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Particle Engineering of Polymers into Multifunctional Interactive Excipients

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Abstract

Both natural and man-made polymers are widely utilized as tablet binders and filler-binders. The physicochemical and mechanical properties such as particle size, shape and deformation behavior of polymeric binders are key in their effective use. Many such binders are applied as solution in a wet granulation process, which facilitate its facile distribution leading to improved effectiveness as a binder. Direct compression and dry granulation are recognized as routes with reduced process complexity and cost. These processes require a binder to be employed in a dry form and it can be more difficult to obtain a homogeneous distribution of a dry binder in a powder formulation. Therefore, these binders are required in high proportions to generate mechanically strong tablets. At lower proportions, they often are insufficient to create mechanically strong tablets. Recently, innovations in the generation of co-processed excipients have been proposed. Co-processing is a popular means of improving excipient functionalities, where two or more existing excipients are combined by some suitable means to generate new structures with improved and often combined functionalities as compared to the component excipients. Particle size reduction is known to improve the binder properties of an excipient, but also makes it highly cohesive and hard to blend. Via particle engineering, surface structure of smaller particles can be tailored to optimize the cohesive-adhesive balance (CAB) of the powder, allowing formation of interactive mixtures. This chapter reviews recent efforts to engineer surface-modified polymeric micro-excipient structures with the inherent ability to not only form an interactive mixture efficiently and provide flow enhancement, but also to create harder tablets at lower proportions. Hence, this approach represents a potential novel multifunctional prototype polymeric micro-excipient for direct compression and dry granulation processes.

Keywords: Particle engineering, powder technology, interactive mixtures, tablets, binder, multifunctional excipients

1.1 Introduction

The modern pharmaceutical market is under relentless pressure from slowing new product approvals, patent expiries and global competition. In addition, new opportunities

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exist with an evolving patient population, numerous unmet medical needs and growing disease awareness. The pharmaceutical industry must evolve and improve product developing and manufacturing efficiencies for sustainable performance. Efficient and cost-effective product development and manufacturing are continually being explored to meet the challenge of not only reducing cost but also reducing the risk of product recalls.

Tablets are the most commonly used pharmaceutical preparation, accounting for more than 80% of all dosage forms administered [1]. The principal reasons for their continued popularity include convenience of administration and patient preference, high-precision dosing, stability and cost effectiveness [2].

Tablets are typically manufactured by applying pressure to active pharmaceutical ingredient(s) (APIs) and excipients powder blends in a die using a punch, which compresses the powder into a coherent compact. Under compression, bonds are established between the particles, thus conferring a certain mechanical strength to the compact. A formulation must exhibit good flow and high compactability for an API to be transformed into tablets of satisfactory quality. Good flow is necessary to ascertain the rapid and reproducible filling of powder into the die to minimize weight variation; while high compactability is required to ensure that the tablets are sufficiently strong to withstand handling during manufacturing and transportation [3].

The majority of API(s) lack the requisite flow and compactability for direct tablet manufacturing [4]. Therefore, the flow and compactability of the API(s) need to be adjusted to ensure formation of high-quality tablets. Typically, the flow and compactability of a tablet formulation is improved by a granulation step (wet or dry granulation) in which the particles of API(s) and excipients are agglomerated into larger particulate structures referred to as granules. Wet granulation of the input materials can improve the flow properties for further processing and can create non-segregating blends of powder ingredients [5]. However, it involves multiple manufacturing steps, which can add significant time and cost to the process. Conversely, direct compression

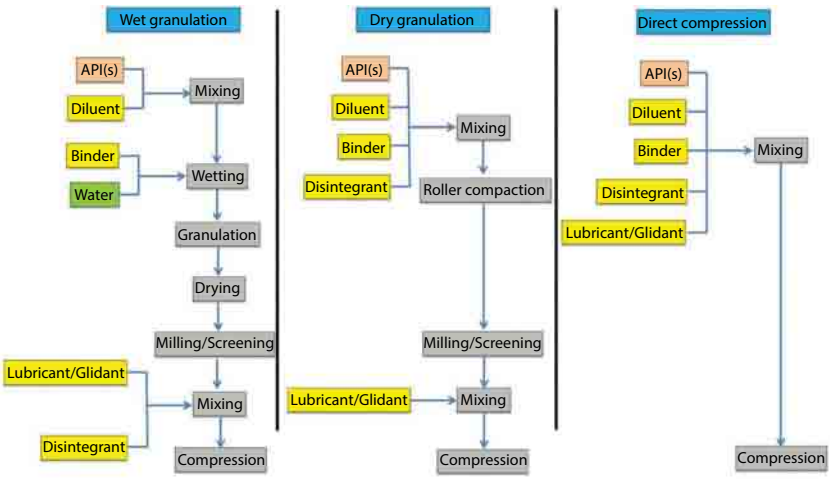

Figure 1.1 The various steps involved in wet granulation, dry granulation and direct compression tablet manufacturing. Adapted and modified from [6].

merely involves mixing of API(s) and excipients followed by immediate compression (Figure 1.1). Therefore, direct compression is an attractive manufacturing process, with fewer steps, for reducing cost and improving manufacturing output.

1.2 Polymers as Excipients

Excipients form an integral part of any pharmaceutical tablet formulation. They play the fundamental role in creation of robust tablet formulations by carrying out an extensive range of functions such as fillers, binders, disintegrants, lubricants, glidants, coating agent and anti-adherents. Currently, a wide range of polymeric materials are used as excipients [6,7], and polymers are the largest overall consumed product segment for the global excipients market, accounting for over 30% [8]. The excipient market is expected to grow at an annual rate of 5.2% from 2013 to 2018, to reach around $7.35 billion by 2018 [8].

Polymers of natural, semi-synthetic and synthetic origin are used especially in the role of binder and filler-binder (see Table 1.1). Polymeric excipients are popular as they can be tailored for many applications by altering their chain length and by chemical functionalization. This can achieve new materials with various optimized physicochemical and mechanical properties for such specific applications.

Table 1.1 List of polymeric excipients, their source and functionalities. This table is compiled from the information given in the *Handbook of Pharmaceutical Excipients* [9].

Polymeric Excipient	Source	Functionality
Natural		
Zein	Extracted from corn gluten	Binder, Coating agent
Cellulose	Extracted from fibrous plant material	Diluent, Disintegrant
Alginic acid	Extracted from various species of brown seaweed	Binder, Disintegrant
Acacia	Exudate from the stems and branches of Acacia Senegal	Binder
Guar gum	Extracted from the endosperm of the Cyamopsis tetragonolobus	Binder, Disintegrant
Inulin	Extracted from the tubers of Dahlia variabilis, Helianthus	Binder
Chitosan	Extracted from shells of crustaceans such as shrimps and crabs	Binder, Coating agent

(*Continued*)

Table 1.1 (Cont.)

Polymeric Excipient	Source	Functionality
Semi-synthetic		
Sodium alginate	By neutralized alginic acid with sodium bicarbonate	Binder, Disintegrant
Calcium alginate	By treating sodium alginate with calcium salts	Disintegrant
Methyl cellulose	By treating wood pulp with alkali followed by methylation	Binder, Disintegrant, Coating agent
Carboxymethyl cellulose sodium	By treating wood pulp with alkali followed by reaction with sodium monochloroacetate	Binder, Disintegrant
Carboxymethyl cellulose calcium	By treating wood pulp with alkali followed by methylation and then converting to calcium salt	Disintegrant
Cellulose acetate	By treating cellulose with acid catalysis and acetic anhydride	Diluent, Coating agent
Cellulose acetate phthalate	By reacting cellulose acetate with phthalic anhydride	Coating agent
Microcrystalline cellulose	By controlled hydrolysis of cellulose with mineral acid	Binder, Diluent, Disintegrant
Hydroxypropylmethyl cellulose	By treating alkali cellulose with chloromethane and propylene oxide	Binder, Coating agent
Hydroxypropylmethyl cellulose acetate succinate	By the esterification of hydroxypropylmethyl cellulose with acetic anhydride and succinic anhydride	Film coating, Enteric coating
Hydroxypropylmethyl cellulose phthalate	By the esterification of hydroxypropylmethyl cellulose with phthalic anhydride	Enteric coating
Ethylcellulose	By ethylation of the alkali cellulose with chloroethane	Binder, Diluent, Coating agent
Low substituted-hydroxypropyl cellulose	By reacting alkaline cellulose with propylene oxide	Binder, Disintegrant
Ethyl cellulose	By ethylation of the alkali cellulose with chloroethane	Binder, Diluent, Coating agent
Hydroxyethyl cellulose	By reacting alkali cellulose with ethylene oxide	Binder, Coating agent

(*Continued*)

Table 1.1 (Cont.)

