73] reported that the mode of incorporation of superdisintegrants had no significant effect on tablet characteristics, including dissolution. These differences could be related to the granulation methods, levels, and types of disintegrants used or the physicochemical properties of tablet constituents. Effect of reworking on the dissolution of tablets containing superdisintegrants was studied by Gould and Tan.[74] The superdisintegrants, sodium starch glycolate, croscarmellose sodium, and crospovidone, were used extragranularly and recompression improved dissolution. For tablets with intragranular disintegrants, recompression decreased dissolution of tablets containing croscarmellose sodium and crospovidone but increased the dissolution rate for sodium starch glycolate. Effect of sorbed moisture on the functionality of disintegrant had also been studied. Bele and Derle[67] noted that moisture increased plasticity of polacrilin potassium and optimal moisture content can improve the compressibility of disintegrants. Thus, brands of polacrilin potassium that were more hygroscopic were more sensitive to sorbed moisture affecting their disintegrant performance. Differential scanning calorimetry and dynamic vapor sorption analysis were performed for different grades of crospovidone with different particle sizes to evaluate their differences in water uptake, water distribution characteristics, and water polymer interactions.[75,76] Glass transition temperature was reduced with increase in moisture content indicating that water plasticized the disintegrant. Even though there were differences in particle size, abilities for water uptake and water distribution were not significantly different. Dynamic vapor sorption measurements also confirmed that the water interaction profiles were similar for all crospovidone grades.

Stability of disintegrants under different storage conditions was studied by Marshall et al.[77] It was found that the swelling force performance was highly affected for disintegrant, alginic acid, when stored above 30°C and 75% RH over a year and sodium starch glycolate was somewhat affected. Quodbach and Kleinebudde[78] recently accomplished a systematic study to understand the impact of storage conditions (different RH conditions) and relative tablet density on the functionality of tablet disintegrants. Storage conditions highly affected water uptake and force development for sodium starch glycolate. However, disintegrant function was not much affected for crospovidone, croscarmellose sodium, and polacrilin potassium. The impact of tabletting pressure and the resultant relative tablet density was most severe for crospovidone. High tabletting pressure and relative density helped to promote disintegration of tablets containing crospovidone. The effect of storage on the dissolution of tablets containing disintegrants was also investigated.[79] Wet granulated tablets containing croscarmellose sodium was affected to a larger extent than crospovidone and sodium starch glycolate. Apart from the disintegrant, tablet matrix also plays a very important role in determining the disintegration phenomena. In general, disintegrants performed better when formulated with insoluble fillers (e.g., dicalcium phosphate) than soluble fillers (e.g., lactose and mannitol). Differences in the disintegration rate due to soluble or insoluble components were studied and a disintegration model was proposed.[80-83] Based on this model, 2 mechanisms were put forth—an interface-controlled mechanism and a diffusion-controlled mechanism.

$$\frac{F}{F_\infty} = 1 - \exp(-kt^n)$$

where F is the disintegration force measured as a function of time, F_∞ is the maximum developed force, k is an expansion rate constant and n signifies the characteristic of the disintegration mechanism. According to this model, the 2 disintegration mechanisms reported may be characterized. By the interface-controlled mechanism, particles detach from the solvent or tablet interface, whereas for the diffusion-controlled mechanism, particles diffuse away from that interface. For interface-controlled mechanism, n was found to be greater than 0.9, whereas a relatively small n value denoted the diffusion-controlled mechanism. Tablets with a soluble matrix follow the diffusion-controlled mechanism where matrix solubilizes first and water acts as a plasticizer, reducing the generation of disintegration force. When an insoluble matrix is present, disintegrants are more effective at breaking up the tablet interfacially or by an interface-controlled mechanism and thus disintegration is more effective.[14] Clearly, the view of Marshall et al.[77] that an information library should be generated for each disintegrant with all the effects of formulation, stability, and process parameters collated is valid. This compiled information could be useful when selecting the appropriate disintegrant with the aim of optimizing formulation performance.

Evaluation of Functionalities of Disintegrants

Many approaches have been undertaken to quantify swelling, wettability, and capillary action of free particles and compacts with the aim of defining disintegrant function. Enslin determined water uptake by non-compacted porous powder bed in the glass vessel. A calibrated pipette was used to determine the volumetric quantity adsorbed accurately. Based on these measurements, the Enslin number was calculated and it represents the amount (g) of liquid taken up by 1 g of powder.[21] Swelling of powder beds or tablets and water uptake were sometimes considered interchangeably. However, water uptake and penetration may be high without any significant swelling. Penetration of water into powder bed (penetration depth) and swelling were measured separately by Nogami et al.[84] Water penetration depth was measured using tapped disintegrant powder in a graduated tube immersed into water. For measuring water uptake and swelling of disintegrants, a test method and apparatus called water uptake apparatus was developed.[84] Figure 4 shows the schematic diagram of the water uptake apparatus. Briefly, the disintegrant powder was packed and placed on a moistened glass filter plate over a water reservoir connected to a graduated pipette where imbibed water over time could be quantified.

