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# Characterisation and surface profiling techniques for composite particles produced by dry powder coating in pharmaceutical drug delivery

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## Highlights:

- Dry powder coating is a promising one-step process to produce composite particles with improved functionalities.
- Blend characterisation is based on the use of proper sampling techniques
- The selection of the right surface characterisation technique is essential to determine resultant functionality and optimisation of process parameters

## **Abstract**

Production of composite particles using dry powder coating is a one-step environmentally-friendly process for the fabrication of particles with targeted properties and favourable functionalities. Diverse functionalities such flowability-enhancement, content-uniformity and dissolution can be developed from dry particle coating. The overarching aim of this review is to enable a holistic understanding of particle functionalities that can be tailored and the selection of relevant characterisation techniques to understand their molecular basis. Key features in powder blend sampling process will be initially addressed, followed by exploring the relevant characterisation techniques within two domains. The first part discusses the functionality delivered by dry coating. The second section will focus on surface profiling that explores the dynamics and surface characteristics of the composite blends.

*Key Words: Composite particles, dry-powder coating, guest, host, powder sampling, surface profiling.*

Powder coating methods to improve particle properties is increasing in popularity especially in the production of functionalised particle surfaces. Currently employed methods which include; film coating; electrospraying; phase inversion nanoencapsulation and emulsion polymerisation are useful in producing particles with desired properties however require multiple steps and can often result in the chemical alteration of the materials during processing or within the resulting particles [1-4]. Dry particle coating is a one-step high shear process whereby small guest particles are adhered on to the surface of a larger host particle. The process is environmentally friendly as it does not require addition of solvent or a drying process and primarily utilises the attractive forces generated between fine guest particles and host particles (mainly Van der Waals, electrostatic or hydrogen bonding) to improve properties or produce new functionalities, resulting in a cost effective method of producing high quality stable functionalised particles [5].

Dry powder coating or hybrid mixing is a process where fine guest particles are adsorbed on to the surface of host particles under high impaction and shear forces [6-15] and Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011]. The process generates forces of attraction between guest and host particles that are stronger than the weight of an individual fine guest particle resulting in deposition of the fine particles and synthesis of composite particles with improved functionalities or new properties. The forces of attraction range between van der Waals, electrostatic, hydrogen bonding and capillary forces (only generated in blends with some moisture content) [16-20]. Several applications in the pharmaceutical industry have been reported for dry coated particles and include enhancement of flowability and dispersibility of cohesive actives [10, 12, 16, 21], improvement in content uniformity and modified drug dissolution [22-24]. These applications can produce significant advantages for enhancing process and manufacture of pharmaceuticals as well as address clinical challenges encountered in drug delivery [22-24]. A thorough overview of technologies used in dry coating was reported in our recent review [5]. When compared to engineering, the application of dry coating in pharmaceutical industry is underutilised owing to the limitations encountered with the current technologies such as heat generation (as in mechanofusion), particle attrition (as in hybridiser) or contamination (as in magnetically assisted impaction coater) [5, 15, 23, 25-27]. Nevertheless, the

process is promising being a one-step, environmentally friendly, solvent-less process that does not require additional drying or produce by-products [6, 9, 10, 15, 28, 29]. As there is currently little information available on the characterisation of the composite particles produced using dry coating, this review discusses powder sampling techniques which are key in pharmaceutical processing followed by a comprehensive evaluation of relevant characterisation techniques. The present work will highlight powder blend sampling process followed by evaluation of the different functionalities that can be introduced through dry coating. The last section will discuss the different surface profiling techniques to determine the extent and efficiency of surface coating. The overall objective of this article is to inform the reader of the various potential functionalities that can be introduced through the different dry coating processes (completely solvent free as opposed to techniques which utilise dry deposition as a part of the process) and the recent advances in surface characterisation tools to study changes in particle surface properties.

### **Powder sampling**

#### **Poor blending or inaccurate sampling?**

More than 75% of the pharmaceutical dosage forms are formulated as tablets or capsules that are processed using powder blends. Therefore, blend homogeneity is vital and reliable sampling and characterization methods are critical processes [30, 31]. Content uniformity in the final dosage form cannot be attained without a uniform mix that does not undergo any rearrangement between blending and compression-filling operations [32, 33]. The ultimate purpose of sampling is to collect a specific quantity of the powder that is expected to be representative of the entire powder bed. It entails a high level of accuracy to ensure content uniformity and physical homogeneity (e.g., particle size). Representative sampling encapsulates the process of identifying the appropriate samples with respect to location and time from within the wider powder bed as well as the selection of suitable sampling techniques [30, 34] and P.M Portillo, PhD thesis, The State University of New Jersey, 2008]. The two most important factors in accurate characterisation of the blend are sampling procedures and sampling tools as depicted in Figure 1 [31, 35].