Polymeric Excipient	Source	Functionality
Maltodextrin	By heating starch with acid and/or enzymes	Binder, Diluent, Coating agent
Sodium starch glycolate	By reacting starch with sodium chloroacetate followed by acidic neutralization	Disintegrant
Hydroxypropyl starch	By reacting starch with propylene oxide in the presence of alkali	Binder, Disintegrant
Dextrates	By controlled enzymatic hydrolysis of starch	Binder, Diluent
Dextrin	By the incomplete hydrolysis of starch	Binder, Diluent
Lactose monohydrate	By crystallization from supersaturated lactose solutions	Binder, Diluent
Spray-dried lactose	By spray drying a suspension of α-lactose monohydrate	Binder, Diluent
Pregelatinized starch	By heating an aqueous slurry of starch with salts or bases and surfactants	Binder, Diluent, Disintegrant
Synthetic		
Poloxamer	By reacting propylene oxide with propylene glycol followed by addition of ethylene oxide	Lubricant
Polyethylene oxide	By polymerization of ethylene oxide	Binder, Coating agent
Polyethylene glycol	By reacting ethylene oxide and water under pressure	Coating agent
Polyvinyl acetate phthalate	By reacting phthalic anhydride, sodium acetate, and a partially hydrolyzed polyvinyl alcohol	Coating agent
Polyvinyl alcohol	By hydrolyzing of polyvinyl acetate	Coating agent, Lubricant
Polyvinylpyrrolidone (PVP)	By reacting acetylene and formaldehyde followed by hydrogenation to form butyrolactone and reacting it with ammonia	Binder, Disintegrant
Copovidone PVP/VA	By free-radical polymerization of vinylpyrrolidone and vinyl acetate in a ratio of 6 : 4	Binder
Crospovidone	By polymerizing vinylpyrrolidone	Disintegrant
Polymethcrylate	By the polymerization of acrylic and methacrylic acids	Binder, Diluent
Carbomer	By crosslinking acrylic acid	Binder

In wet and dry granulation, the properties of the individual API and excipients particles are significantly altered by their agglomeration into granules. Such structures can hide the undesirable properties of individual components (of both API(s) and excipients) of the blend. In wet granulation, a binder can be sprayed into the powder as a solution, and so is easily distributed onto the particle interfaces, so facilitating the binding action. For dry granulation, a binder must be added in dry particulate form. Tablet formulations involving a granulation step can be less sensitive to binder excipient performance and variation than for direct compression. In direct compression, the original particle's structure remains largely unaltered, so individual particle properties (API(s) and excipient) have a more critical and direct impact on formulation properties, such as flow and compactability, and decide the success or otherwise of tablet formation. Consequently, excipients, particularly filler-binders, which play a critical role in direct compression, can be very different in nature to the excipients used in wet/dry granulation. Therefore, there is a great interest in generating ready-made multifunctional filler-binders with improved flowability and binder activity (API uptake capacity) for robust tablet manufacturing using direct compression.

The main focus of this chapter is to examine the critical material properties that influence polymeric binder and filler-binder performance of directly compressible excipients, and how these material properties can be optimized and integrated with other functionalities via particle engineering.

1.3 Material Properties Affecting Binder Activity

The material properties such as particle size and deformation mechanism (elasticity-plasticity and fragmentation) and compressibility have been identified as affecting the ability of a binder to create strong tablets [10–14].

1.3.1 Particle Size

Previous studies have indicated that the optimal amount of binder corresponds to that providing a surface area ratio of unity to the corresponding API, i.e., the amount needed to form a monoparticulate layer of binder particles around the API particles [10]. This suggests that if the particle size of the binder and API is similar (as desirable in direct compression powder blends to avoid segregation), higher proportions will be required to achieve monoparticulate layer of binder around the API particles. However, if the binder particles are smaller than the API, lower proportions of binder particles can form a monoparticulate layer. This concept is illustrated in Figure 1.2. The limited efficacy of the binders in direct compression formulations (and also in dry granulation) may partly be attributed to this concept, i.e., that the binder added in its dry state can be more difficult to disperse homogeneously than when added as a solution [10]. Other physical material properties such as shape and surface energy have also been demonstrated to have a significant impact on the tableting performance of the excipients [15–18].

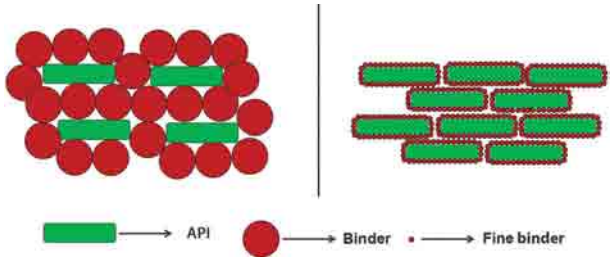

Figure 1.2 Effect of particle size on surface coverage of API particles with binder.

1.3.2 Deformation Mechanisms

Polymers are typically considered to be as excellent binders owing to their good bonding properties [6,7]. The polymers such as PVP and PEG are also available in a variety of molecular weights, and their deformation behavior under compression can be altered by altering their molecular weight [14]. However, the compaction of polymers is greatly affected by the speed of tableting. This has been attributed to the high elasticity of the excipients at high rates of strain [19]. Large stress relaxation yields porous and consequently weak tablets. Figure 1.3 schematically depicts relations between stress and strain for several materials. For a plastic solid, stress (σ) is directly proportional to deformation (strain, γ):

$$\sigma = E^{*}\gamma \tag{1.1}$$

The proportionality constant (E) is the elastic or Young's modulus [20]. It is a measure of the stiffness or resistance against deformation. The material behaves elastically up to the yield point (P_y) at which the stress is called yield stress (σ_c). Beyond this point the material behaves as a plastic, rather than as an elastic solid. Brittle materials can be distinguished from plastic materials by the absence of the P_y: stress increases proportionally with strain until the material breaks.

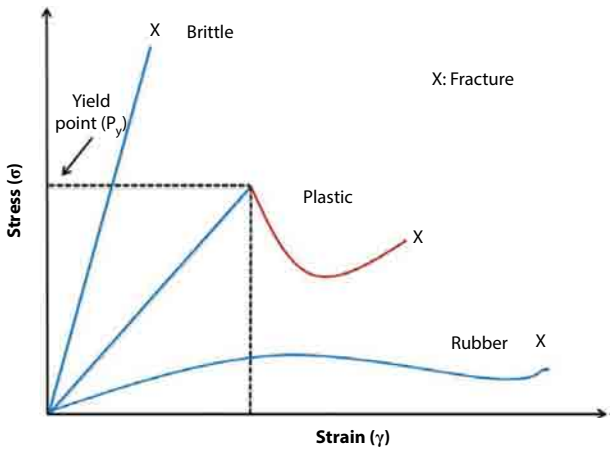

Figure 1.3 Stress-strain behavior of brittle, plastic and rubbers. The point Py indicates the yield point with corresponding yield strength. Adapted and modified from [21].

1.3.3 Glass Transition Temperature (Tg)

The amount of energy stored during densification is manifested as the stress relaxation propensity of the material. Large stress relaxation yields porous and consequently weak tablets. At a high temperature difference (i.e., tableting temperature is much lower than the Tg), the polymer exhibits higher resistance to deformation and the amount of stored energy is large, resulting in highly porous and weak tablets. The Tg of amorphous polymeric materials appears to be a critical parameter with respect to mechanical properties (i.e., plastic/elastic character) of polymers [20]. At temperatures substantially below the Tg, an amorphous material is in the glassy state and its Young's modulus is high, resulting in greater resistance to deformation. However, at temperature close to the Tg a material undergoes the change from a hard glassy form to a more plastic structure or a viscous fluid and the resistance against deformation decreases dramatically. This change is related to the onset of a certain degree of movement in the main chain and the rotation of side segments. Consequently, the performance of polymeric excipients during processes such as compaction strongly depends on their Tg [21].