Various contraptions of the apparatus were used for water uptake study.[25,77,85] van Kamp et al.[21] improved the measurement of water uptake of tablet or powder bed. A re-designed apparatus included a glass tube (with glass filter at the lower side) to place tablet or powder, graduated burette (connected with glass tube) filled with water from a supply, and reservoir on a microbalance linked to a computer record weight loss during water uptake (Fig. 5).

Caramella et al.[86] determined the swelling or disintegrating force developed inside the tablet along with water uptake and evaluated swelling efficiency. A parameter, “equivalent force,” was proposed to denote the capability of the disintegrant to transform water uptake into a disintegrating force. Based on Caramella's work, Quodbach and Kleinebudde[63] designed a disintegration force tester that measured water uptake and force development simultaneously.

Swelling capacity of a disintegrant (bulk swelling) was determined by dispersing a fixed weighed amount of disintegrant in a graduated cylinder with water. The sedimented volume of the disintegrant was obtained after a day and was used to calculate the swelling capacity or ratio of the swollen volume to the dry bulk volume of the disintegrant.[87,88] Water infiltration rates in different disintegrants at tapped densities were also measured by capillary rise experiments in which rates were determined by the speeds of ascending color solutions entering the sample columns from bottom to top.[89] Contact angle measurement was the other method used to determine the wetting properties of excipients.[90] Water vapor sorption and differential scanning calorimetry studies were also performed to study the moisture uptake and thermal behavior of disintegrants.[91] Coulter counter technique was used to measure the individual particle swelling.[86]

Image analysis has been used to visually quantify disintegrant action and for eliciting disintegrant mechanisms such as swelling, wicking, and deformation. The imaging technique offers accuracy, versatility, rapidity, and easy availability. Image analysis has been used to understand different motion-related phenomena.[92] The deformation of starch grains had been studied using the light

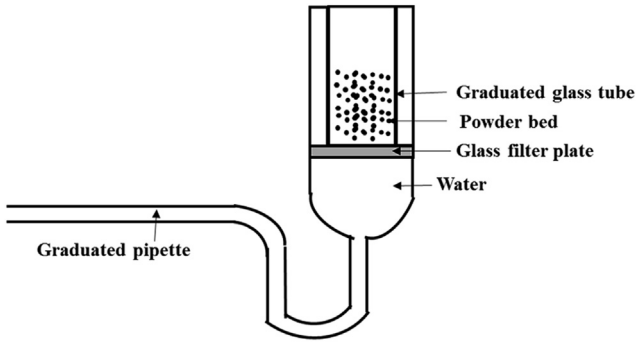

Figure 4. Nogami apparatus for the quantification of water uptake and swelling of powder bed. Adapted from Nogami et al.[84]

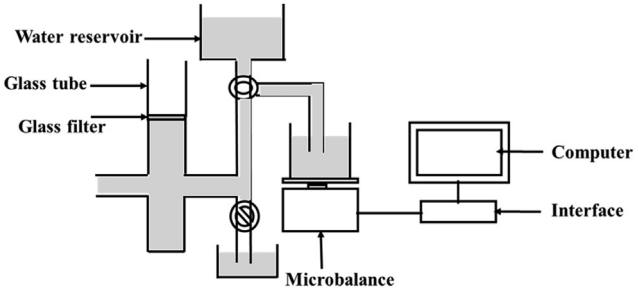

Figure 5. van Kamp apparatus for the quantification of water uptake.[21]

microscope and scanning electron microscope.[30] The swelling of tablet disintegrants was determined using a video camera mounted on a microscope.[93] A technique based on image analysis was used to study water uptake in tablets.[94] The fabricated wetting apparatus and the image analysis algorithm enabled the visualization with simultaneous thickness and diameter quantifications. The results showed that the various types of disintegrants and their concentrations changed the manner of tablet swelling, in particular along the axial direction. The researchers concluded that the image analysis–based technique is a rapid and accurate method to study tablet swelling. Imaging techniques were further used to examine the swelling of disintegrant particles[9,85,95] and to visualize tablet disintegration.[96,97] The dynamic tablet disintegration process of directly compressed tablets containing superdisintegrant, sodium starch glycolate, croscarmellose sodium, or crospovidone was evaluated using a digital video camera.[98] The disintegration process was calibrated by the size of disintegrated particles in addition to the time of occurrence. Thus, video imaging helped to clarify the differences in the dissolution time of aspirin tablets formulated with different superdisintegrants. In a more recent study, high-speed video imaging was used to visualize and elucidate the mechanisms of action of disintegrants when incorporated into compacts and as free disintegrant particles.[31] Analysis of the acquired images enabled the quantification of changes in the compact area and particle mobility. The technique successfully monitored swelling, wicking, and strain recovery phenomena for various disintegrants and provided a detailed explanation of the functionality of disintegrants. Real-time magnetic resonance imaging has also been applied to evaluate the disintegration phenomena of tablets.[13] An innovative method to evaluate efficiency of disintegrants by measuring the sizes of disintegrated particles was also proposed.[99] Particle sizes at the start and end of the disintegration process differ from each other and follow a first-order exponential decay model. Parameters of the model can depict the functionality of different disintegrants.