## Sampling technique

Although the best sampling technique is to test the final dosage form for content uniformity, in process testing provides the formulator with the option of identifying any intervention if needed [36, 37]. Sampling locations and the number of samples to be collected are the two main variables in sampling procedure. To develop an effective sampling procedure, proper understanding of the basic dynamics of the blending equipment and the limitations of powder sampling should be initially addressed. Effective sampling requires collection of adequate number of representative samples from the entire mix taking into consideration areas of poor mixing (identified through prior evaluation of blending device) whilst obtaining enough samples to create accurate and reproducible results without the need for over-sampling. Although, greater number of samples usually led to more accurate results, the objective of any sampling scheme is to gather reliable results with the fewest number of samples [36, 38-40].

Prior to commencing sampling, the following needs to be determined as summarised in Figure 1: appropriate blending time, speed range, dead spots in the device as well as the location where segregation could occur particularly in the intermediate bulk containers. To measure the true uniformity of the blend, sample size should be identified and the effect of sample size should be studied [41]. Sample size could vary between 1-10 times the final dosage units and the Food and Drug Administration (FDA) guidance states that justification for sample size needs to be provided when the size exceeds 3 times the final unit dosage form [38]. However, in dry powder coating, the process may need to be tuned as the time to obtain the sample is crucial and dependent on the duration for the formation of composite particles which in turn is dependent on the type of equipment used as well as the processing conditions.

The FDA recommendations for sampling process involve collection of three replicates from each location. A total of 10 locations need to be selected from different zones in the powder bed and assayed. Relative standard deviation (RSD)  $\leq 5\%$  is essential for all the samples tested while individual results need to be within  $\pm 10\%$  of the mean value of the final unit dosage form [38].

Variability within the sampling could be attributed to either the sampling technique, analytical method or the mixture homogeneity [38, 41]. For cohesive powder blends, the variation in content within different regions could be attributed to the presence of agglomerates [38].