It was reported that the compaction at a temperature of about 20 K under Tg yields circumstances for which the amount of stored energy has a minimum [21]. The Tg of the material depends on its chemical structure, the presence of a plasticizer and, in the case of polymers, on the molecular weight [22]. Therefore, it may be expected that using polymers with lower Tg (preferably near room temperature) would be advantageous for improved binder activity.

1.4 Strategies for Improving Polymeric Filler-Binder Performance for Direct Compression

The development of excipients of new chemical composition requires extensive toxicology tests. This is a costly preposition and so, in the last three decades, only a few such new excipients have been introduced in the market [23]. Therefore, improved filler-binders have mainly been generated via physical manipulation of existing excipient materials, i.e., as the physical mixture of GRAS (generally regarded as safe) materials [24].

Particle size manipulation is a commonly used strategy to modify polymeric filler-binder performance. For example, microcrystalline cellulose, one of the most commonly used polymeric multifunctional excipients, is commercially available in a variety of particle size ranges [25]. In addition, a wide range of multifunctional excipients are also available in different particle size grades (Table 1.2).

The main objective of excipient engineering is to improve both flow and binder activity of the excipients. Flow and compactability both depend on particle size, and these characteristics often compete, making it difficult to achieve an optimum excipient performance [30]. For example, large particle size is typically associated with improved flow (Table 1.3). However, a smaller particle size is associated with improved compactability due to an increase in the surface area except for brittle materials (as shown in Figure 1.2) [31–33]. Hence there is a fundamental contradiction in designing

Table 1.2 Particle size and flow specification of common commercially available fine-grade polymer powder excipients.

Excipient	Grade	Particle Size	Flow description	Ref.
Hydroxypropyl cellulose	Fine	D_{10} = 16.6 ±5.1 µm D_{50} = 98.8 ±1.3 µm D_{90} = 341.8 ±31.7 µm	BD= 0.3 g/cm^3, TD= 0.4 g/cm^3, CI= 19.9	[26]
	Super fine	D_{10} = 8 µm D_{50} =20 µm D_{90} =50 µm	AOR= 50˚, BD= 0.24 g/cm^3, TD= 0.41 g/cm^3	[27]
Low-substituted hydroxypropyl cellulose	LH-11	D_{50}= 50 µm >150 µm (NMT 2 %)	AOR= 49˚, BD= 0.3 g/cm^3, TD= 0.6 g/cm^3	[28]
	LH-21	D_{50} = 40 µm >75 µm (NMT 10 %)	AOR= 45, BD= 0.3 g/cm^3, TD= 0.6 g/cm^3	[28]
	LH-31	D_{50} = 25 µm >40 µm (NMT 50 %)	AOR= 49, BD= 0.3 g/cm^3, TD= 0.6 g/cm^3	[28]
Microcrystalline cellulose	Avicel PH 102	D_{10} =35.2 ±0.4 µm D_{50} = 109.2 ±0.8 µm D_{90} = 195.5 ±1.14 µm	AOR= 36˚, BD= 0.3 g/cm^3, TD= 0.4 g/cm^3, CI= 20.0	[26]
Ethylcellulose	7 FP	Mean; 7–12 µm; Max; 100 µm	NA	[27]
	10 FP	Mean; 3–8 µm; Max;140 µm	NA	[27]
	100 FP	Mean; 30–60 µm; Max; 150 µm	NA	[27]
Copovidone	Kolidone VA- 64 fine	<50 µm (>90%)	BD= 0.1–0.2 g/cm^3	[29]

BD = Bulk Density
TD = Tapped Density
AOR = Angle of Repose
HR = Hausner's Ratio

a multifunctional excipient where particle size reduction improves binder activity but compromises the flow. There are a number of commercially available polymeric excipients with small particle size and better binder activity but these have relatively poor flow characteristics (Table 1.3).

Efforts have been made to engineer excipients which exhibit both good flow and compactability by co-processing materials. For example, combining excipients with

Table 1.3 Particle size and flow specifications of typical commercially available directly compressible excipients.

Excipient	Composition	Particle Size	Flow description	Ref.
Ludipress	93% Lactose + **3.5% Kollidon® 30 + 3.5 % Kollidon CL**	<63 µm max. 15% <200 µm 40 – 60% <400 µm min. 90%	AOR = 34˚, BD = 0.6 g/cm^3, TD = 0.7 g/cm^3, HR = 1.2	[24,34]
Cellactose 80	75 % α-Lactose monohydrate + **25 % Cellulose powder**	< 32 µm ≤ 20 % < 160 µm = 35–65 % < 250 µm ≥ 80 %	AOR =34˚, BD = 0.4 g/cm^3, TD = 0.5 g/cm^3, HR = 1.2	[24,35]
MicoceLac®100	75 % α-Lactose monohydrate **+ 25 % Microcrystalline cellulose**	< 32 µm: ≤ 15 %, < 160 µm: 45–70 %, < 250 µm: ≥ 90 %	AOR = 36.2˚, BD = 0.5 g/cm^3 TD = 0.6 g/cm^3, HR = 1.2	[24,36]
Pharmatose® 200M	Lactose monohydrate	< 250 µm (100 %)	NA	[37]
Tablettose® 70	α-Lactose-monohydrate	< 63 µm: ≤ 6 % < 200 µm: 30–70 % < 500 µm: ≥ 98 %	BD = 0.5 g/cm^3, TD = 0.7 g/cm^3	[38,39]
Avicel PH 200	**Microcrystalline cellulose**	150 µm NLT 10 % 250 µm NLT 50%	AOR = 36.2˚, BD = 0.3 g/cm^3	[40]
Starlac	85 % α-Lactose monohydrate **+ 15 % Maize starch**	< 32 µm NLT 15% < 160 µm 35 – 65% < 250 µm NLT 80%	AOR = <30˚, BD = 0.6 g/cm^3, TD = 0.7 g/cm^3, HR = 1.2	[24]
Prosolv	**98% Microcrystalline cellulose** + 2 % Colloidal silicon dioxide	< 350 µm NLT 15%	AOR = <30˚, BD = 0.3 g/cm^3, TD = 0.4 g/cm^3, HR = 1.3	[24]
Advantose FS 95	95 % Fructose + **5 % Starch**	170–450 µm	AOR = <25˚, BD = 0.6–0.8 g/cm^3 TD = 0.7–0.8 g/cm^3	[41]

BD = Bulk Density
TD = Tapped Density
AOR = Angle of Repose
HR = Hausner's Ratio"
min. = Minimum proportion
max. = maximum proportion

brittle and plastic compression behavior prevents storage of excessive elastic energy during the compression (Table 1.4) [42], which results in a reduced stress relaxation and a reduced tendency of capping and lamination. The brittle property also facilitates fragmentation under compression to generate reduced particle sizes *in situ.*

Table 1.4 List of co-processed excipients created by combining plastic and fragmenting excipients.

Excipient	Component ingredients	
	Brittle excipient	**Plastic excipient**
Ludipress	α –Lactose monohydrate (93.4%)	PVP (Kollidon 30) (3.2 %) and Crospovidone (Kollidon CL) (3.4 %)
Cellactose	α –Lactose monohydrate (75 %)	Cellulose (25%)
Prosolv	Fumed colloidal silicon dioxide (2%)	Microcrystalline cellulose (98%)
Pharmatose	Anhydrous lactose (95%)	Lactitol (5%)
Xylitab	Xylitol (>96.5%)	Sodium caboxymethyl cellulose (<2 %)
Advantose	Fructose (95%)	Starch (5%)
Formaxx	Calcium carbonate (70 %)	Sorbitol (30 %)
Microcelac	Lactose (75 %)	Microcrystalline cellulose (25 %)

However, improvement in binder activity achieved using this approach is relatively limited and large proportions of such excipients are needed to create robust and mechanically stable tablets [43], so directly compressible excipients are only used where a low-dose of API is needed. At higher API loads (>500 mg), this may result in large tablets which are difficult to swallow. Therefore, tableting using these direct compression multifunctional excipients is only considered suitable for high/intermediate potency APIs.

Another key aspect of particle size relates to powder segregation. The particle size and size distribution of excipients should also be able to generate a homogeneous and segregation-resistant blend with the API(s). This can be achieved via matching the particle sizes of API and excipients. A number of product recalls identified excipient variability as a contributor to failure of the pharmaceutical product [44], indicating the lack of understanding and control over excipient manufacturing and functionality.