Pertaining to tablet formulation, disintegrants were evaluated for compressibility properties, amounts used, and disintegrant combinations in formulations. An expert system was proposed for determining the suitability of disintegrants for direct compression formulation.[100] Physical characteristics of 42 brands of disintegrants were provided to the system, based on which the index of good compression was determined. All disintegrant brands from the microcrystalline cellulose family were found to be highly suited for direct compression (index of good compression close to or greater than 5). For other groups of disintegrants, index of good compression values differed for different brands. Statistical design of experiments (DoE), an important paradigm of quality by design, has been proven to be an effective tool to study the effect of excipients and process variables on the performance of the formulation. For example, a disintegrant and its optimized level were chosen by a DoE study to achieve high dispersibility of poorly wettable micronized drug.[72] Three-factor face-centered experimental design was useful for determining the better disintegrant choice in a particular wet granulated tablet formulation. The central composite design has also been applied to identify the best disintegrant and optimal compression force in directly compressed tablets employing lactose or mannitol as diluent.[54] Among the disintegrants used, disintegration time was longest for microcrystalline cellulose and shortest for crospovidone with both diluents. Crospovidone, pregelatinized starch, and low-substituted hydroxypropyl cellulose were more sensitive to compression force than amount used, whereas the performance of microcrystalline cellulose and sodium starch glycolate were substantially influenced by their concentration. The DoE approach was applied to find the binder-disintegrant combination for optimized roxithromycin dispersible tablet formulations.[101] After accomplishing the central composite design study along with response surface methodology, researchers concluded that vinylpyrrolidone or vinyl acetate copolymer (binder) and crospovidone (disintegrant) made the best combination. As disintegrants function by different mechanisms, there is the possibility of synergism between disintegrants. The synergistic effects of disintegrant mixtures were studied by a systematic DoE.[102] Drugs of different water solubilities and different disintegrants were used to prepare tablets by direct compression. At particular compression pressures and disintegrant amounts, synergism was found for sodium starch glycolate-crospovidone and croscarmellose sodium-crospovidone combinations for aspirin and ibuprofen tablets, respectively. Differences in the dominating disintegrant mechanisms such as strong swelling of sodium starch glycolate and croscarmellose sodium and strain recovery of crospovidone could be responsible for the observed synergism. A similar synergistic property of the sodium starch glycolate-microcrystalline cellulose combination was observed when sodium starch glycolate and microcrystalline cellulose were used together as co-disintegrants in polymer film formulation, prepared for immediate release purpose.[103] Polymer films containing this disintegrant combination provided the fastest drug release in comparison with films prepared with either of the disintegrants at the same total disintegrant amount.

Discussion and Future Directions

The common mechanisms by which disintegrants work are schematically presented in Figure 6. These mechanisms are not independent and are sometimes complementary to one another. Imbibition of water into the compact is the first stage of the disintegration process and thus capillary action is of primary importance as it will affect all the other disintegrant mechanisms. Fast capillary action will enable water to be rapidly and readily available to disintegrants present in the compacts. Disintegrants working by swelling or strain recovery mechanisms will almost instantaneously generate high disintegration pressure following a fast capillary action. In addition, any change in the accessibility of water will impact the gas generation process for effervescent systems. A reported study has also provided support for the relationship between swelling and enthalpy change of the system.[104] Similarly, changes in the wetting property will influence the thermodynamic characteristics of a compact. There is an established relationship between water uptake and disintegrating force.[86] However, it is difficult to characterize whether the pressure generated during the disintegration process is due to swelling or strain recovery of the disintegrant. Most probably, moisture provides the plasticizing action on the disintegrant polymer chain and initiates the strain recovery process. The same moisture can also be absorbed by the disintegrant polymer and causes swelling. Break-up of the tablet matrix and disruption of particle-particle

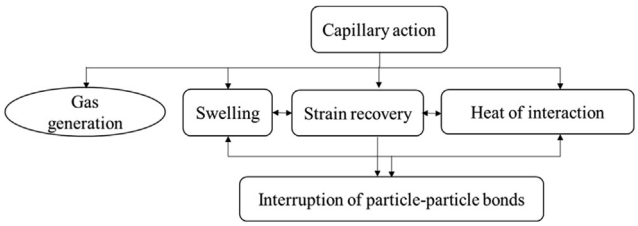

Figure 6. Schematic representation depicting the relationship between the mechanisms of disintegrant action.