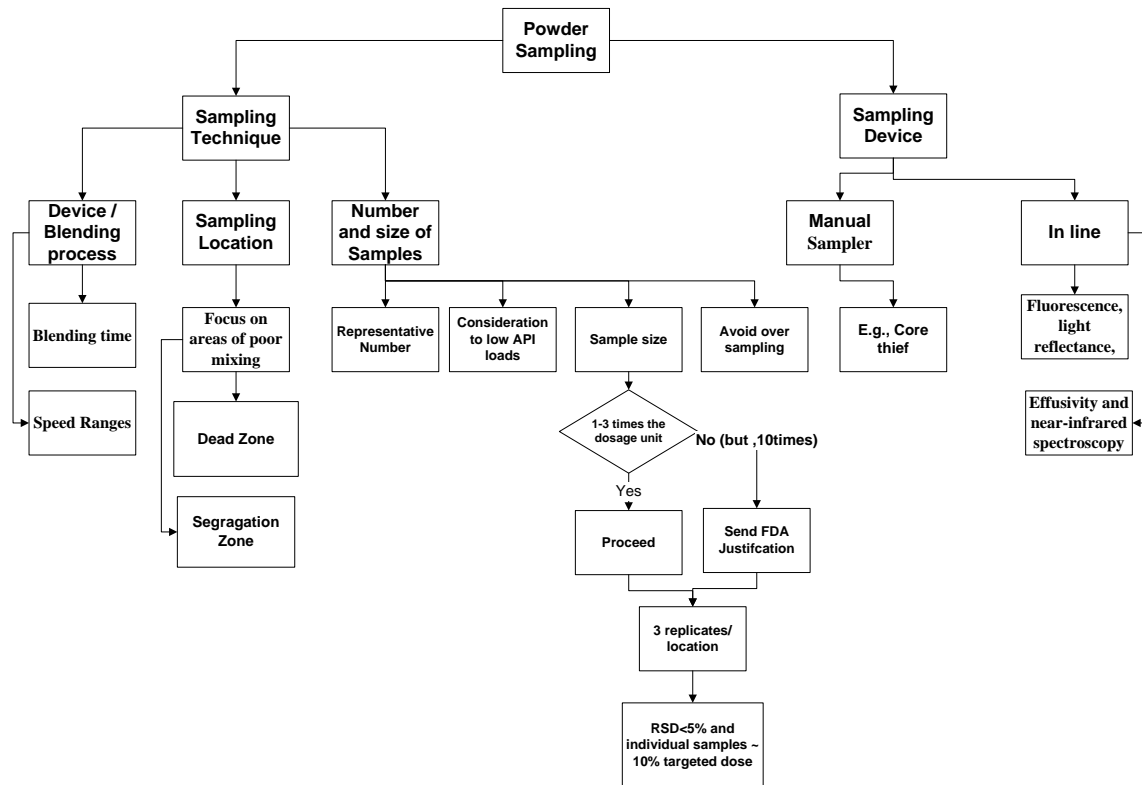


Figure 1: Flow chart highlighting the powder sampling process elements. The main components are sampling technique and the sampling device.

The blending uniformity working group (BUWG) from Product Quality Research Institute (PQRI) set recommendations on the use of stratified sampling of blend and dosage units in order to demonstrate the adequacy of mixing within the blends [38]. Based on the report, the FDA established the guidance for industry on stratified in-process sampling. Stratified sampling is a sampling method for dosage units that is collected according to predefined intervals and targeted locations (anticipating the locations with greatest potential to produce non uniform content). Results from these tests are used to monitor manufacturing process (i.e., the selected process for monitoring is the one responsible for causing the greatest variability in the final dosage form) [38, 42]. A recent study has developed an in-line NIR (near infra-red) spectroscopy coupled with fibre optic to measure content uniformity [41].

The fibre optic probe measures the intensity of the reflected light from the powder bed surface using photocells and can be used to determine sample homogeneity.

### **Sampling devices**

A lot of the generally used sampling devices lack accuracy and could result in disruption of the powder bed during sampling as concluded by Muzzio and colleagues [31]. Besides, sampling errors could result from poor flow of the cohesive mixtures into the sampling device. The most accurate and reliable results were produced when the core sampler was used. The core thief sampling device is based on the principle of enveloping a static portion of the powder bed and can be used to obtain sample without disturbing the bed structure. Withdrawal of the sample prevents segregation and further contamination/mixing with the other regions within the powder bed [30, 31]. Sampling tool and technique also vary according to the powder characteristics (cohesive versus granular free flowing). Although thief sampling remains the most commonly used sampling technique to assess powder mixing efficiency, other in-line analytical techniques were introduced that include light-induced fluorescence, light reflectance, effusivity and NIR spectroscopy [30]. For dry coated particles, sampling would probably follow the requirements of free flowing powders as opposed to cohesive blends as dry coating has been shown to significantly enhance flowability of cohesive powders. However both the duration and the sample location need to be determined depending on the type of the equipment chosen to produce the dry coated particles.

### **Characterisation techniques**

#### **Functionality characterisation (characterisation of powder behaviour)**

Dry powder coating has been extensively employed to improve various functionalities with a focus on enhancement of flowability, fluidisation, aerosolization and dispersion properties [11, 12, 14, 16, 17, 23, 24, 43, 44]. Inclusion of sub-micron fine guest particles on to the surface of micro-sized cohesive host particles resulted in the formation of surface asperities that reduce surface contact between cohesive particles thereby enhancing flowability, dispersibility or fluidisability [11, 17, 19, 45, 46]. Furthermore, production of homogenous blend using dry coating was reported in multiple studies [14,

29, 47]. In other applications, research from [15, 29, 48-59] investigated the use of dry coating to enhance the dissolution behaviour of insoluble actives based on the principle of dispersion of agglomerated cohesive particles which in turn maximises the surface area and results in enhanced dissolution. Various different hydrophilic polymers have been studied whereby the fine guest particles (drug) were deposited on to the surface of wettable hosts which in turn produced a synergistic effect in drug dissolution because of the fine drug particles (larger surface area) and the wettability of the host particles. The different techniques to study the characterisation of the resultant particles have been described in detail in the section covering techniques for dry coating characterisation.

**Flow properties (flowability, dispersibility and fluidisability)**

Owing to the importance of flow behaviour of powders, various characterisation techniques have been developed to describe the flow behaviour that relates to the surface interaction between components of the dry coated blend [60]. Upon dry coating, composite particles with improved flowability, dispersibility, and fluidisability were produced [61]. The following techniques were employed in characterising these properties. Each technique possesses its advantages and limitations as summarised in Table 1.