With the US Food and Drug Administration's (US-FDA) Quality in the 21st Century initiative, which includes the quality by design (QbD) and process analytical technologies (PAT), it is becoming increasingly important to understand the impact of formulation process as well as material variability on the performance and manufacturability of new pharmaceutical products [45]. The variability in both APIs and excipients can have a significant impact on the critical quality attributes (CQAs), thereby the performance and manufacturability of the pharmaceutical product [23,46–51]. The intrinsic lot-to-lot variability within a single grade of each excipient in a given formulation is dictated by the degree of process control implemented by each excipient vendor. Managing excipient variability is an essential element in designing and manufacturing robust solid oral products and is an integral task when applying QbD principles. Tables 1.3 and 1.4 show excipients are provided with relatively wide particle size limits. In a QbD world such wide limits may not always be appropriate. This, therefore, presents an additional risk and cost to the overall product.

1.4.1 Interactive Mixing

It was proposed that the knowledge and understanding of interactive mixing may be applied to create improved excipients. We proposed that binder with appropriate particle size and surface properties can exhibit improved performance due to the ability to interactively blend with the API(s). Interactive mixing is a practical powder blending strategy to achieve the homogeneous distribution of small particles over relatively large particles. A fundamental principle of interactive mixing is that small particles with appropriate size and surface properties adhere to the coarse particles by interparticle interaction forces, which results in a uniform and segregation-resistant blend [52–55]. Such mixtures have wide application in the preparation of dosage forms containing relatively small doses of highly potent micronized API(s) in inhalation and tablet formulations [56–58]. As the particle becomes smaller their interactive ability increases and particles below 10 μm are considered to be highly interactive and tend to exhibit high degrees of adhesion to surfaces and cohesion to neighboring particles [59,60]. This is because the interparticle forces (cohesive forces arising from electrostatic, capillary or van der Waals interaction for particles in this larger size range) significantly exceed external forces such as gravity [61].

In an interactive mixture of components A (coarse) and B (fine), the interaction between fine particle and coarse particles (A-B) or between two fine particles (B-B) represents the typical particle-particle interactions (Figure 1.4). However, if the coarse particles are uniformly and sufficiently coated with fine particles, then the contacts between fine particles will represent the majority of particle-particle interactions. Thus, in such mixtures, the force of interparticle interactions between fine particles will determine the flow of the mixture. Since interparticle cohesion of fine particles depends heavily on their surface energy, it is also proposed that lowering the surface energy of fine particles may lower the overall forces of interparticle interaction and improve the flowability of an interactive mixture. However, this hypothesis is based on the assumption that the fine particles form a uniform surface coating regardless of the difference in their surface energy and interparticle cohesion. Thus, interactive excipients could also exert a flow additive action, as typically observed with benchmark flow aids such as silica [62,63]. We proposed that the interactive excipients with appropriate particle size and surface

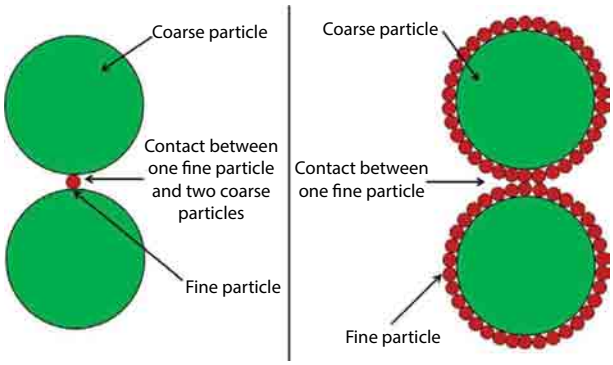

Figure 1.4 Interparticle contact models in an interactive mixture.

properties could be a practical solution to the complex problem of achieving excellent content uniformity, improved flow performance and high binder efficiency in directly compressible formulations.

1.4.2 Challenges to Interactive Mixing

To form an interactive mixture, mixing must overcome the cohesion forces acting between the individual components of an interactive mixture. Small particles (< 10 μm) are considered to be highly cohesive in nature, as the interparticle forces significantly exceed external forces such as gravity, resulting in agglomeration [55]. The ability of the mixing process to split agglomerates into individual particles decreases with increasing interparticle cohesion forces, which makes it difficult to break agglomerates of particles during the mixing process [64]. This may compromise the ability of smaller excipient particles to form interactive mixture with larger API particles, affecting its functional performance as excipient. Therefore, controlling interparticle cohesion is considered to be a key aspect of designing such excipients, to facilitate easy de-agglomeration of interactive excipient, and thereby preferential adhesion to larger API particles.

Micronized particles usually interact with coarse particles via van der Waals forces in interactive mixtures [65,66]. Other attractive forces, such as capillary and electrostatic forces may also operate; but in general, they are smaller than the omnipresent van der Waals force in dry powders [66]. The magnitude of van der Waals force depends on the properties of both the fine and coarse components of an interactive mixture. It has been demonstrated that factors such as particle size, shape [67], particle size distribution [68,69], roughness [70–72] and surface energy [72] affect the phenomenon of particle adhesion in an interactive mixture. A change in any of these factors can change the magnitude of the van der Waals forces and hence the cohesion and adhesion strength of the particles [65].

The work of adhesion, W_{ad}, is defined as the free energy required to separate unit areas of two different surfaces from contact to infinity in vacuum, whereas, the energy required to separate unit area of similar surfaces is referred to as the work of cohesion, W_{co} [65]. The adhesion between particles of different materials only occurs if the energy that is released during adhesion is larger than the energy that is required to break up the cohesion contacts of particles of individual material. Thus, adhesion will be an energetically favored phenomenon for such powders [60]. However, it only has importance for those powder mixtures which are classified as interactive, i.e., where one component is much smaller than the other. Also, this concept disregards the influence of other factors on adhesion such as surface roughness, hardness, elasticity, etc. Cohesion (i.e., agglomeration of fine micronized particles) can also be of energetic advantage and can explain why micronized powders are often heavily agglomerated. So, one can assume that the fine particles will only adhere to coarse particles when the energy of cohesion is lower than the energy of adhesion (Figure 1.5). Hence, the performance of interactive mixtures is a function of the relative magnitudes of cohesive and adhesive interparticulate forces.

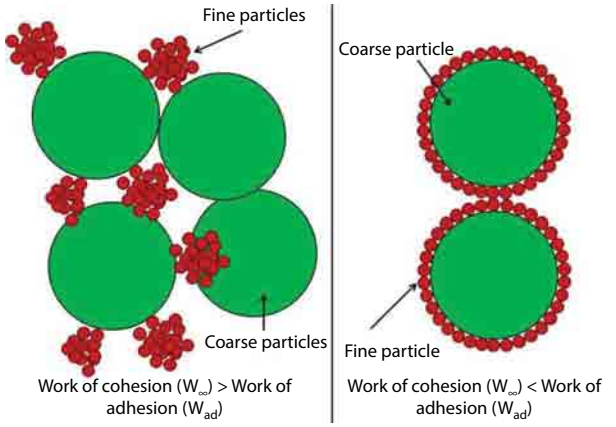

Figure 1.5 Effect of cohesive and adhesive forces on particle distribution in interactive mixtures.

1.4.3 Controlling Interparticle Cohesion

Engineering surface properties has evolved as one of the main strategies for reducing the interparticle cohesion of fine particles. The surface-altering excipients act as lubricants between surfaces, thus reducing cohesion and improving dispersibility [73,74]. These techniques were mainly explored in the area of dry powder inhalers, where particles 1–5 μm with low cohesion and good dispersibility are desirable for their efficient delivery to the lungs [75,76]. Of these, the co-spraying with L-leucine has been previously employed as a remarkably effective strategy to improve the aerosolization of spray-dried micron-sized inhalation formulations [77–80]. In spray drying, the formation of a surface layer relies largely on the properties of excipient materials to accumulate at the air-solvent interface of droplets before drying takes place [81]. Therefore, a coating layer is formed during the drying of droplets and a uniform and coherent coating is easy to achieve [77].