bonds would be the consequence of swelling, strain recovery, or heat exchanges. Suffice to mention, any of the mechanisms would require disruption of the compact matrix and bonds present. Pressure generated by swelling or strain recovery will not be able to effectively break up the compact if particle-particle bonds are very strong. Similarly, high porosity may help with the capillary function but disintegrants may not be able to generate sufficient pressure in a porous compact mass to degrade the matrix effectively. As mentioned earlier, disruption of particle-particle bonds is therefore considered an important passive mechanism.

All the disintegrants discussed in the review have already a rather long history of use as formulation additives in tablet dosage forms. Even though the disintegrants generally could function well, it still would be beneficial to explore the possibility of finding or designing novel disintegrants that are more efficient in functionality and processability, that is, good flowability and compressibility. For example, nanocrystalline cellulose was recently developed and it proved to have promising potential as a successful disintegrant.[105] Another sparsely explored area in the disintegrant field is the design and formulation of co-processed disintegrants. It is clear by now that disintegrants work by different mechanisms and creating a co-processed excipient (by combining disintegrants or disintegrants with other additives) will be helpful as it may impart superior performances. In a study, sodium starch glycolate-crospovidone co-processed disintegrant was prepared by granulation.[53] This intimate mixture of disintegrants improved flow and compression properties. Tablets produced had fast disintegration and dissolution, as seen for cefixime trihydrate and ibuprofen tablets. More research effort could be directed at alternative novel disintegrants, in particular, targeted at newer dosage forms such as orally disintegrating tablets, minitablets, and melt or molded tablets. Optimized combinations of existing disintegrants to provide synergistic action of disintegrants and mask their unwanted properties would be the easiest way forward.

Continuous manufacturing is considered to be the future style of pharmaceutical manufacturing.[106] One of the requirements for continuous manufacturing of coated tablets would be to coat the tablets immediately after their compaction. For this goal to be achieved, the latent recovery of the tablets should not be high. Even though disintegrants are used in small amounts in tablet formulations, they may have significant effect on the latent recovery of tablets as they are polymeric in nature. In this scenario, it is important to understand how different disintegrants affect the latent recovery. A systematic study employing different commonly used disintegrants in the tablet formulation (while keeping the drug and other excipients the same) was conducted to investigate the effect of different disintegrants on latent recovery. Low-substituted hydroxypropyl cellulose showed the least latent recovery and recovery values for other disintegrants were also studied.[107] Excipients commonly used as disintegrants have been well studied for their performance as disintegrants when employed in tablet dosage forms. However, these excipients are sometimes used in applications other than in tablet dosage forms, for example, microcrystalline cellulose as spheronization aid.[108] However, it is not fully clear how these excipients function when used in other applications and the exact advantages they render when employed. For example, performance of disintegrants in biocompatible polymer films has not been thoroughly evaluated. It has been found that disintegrants improve the dissolution of APIs when incorporated in polymeric oral strip films.[109,110] Recently, superdisintegrants were also employed to improve the viscosity in biocompatible polymer films containing drug-encapsulated nanoparticles.[111] In the study, it was identified that the superdisintegrants improved drug content uniformity and film performance more effectively in comparison with the traditional viscosity enhancers without compromising dissolution. As regulatory authorities have already accepted currently employed disintegrants, it would be valuable to study their additional applications in different dosage forms in addition to disintegration-dissolution improvement.

Concluding Remarks

A comprehensive knowledge of materials used in a formulation together with process parameters influencing the product design is crucial to the formulation scientist when designing or enhancing a good quality tablet product. When reviewing the research work on disintegrants, it was apparent that disintegrants play a central role in ensuring the intended biopharmaceutical performance of the dosage form. This review has provided an updated overview of different disintegrant types, their mechanisms of action, and physicochemical characteristics influencing disintegration phenomena. Disintegrants are associated with different mechanisms of action, namely swelling, wicking, strain recovery, interruption of particle-particle bonds, and heat of interaction. Their performance is also dependent on the particular formulation. Some factors such as particle size, compression force, mode of incorporation, and moisture content can impact the performance of disintegrants. It is evident from the literature search that the advances in measurement tools have created new opportunities to study the disintegration process. Various materials have been proposed as potential disintegrants although adoption had been relatively few. Nevertheless, there remain opportunities to expand the understanding of the disintegrants and provide deeper insights into the disintegration phenomena.

Acknowledgments

The authors would like to acknowledge research funding support from GEA-NUS PPRL fund (N-148-000-008-001) and A*STAR SERC Grant No. 102 161 0049 (R-148-000-157-305).

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