**Angle of repose (AoR)**

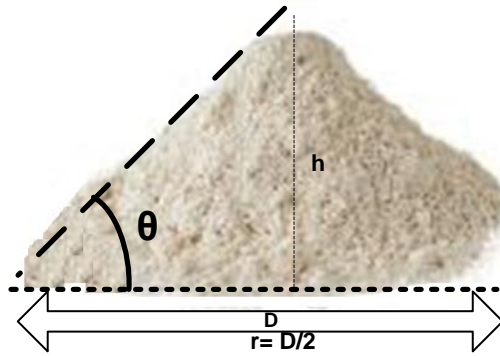
AoR is a direct measure of flowability; the test reflects the resistance of material to movement as a result of interparticulate friction. It is one of the official compendial tests (USP <1174>) for flowability measurements. Although the results could vary according to the procedure used, it has its applications in pharmaceutical industry owing to the ease of equipment set up and use. AoR is a measure of the internal angle formed between the cone-like pile of the powder and the horizontal base (Figure 2) using either a static funnel height or fixed base diameter [60]. The diameter and height of the powder cone are measured and angle of repose (AoR=  $\theta$ ) is calculated using equation 1:

$$\theta = \tan^{-1} \times \frac{h}{r} \dots \dots \dots Eq. 1$$



Table 1: Summary of flow properties analysis techniques highlighting the main advantages and limitations

Measured Flow Property	Techniques	Advantages	Limitations	References
<b>Flowability and Interparticulate friction</b>	Angle of repose	<ul style="list-style-type: none"> <li>• Ease in processing.</li> <li>• Cost effective that is based on basic laboratory devices</li> <li>• Ideal for initial screening and investigation of improvement in flow properties upon dry coating</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitive to the method used, low precision with high inter and intra subject variability.</li> <li>• Difficult to calculate the angle in non-uniform heaps with low reliability for cohesive powder</li> </ul>	[60, 62, 63] and*
	Bulk and tapped density	<ul style="list-style-type: none"> <li>• Compendial procedure</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitive to the device used</li> <li>• High subjectivity particularly in cohesive powder not levelling well in the cylinder</li> <li>• Cohesive powder adhere to walls of the cylinder thus affecting volume</li> </ul>	
	Hausner ratio and Carr index		<ul style="list-style-type: none"> <li>• Indirect measures based on bulk and tapped density</li> </ul>	
<b>Fluidisability/ Flowability</b>	Aeration test	<ul style="list-style-type: none"> <li>• Indicate the changes in flowability upon aeration</li> <li>• Enable conditioning of the sample prior analysis</li> <li>• Resemble actual manufacturing process</li> </ul>	<ul style="list-style-type: none"> <li>• Requires special device</li> </ul>	[24]
	Vibrated packing density	<ul style="list-style-type: none"> <li>• Initial fluidisation and ultrasound measurement of volume.</li> <li>• Less subjectivity</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitive to the used device.</li> <li>• Higher cost tag compared with aeration test</li> </ul>	Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011].
	Shear Test	<ul style="list-style-type: none"> <li>• Thorough and precise measurement of fluidisability/flowability</li> <li>• Shows the properties in consolidated state</li> <li>• Compendial procedure</li> </ul>	<ul style="list-style-type: none"> <li>• Requires special devices</li> <li>• Requires pre-conditioning by the application of consolidation force</li> <li>• Results varies according to the used device</li> </ul>	[60] and*
<b>Dispersibility</b>	Aerosizer	<ul style="list-style-type: none"> <li>• The change in particle size upon the increase in dispersion pressure</li> </ul>	<ul style="list-style-type: none"> <li>• Requires special device</li> <li>• High cost tag</li> </ul>	[61]
	Near infrared spectroscopy to a flowing powder	<ul style="list-style-type: none"> <li>• Determine the noise resulting from the flow of powder</li> </ul>		[64]
<p>*see: <a href="http://nordicrheologysociety.org/files/2013/10/16-Schulze-Shear-Testing-of-Powders-for-Process-Optimization.pdf">http://nordicrheologysociety.org/files/2013/10/16-Schulze-Shear-Testing-of-Powders-for-Process-Optimization.pdf</a>.</p>				



**Figure 2:** Schematic diagram for Angle of Repose (AoR) highlighting the angle formed between the horizontal surface and the cone like powder formed after passing through funnel.