1.5 Preparation and Characterization of Interactive Excipients

We spray dried PVP as a polymeric binder (6% w/v) with L-leucine (0.6 % w/v) as a surface modifying agent to control interparticle cohesion of fine spray-dried particles [82]. PVP was spray dried with and without L-leucine to generate small interactive excipients. The effect of L-leucine on the surface composition, surface energy and bulk cohesion of spray-dried formulation was assessed. The surface composition of these formulations was examined using state-of-the-art technique X-ray photoelectron spectroscopy (XPS). To then understand the bulk surface interactions, which may be influenced by molecular orientation at the surface, the surface energy was determined using inverse gas chromatography (IGC). The data obtained were used to explore how surface leucine concentration and molecular state affects morphology, surface energy, solid-state properties and the resulting change in bulk properties such as interparticle cohesion.

1.5.1 Particle Size and Size Distribution of Excipients

The particle size of spray-dried and commercial PVP was measured using a standard validated Malvern Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, UK) dry cell method. Table 1.5 shows the particle size and size distribution (span) of PVP, PVP-SD and PVP-Leu. The results indicated that PVP exhibited a particle size D_{90} of 56.7 μm, whereas the spray-dried interactive excipients, i.e., PVP-SD and PVP-Leu, exhibited particle sizes D_{90} of 4.3 and 5.6 μm, respectively. It was also noted that the particle size of PVP-SD and PVP-Leu was approximately the same, suggesting that L-Leucine does not significantly affect the particle size of spray formulation. The particle size distribution plots of each PVP, PVP-SD and PVP-Leu are represented in Figure 1.6 which shows that particle size distribution of PVP, PVP-SD and PVP is mono-modal in each case. The inability to tightly control particle size and size distribution is considered to be a potential source of excipient variability amongst batches. Therefore, controlling variation in particle size and size distribution could minimize the excipient related variations in the formulations. The results demonstrated that spray drying could be successfully employed to generate particles sizing < 10 μm with narrow particle size distribution.

Table 1.5 Particle size of PVP, PVP-SD, PVP-Leu and paracetamol. Adapted from Mangal *et al.*, 2015 [82].

S. No	Composition	Particle Size (μm)			Span
		D_{10}	D_{50}	D_{90}	
1	PVP	8.2 ± 0.1	26.6 ± 0.2	56.7 ± 0.6	1.8 ± 0.0
2	PVP-SD	1.1 ± 0.1	2.13 ± 0.1	4.3 ± 0.1	1.5 ± 0.1
3	PVP-Leu	1.4 ± 0.1	2.8 ± 0.0	5.6 ± 0.1	1.5 ± 0.1
4	Paracetamol	3.7 ± 0.1	21.4 ± 0.3	151.5 ± 5.00	6.8 ± 0.2
The data represents mean ± SD (n = 3). n = number of batches					

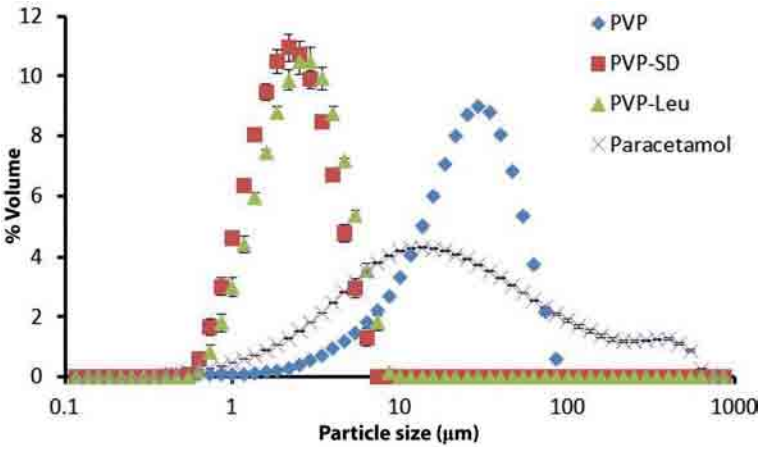

Figure 1.6 Particle size distribution plots of various excipients. Adapted and modified from Mangal *et al.*, 2015 [82].

1.5.2 Effect of L-leucine on Surface Morphology

The shape and surface morphology of the various excipients were visualized by scanning electron microscopy (SEM, Phenom, FEI Company, Hillsboro, Oregon, USA). From SEM images, the surface of PVP and PVP-SD particles was observed to be relatively smooth without visible wrinkles or corrugation. In contrast, PVP-Leu particles were more corrugated and wrinkly (Figure 1.7). The SEM image showed that PVP-SD appeared highly agglomerated, whereas, PVP-Leu appeared as more discrete individual particles, suggesting that L-leucine could potentially overcome the cohesive forces between PVP particles. However, this was further confirmed by the bulk cohesion and surface energy analysis of PVP-SD and PVP-Leu.

1.5.3 Effect of L-leucine on Surface Composition

Surface fractions of PVP and L-leucine in spray-dried formulations were estimated using X-ray photoelectron microscopy (XPS, Kratos Analytical Inc., Manchester, UK) based on the C 1s and N 1s high resolution spectra. No L-leucine was detectable on the surface of PVP-SD particles, whereas, L-leucine formed a significant proportion of surface of PVP-Leu formulation [82]. L-leucine achieved much higher concentration (> 80 %w/w with merely 9.1 %w/w L-leucine) on the surface of the spray-dried particles compared to PVP, confirming the formation of core-shell particulate structures (Table 1.6). This suggests that L-leucine tends to enrich the surface of the spray-dried formulations. The results presented here are consistent with the previous findings [83]. However, the mechanism by which L-leucine enriches the surface of the spray-dried formulations is debatable. Both interfacial activity and low water solubility of L-leucine are considered to be the factors explaining the ability of L-leucine to enrich the surface of the spray-dried formulations [79,84].

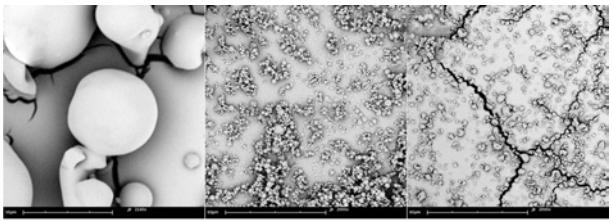

Figure 1.7 SEM images of PVP (a), PVP-SD (b) and PVP-Leu (c).

Table 1.6 Surface PVP and L-leucine composition (%w/w) of PVP-Leu spray-dried formulation. Adapted form Mangal *et al.*, 2015 [82].

Formulation	%w/w PVP and L-leucine surface concentration			
	PVP (C 1s)	L-leucine (C 1s)	PVP (N 1s)	L-leucine (N 1s)
PVP-SD	100.0 ± 0.0	0.0 ± 0.0	100.0 ± 0.0	0.0 ± 0.0
PVP-Leu	18.3 ± 1.8	81.7 ± 1.8	19.7 ± 1.9	80.3 ± 1.9

1.5.4 Effect of L-leucine on Surface Energy

Surface energy (γ) is the average free energy per unit area of surface of a material. Surface energy is considered to be directly related to interparticulate interactions or forces of cohesion and adhesion [85,86]. The total surface energy of a material is the additive effect of both the dispersive (γ^D) and polar (γ^P) components [87]. The dispersive surface energy (γ^D) represents the surface energy for non-polar interaction sites and polar energy (γ^P) represents the surface energy for polar interaction sites of the materials. Upon determination of the dispersive and polar surface energies, the work of adhesion (W_{ad}) for interactions between dissimilar particles and the work of cohesion (W_{co}) for interactions between similar particles can be calculated [88,89]. The energy of interaction between the small component and large component (W_{ad}) must be greater than the energy of interaction between individual components of the mixture (W_{co}) to allow preferential adhesion of smaller component of the mixture with larger component. This concept is also known as the cohesive-adhesive balance or CAB [90,91]. The PVP was co-sprayed with L-leucine to control cohesive energy of the interaction of spray-dried formulation and the effect of L-leucine on surface energy profile, and energy of the cohesive interaction (W_{co}) was determined.

The surface energies (polar, non-polar and total) of PVP-SD and PVP-Leu were determined using inverse gas chromatography at infinite dilution and the data is presented in Figure 1.8. It was noted that the surface energy of PVP-SD was high and L-leucine resulted in a significant reduction in the polar surface energy, whereas no change was noted in the non-polar surface energy of the spray-dried formulations. The Wco of PVP-SD (281 ± 21.5 mJ/m^2) was also substantially lower compared to PVP-Leu (117 ± 5.5 mJ/m^2), suggesting that L-leucine contributes significantly to overcome the energy of cohesive interaction between fine particles and thereby prevents agglomeration, as evident from SEM images. This can help in the understanding of the role of L-leucine in particle formation and its impact on bulk powder characteristics such as cohesion.