Where (h) is the height of the powder cone and (r) is the radius. Values of AoR exceeding 45° indicate poor flowability. When the AoR is  $\leq 40^\circ$ , the powder is said to have fair flow properties and inclusion of flow aid is not required. On the other hand,  $31^\circ \leq \text{AoR} \leq 35^\circ$  is considered as good flowing powder while values  $\leq 30^\circ$  represent a powder with excellent flowability [60].

### **Bulk and tapped densities / Carr Index and Hausner ratio**

Bulk and tapped densities provide information on the packing properties of powder. Carr index and Hausner ratio are derived from both bulk and tapped density. Bulk and tapped densities are determined using graduated cylinder technique. A powder is poured into a graduated cylinder without compacting. The weight (M) and the apparent bulk volume ( $V_0$ ) are measured and used to calculate the apparent bulk density ( $P_b$ ) using equation 2:

$$P_b = M/V_0 \dots \dots \dots \text{Eq 2}$$

The bulk density gives an indication of the flowability with flowable powders demonstrating high bulk density [65]. Tapped density is the density change due to the mechanical tapping of the cylinder containing the powder mix. Upon tapping of the powder mix, tapped volume ( $V_t$ ) is recorded and tapped density ( $P_t$ ) is calculated from equation 3:

$$P_t = \frac{M}{V_t} \dots \dots \dots \text{Eq 3}$$

Carr index and Hausner ratio parameters are interrelated and results from tapped and bulk densities are used to calculate flowability [60, 66]. Carr index (I) is calculated using equation 4:

$$I = \frac{(\rho_t - \rho_b)}{(\rho_t)} \times 100 \dots \dots \dots \text{Eq 4}$$

Where  $\rho_t$  is the tapped density,  $\rho_b$  is the bulk density. Values less than 15% indicate powder with good flow characteristics. Whereas, (I) over 25% represents a powder with poor flowability [60].

Hausner ratio (HR) is an indirect representation of the flow properties that can be calculated from equation 5:

$$HR = \frac{P_t}{P_b} \dots \dots \dots \text{Eq 5}$$

Where ( $P_t$ ) is the tapped density and ( $P_b$ ) is the bulk density. USP-29 [77] specifies that a ratio of < 1.25 represents a powder with good flow properties. Ratio >1.34 is an example of a powder with poor flow properties. It is worth mentioning that angle of repose, Hausner ratio and Carr index are not intrinsic properties of the powder and are related to the procedure used to test them [60].

Research from [43] investigated the impact of dry coating particles to determine changes on their flowability. Three model cohesive drugs including salbutamol, triamcinolone and salmetrol were studied for flowability changes. All the three drugs had low bulk density possibly due to agglomeration of the fine particles. However, upon dry coating, the results showed that there was an increase of 50-100% in bulk density. The particles from flowable powder (upon dry coating) did not show a substantial change in tapped density when compared to bulk density as would be expected from a free flowing powder.

No single test can provide a comprehensive view of the flowability of powders [Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011]. Overall the above tests provide an insight of the interparticulate adhesiveness [11, 67]. Fluidisability of the powder bed is usually measured using aeratability using powder rheometer [68].

### Aeration test

Aeration test is used to measure changes in flowability/ fluidisability of the powder upon aeration. The procedure involves placing a vessel over a perforated base that is connected to air inlet with conditioning blade (Figure 3A). Increasing air pressure is introduced into the system coupled with measuring the force required to move the blade (aeration energy). The higher the aeration energy needed for fluidisation, the poorer the flow properties of the powder (Figure 3B). The ratio between aeration energy to air velocity is termed the basic flowability energy (BFE), and the aeration energy at air velocity of 10mm/s is known as aeration ratio (AR) [24]. Zhou *et al.* [24] used the test to determine the enhancement of fluidisation behaviour of dry coated micronized lactose with magnesium stearate as guest particles.