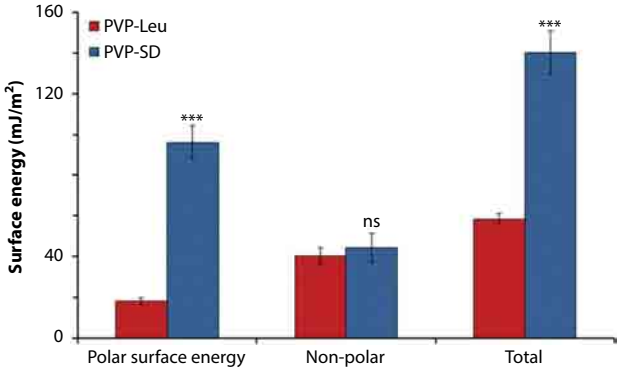

Figure 1.8 Surface energies of PVP-SD and PVP-Leu spray-dried formulations. Adapted form Mangal *et al.*, 2015 [82].

1.5.5 Effect of L-leucine on Interparticle Cohesion

An FT4 powder rheometer system (Freeman Technology Ltd., Worcestershire, UK) was used to determine the cohesion and flow function co-efficient (FFC) of PVP-SD and PVP-Leu. Shear cell data indicated that the PVP-SD demonstrated a high cohesion and a low FFC (Table 1.7). As per FFC classification, PVP-SD can be referred to as very cohesive [59]. Co-spraying with L-leucine resulted in a marked reduction in cohesion and a significant increase in FFC. Our results showed that L-leucine resulted in a marked reduction in surface energy and a substantial change in the surface morphology of the spray-dried particles from smooth to corrugated; both of these explanation have been previously used for describing the ability of L-leucine to reduce cohesion [85,86,92]. However, the predominating mechanism that can explain L-leucine's ability to reduce cohesion is still debatable. We propose that both mechanisms cooperate to efficiently reduce bulk cohesion of fine spray-dried particles, and this needs further investigation.

1.6 Performance of Interactive Excipients

The functional performance of spray-dried interactive excipients was investigated using paracetamol, which is a standard poorly flowable and poorly compactible API for such purposes [93,94].

1.6.1 Blending Ability

The excipients were blended with paracetamol in a glass jar using a Turbula mixer (Quadro Engineering, Waterloo, Ontario, Canada). The blends of paracetamol with PVP, PVP-SD and PVP-Leu were denoted as PVP/Para, PVP-SD/Para and PVP-Leu/Para, respectively.

SEM images of the blends were obtained to visually examine and inspect the mixing behavior of the interactive excipients. The SEM images showed that the PVP-Leu and PVP-SD appeared to adhere to the surface of paracetamol (Figure 1.9). This may be attributed to their small particle size given that fine particles are known to adhere to coarse particles mainly by van der Waals forces [55]. Furthermore, PVP-Leu appeared to form a more uniform monolayer, whereas PVP-SD appeared as more irregular clumps or agglomerates over the surface of API particles. This may be attributed to lower

Table 1.7 Shear cell data, i.e., cohesion and flow function coefficient (FFC) of PVP-SD and PVP-Leu. Adapted form Mangal *et al.*, 2015 [82].

S. No.	Material	Cohesion (KPa)	Flow function co-efficient
1	PVP-SD	3.8 ± 0.4	1.3 ± 0.1
2	PVP-Leu	0.7 ± 0.0	5.8 ± 0.1
The data represents mean ±SD (n = 3). n = number of batches			

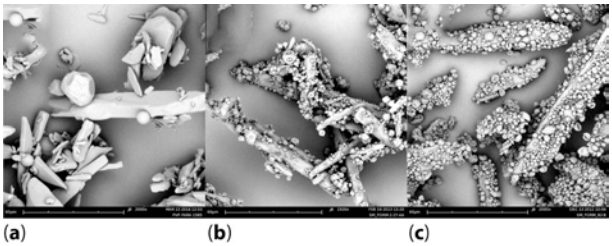

Figure 1.9 SEM images of PVP/Para (a), PVP-SD/Para (b) and PVP-Leu/Para (c).

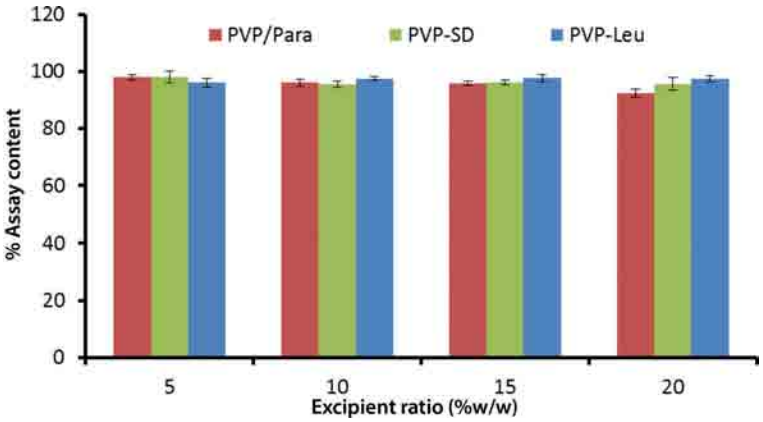

Figure 1.10 Content uniformity data of various API excipient blends. Adapted and modified form Mangal *et al*., 2015 [82]

interparticles cohesion of PVP-Leu, which allowed PVP-Leu to homogeneously distribute over API particles, whereas, higher cohesion as observed with PVP-SD prevents its de-agglomeration, resulting in less homogeneous distribution over API particles, via mixing. However, both PVP-SD and PVP-Leu achieved excellent content uniformity (Figure 1.10), suggesting interactive mixing as a potential strategy to achieving uniform mixing (if not homogeneous distribution) of the interactive excipient in the blend.

It was noted that PVP-SD was extremely cohesive and did not appear to de-agglomerate and disperse homogeneously over API particles upon mixing. Therefore, controlling cohesion was considered to be critical to facilitate de-agglomeration and homogeneous distribution of interactive excipient over API particles. Incorporation of L-leucine in the spray feed helped reduce cohesion as evident by shear cell data. The XPS data indicated that L-leucine achieved high surface concentration in spray-dried formulations, suggesting formation of core-shell particles. L-leucine also resulted in a marked reduction in both surface energy and bulk cohesion. Reducing cohesion facilitated more homogeneous dispersion of interactive excipient particle over API particles. This could be a potential benefit in the case of excipients not only to ensure content uniformity but also to achieve consistent excipient performance throughout the formulation. In contrast, excipients without interactive mixing ability distribute randomly in the formulation and therefore distribution of such excipient is not the same throughout the formulation, which can not only compromise the content uniformity but can also cause them to exert variable performance within a formulation batch on larger scale production.

1.6.2 Effect on Flow

The effect of various excipients on the flow of paracetamol was evaluated using: (i) conditioned bulk density (CBD), (ii) compressibility and (iii) aeration energy programs of the FT4 (Figure 1.11).

As expected, the addition of PVP had no effect on the flow of paracetamol. Incorporation of PVP-Leu led to an increase in the flow performance of paracetamol in a concentration-dependent manner [82], which may be due to improved flow as well as dispersion of the PVP-Leu/Para blends [95–97]. This may be attributed to the ability of PVP-Leu to adhere to paracetamol particles and therefore reduce cohesion between paracetamol particles, consequently improving the flow. This may be a significant benefit that can be exploited in packing, storage, transport, handling and subsequent processing [59,98]. Surprisingly, despite the ability of PVP-SD to adhere to paracetamol particles, no change in flow of paracetamol was recorded. We propose that this may be attributed to the cohesive nature and high surface energy of PVP-SD.

It should be pointed out here that the reduced cohesion observed in the case of PVP-Leu should not be misinterpreted as better flow of the interactive excipients, as the interactive excipients themselves exhibited poor flow. We proposed that the flow of excipients is not a necessity and is not always relevant to achieve improved formulation flow performance. To investigate this, the impact of interactive excipients of flow of API was assessed. The results suggested PVP-Leu resulted in a marked improvement in the flow of API. This may be attributed to the ability of PVP-Leu particles to act as spacers among coarse particles effectively increasing contact separation distance and therefore decreasing van der Waals attractions between coarse particles, which reduces cohesion and improves the flow [62,63]. This suggests that the flow of excipients is not relevant in the context of small excipients as they adapt a different mechanism to improve flow. This is also true for the benchmark flow additive silica, which itself exhibits poor flow but flows better in combination with another larger formulation component [99]. However, the observation that PVP-SD had no effect on the flow performance of the formulation suggested that controlling surface properties and cohesion is a key to achieving such functionality. The glidant performance of PVP-Leu was also compared against benchmark glidant silica and silica was found to exert a better glidant performance compared to PVP-Leu. This may be attributed to the smaller particles size of silica compared to PVP-Leu, as the contact area of interacting particle surfaces decreases with decreasing particle size with decreasing size of glidant particles [62,100,101]. The surface characteristics such as hydrophilic-hydrophobic nature and surface energy have also been reported to affect the flow additive ability of glidants [62,102]. We proposed that by manipulating the size and surface characteristics such as hydrophobicity and surface energy, glidant performance of such interactive excipients can be optimized.

1.6.3 Binder Activity

To determine the binder activity of various excipients, tablets were manufactured using a computer-controlled tablet press (Gamlen Tableting Ltd., Nottingham, UK) and the crushing strength of the tablets was measured using an Erweka hardness tester

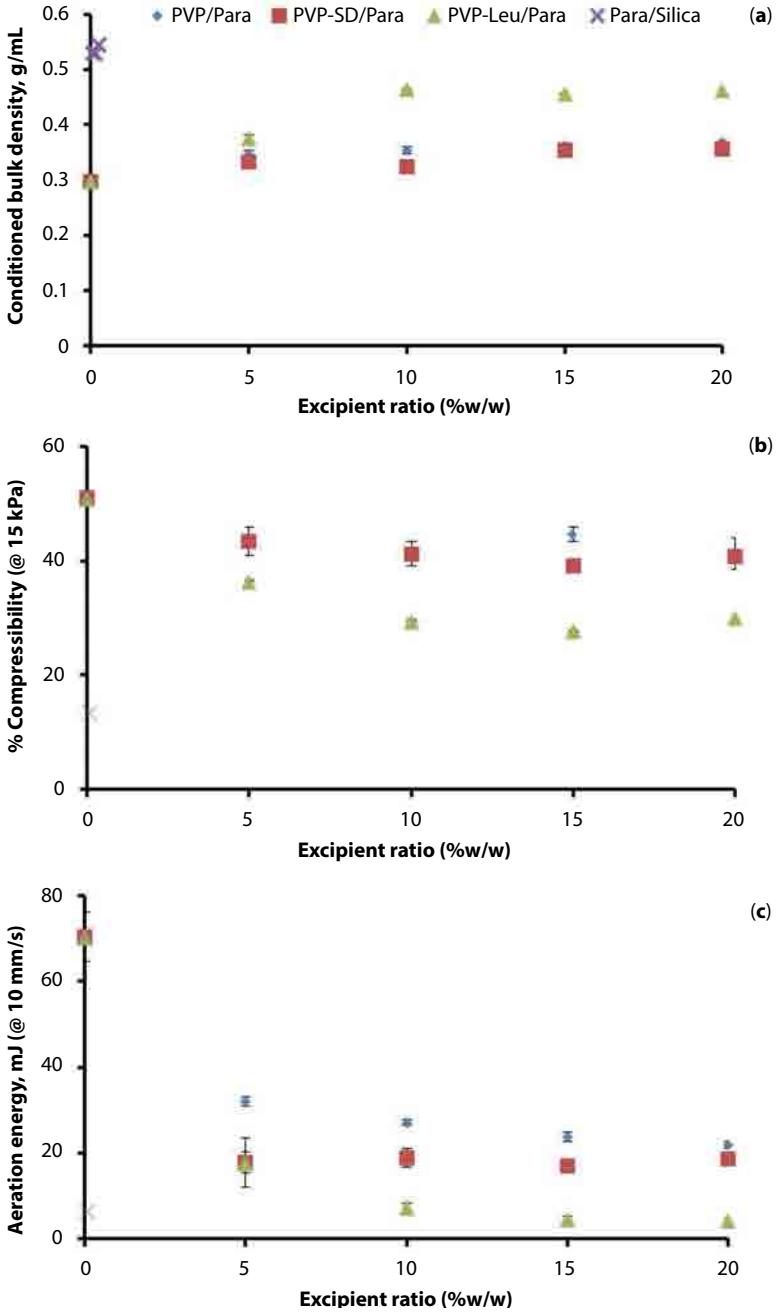

Figure 1.11 Graph showing conditioned bulk density (a), Compressibility (b) and Aeration Energy (c) data of PVP/Para, PVP-SD/Para and PVP-Leu/Para blends. Adapted form Mangal *et al.*, 2015 [82].

(TBH-30, Erweka, Heusenstamm, Germany). The tensile strength of the tablets was calculated by using the following equation [103]:

$$\sigma = \frac{2F}{\pi DH} \tag{1.2}$$

where σ is the tensile strength, F is the breaking force, D is the tablet diameter, and H is the tablet thickness.

The tensile strength relates to the mechanical ability of the tablets to withstand damage due to mechanical handling and transport [104]. Compression of paracetamol resulted in fragile and capped tablets indicating its physicomechanical inability to form coherent tablets (Figure 1.12). Incorporation of PVP-Leu facilitated formation of coherent tablets with no capping or lamination. A tensile strength of > 1.7 MPa is typically considered as suitable for large-scale manufacturing [105]. At lower ratios (5 and 10%), PVP failed to create coherent tablets as evident by the lamination of the tablets. However, PVP-SD and PVP-Leu resulted in the formation of stronger and coherent tablets at as low as 5%.

With a higher PVP-Leu concentration an increase in the tablet tensile strength was recorded which appeared to achieve a maximum at 15% ratio, and no further increase in tensile strength with higher concentrations either with PVP-Leu or PVP-SD. It was noted that PVP-Leu achieved higher tensile strength compared to PVP-SD at lower ratios (5%), suggesting the importance of homogeneous dispersion of interactive excipient on its functional performance. However, PVP-SD tablets achieved similar and then higher tensile strength compared to PVP-Leu with increasing proportion. Some commercially available benchmark directly compressible binders (at 15:85, excipient:API ratio only) were also used to compare the binder performance of PVP-Leu and PVP-SD.

It was noted that the majority of directly compressible excipients, including silicified microcrystalline cellulose (SMCC), lactose monohydrate (Tablettose®70), Ludipress-LCE, Copolyvidone (Kollidone VA-64) and microcrystalline cellulose (Avicel PH-105), failed to create coherent tablets. A commercially available fine-grade hydroxypropylcellulose (HPC-SSL-SFP) was also chosen for the comparison to assess the binder properties of PVP-Leu and PVP-SD. The results suggested that HPC-SSL-SFP could produce

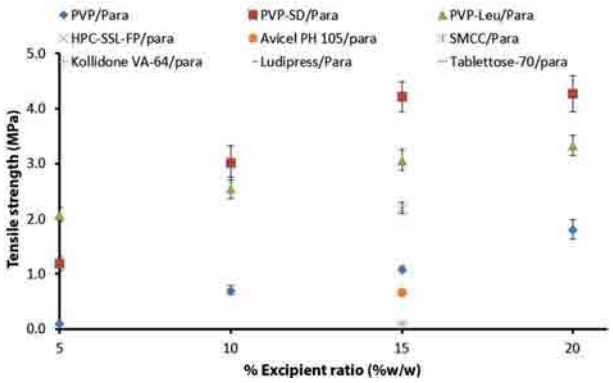

Figure 1.12 Tensile strength of tablets prepared from different excipients. Data represented as mean ±SD. (n = 5). Ludipress, Kollidone VA-64, SMCC and Tablettose failed to produce tablets. Adapted form Mangal *et al.*, 2015 [82].

coherent tablets at the tested ratio; however the tensile strength was significantly lower compared to PVP-SD and PVP-Leu.

Both PVP-SD and PVP-Leu demonstrated an improved binder performance compared to PVP and some other benchmark directly compressible excipients. This suggests that interactive mixing could be a promising approach for enhanced functional performance of the excipients. High cohesion and agglomeration appeared to limit the binder performance of interactive excipients at lower excipient proportions but not at higher proportions. Interestingly, PVP-SD tablets achieved much greater tensile strength compared to PVP-Leu at higher proportions despite its higher cohesion and nonhomogeneous dispersion over API particles. Although we do not fully understand this, we proposed that co-spraying with L-leucine effectively covers the PVP with a L-leucine shell, which could potentially limit its binder activity due to its anti-adhesion and anti-binder activity [106].

1.7 Investigation of the Effect of Polymer Mechanical Properties

We also investigated the effect of mechanical properties of polymers on binder activity. We spray dried PVP of different molecular weights (PVP K10, K-40 and K-90, molecular weight 10000, 40000 and 360000 Da, respectively) with L-leucine. The results show that interactive excipient with lower molecular weight PVP exhibits lower Tg relative to the higher molecular weight PVP (Figure 1.13). With increasing molecular weight the compactability of the binder also decreased, as evident by the higher amount of work (work of compression) needed for compression (Figure 1.14).

The work required to compress powders can give insight into the deformation behavior of powders under compression. Force-displacement curves can serve as an important tool to understand the mechanical bahavior of powders under compression (Figure 1.15). The area under the force-distance curve is indicative of the deformability, where a larger AUC suggests that a material requires more work to deform, i.e., it is difficult to compress and vice versa. The work of compression of interactive excipients was determined to investigate the impact of Tg on mechanical behavior. Results suggested

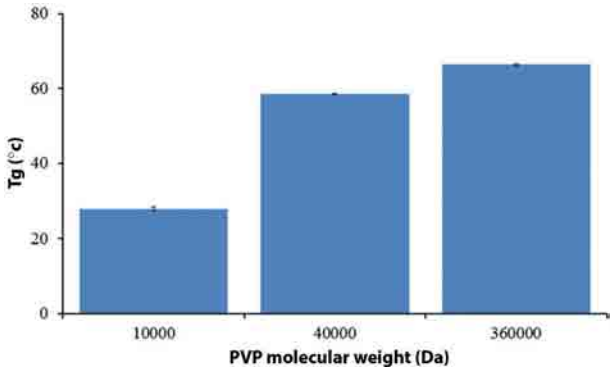

Figure 1.13 Effect of molecular weight on Tg of interactive excipient.

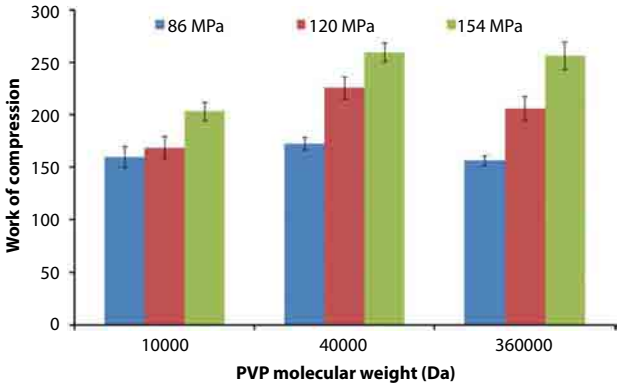

Figure 1.14 Effect of molecular weight of the polymer on the work of compression. Data represented as mean ±SD. (n = 5).

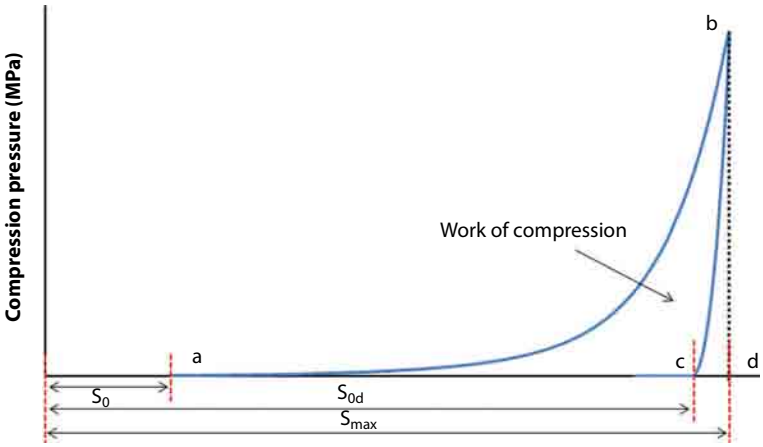

Figure 1.15 A typical labeled force-displacement curve.

that interactive excipient with lower molecular weight and low Tg required lower work of compression, suggesting greater deformability.

To investigate the effect of molecular weight on the mechanical behavior and the binder activity of the excipient under compression, interactive excipients with different molecular weight PVP were mixed with paracetamol and compressed into tablets. The tensile strength of the tablets was determined. The elastic recovery can be calculated using a force-displacement curve using this equation:

$$EF = \frac{\left(S_{max} - S_{od}\right)}{\left(S_{max} - S_{o}\right)} * 100 \tag{1.3}$$

where S_{max} is the maximum upper punch displacement, S_o is the displacement of the upper punch when force is first noticed and S_{od} is the displacement of the upper punch in the decompression phase, as shown in Figure 1.14 [107].

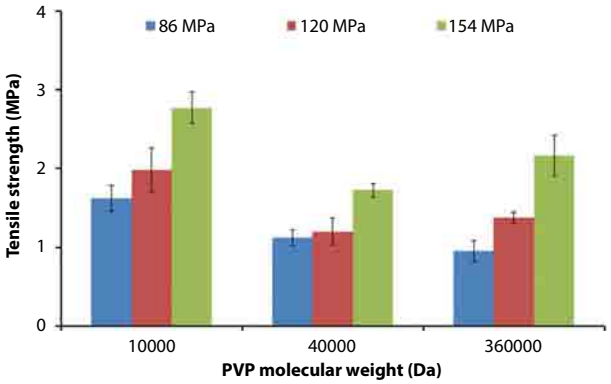

Figure 1.16 Effect of molecular weight on tensile strength of API/interactive excipient blend tablets. Data represented as mean ±SD. (n = 5).

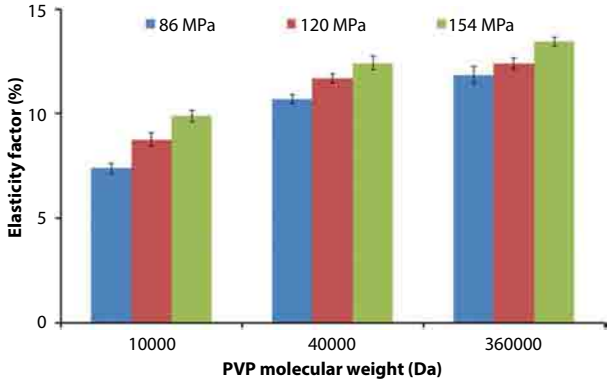

Figure 1.17 Effect of molecular weight on elasticity of API/interactive excipient blend tablets under compression. Data represented as mean ±SD. (n = 5).

The results suggested that the interactive excipient with lower molecular weight resulted in stronger tablets, indicating greater binder activity (Figure 1.16). This may be attributed to the lower Tg/greater deformability of the lower molecular weight excipient. It was also noted that PVP with lower Tg exhibited lower elastic recovery (Figure 1.17), which also indicates the greater deformability under compression. Overall, these results suggested that polymer properties such as molecular weight and Tg can have a significant impact on its mechanical properties, which can consequently affect its binder properties.

1.8 Conclusion

Excipients are not only one of the major components and key factor governing the formulation performance of a tablet formulation, but also one of the key sources of variability in the formulations. Use of multiple excipients and a high proportion of excipients, as well as variations in particle size, and blending behavior, are considered

to be the potential cause of excipient-related variability in the pharmaceutical tablet formulations. Therefore, reducing the number of excipients and the amount of excipient as well as minimizing the variations in the particle size and blending behavior could potentially minimize these excipient-related variations. The results presented here indicate that the interactive excipients with controlled particle size and surface properties exhibit an inherent ability to adhere to drug particles due to their interactive nature. In addition, the interactive excipient also was demonstrated to be an excellent binder as well as having flow additive ability at low proportions to API. Therefore, such excipients could facilitate minimizing excipient- and process-related variations to a certain extent, which could help achieve improved and consistent product performance by Quality by Design approach. In summary, this chapter outlines the application of an interdisciplinary approach of interactive mixing to create high performance excipients. Thus, interactive excipients represent potential high-performance, multifunctional excipient candidates for simplified and efficient tablet manufacturing using direct compression.

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