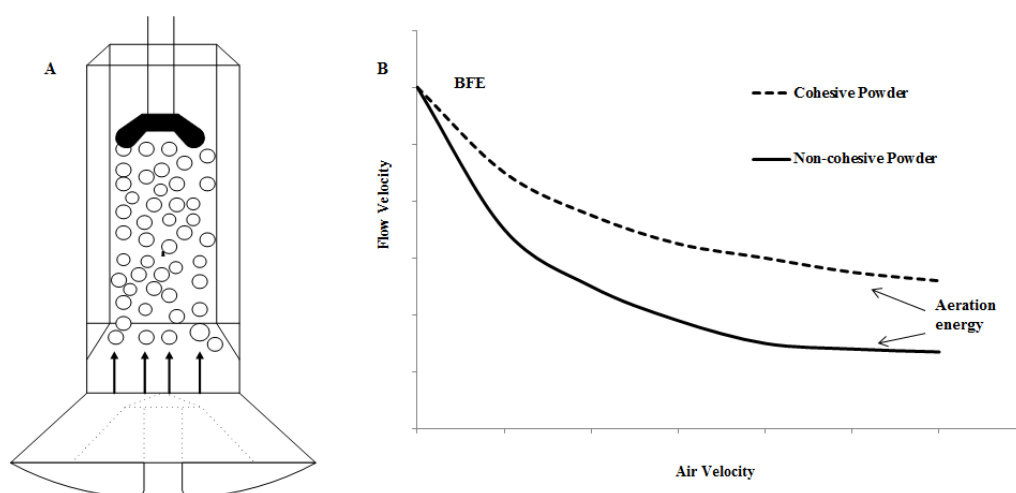


Figure 3: Schematic diagram showing the aeration test (A) where air is introduced from the bottom of the perforated chamber containing the tested powder while testing the aeration energy (B) diagram showing the difference in aeration energy between cohesive and non-cohesive powders.

### Vibrated packing density

Similar to aeration test, this technique measures bulk density for cohesive powders. The test has been employed to identify the improvement in powder flowability upon dry coating process. The process is

built on initial fluidisation of the powder bed followed by allowing adequate time to settle. Ultrasound is used to measure the volume of a predetermined weight of powder to assess the solid fraction. Flowable powders tend to have higher solid fraction than less flowable counterparts [Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011].

### **Shear Cell test**

The USP <1174> describes shear cell method for providing a thorough and precise assessment of the powder flow behaviour [60]. There are various methods employed to measure the shear test and the fundamental principle is based on powder mechanics. The uniaxial compression test is executed when a cylinder is filled with the sample powder followed by application of vertical pressure on to the sample (consolidation stress ( $\sigma_1$ )) as depicted in Figure 4. Upon the presentation of consolidation load, the bulk density and powder strength increases. Then the cylinder is removed leaving the consolidated powder. This is followed by the application of increasing vertical compression strength on the sample until the splitting of sample bed. The stress responsible for breaking the consolidated powder is called the unconfined yield stress ( $\sigma_c$ ) [69] and see: <http://nordicrheologysociety.org/files/2013/10/16-Schulze-Shear-Testing-of-Powders-for-Process-Optimization.pdf>.]. Both bulk density and yield stress increase with the increase in consolidation stress ( $\sigma_1$ ). The value representing  $\sigma_1/\sigma_c$  provides flow function coefficient (FFC). As the strength of the powder needs to be overcome to initiate flow, the higher the value of FFC the better the flowability of the material [see: <http://nordicrheologysociety.org/files/2013/10/16-Schulze-Shear-Testing-of-Powders-for-Process-Optimization.pdf>]. Values of FFC range from 1-10, where a value <4 represents a cohesive powder whereas FFC exceeding 10 is an indication of free flowing powder [14, 61, 68] and Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011].

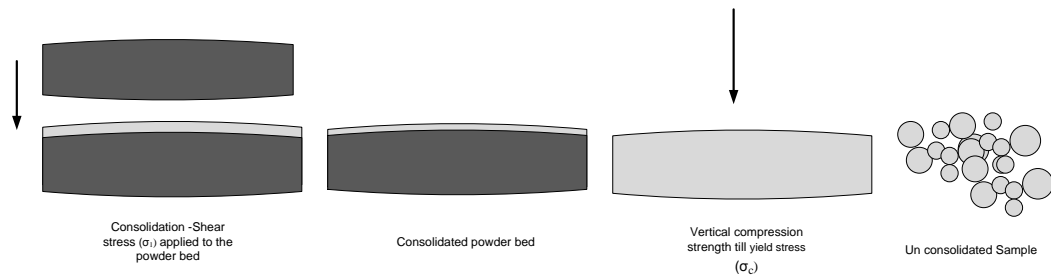


Figure 4: Schematic diagram showing the process of shear test. Consolidated shear stress is applied to a powder bed followed by vertical compression to the consolidated powder till yield stress is obtained to produce unconsolidated powder.

Yield limit is a measure of the shear stress needed to initiate powder flow. Shear test is carried out as described above where the consolidated powder bed is split using an increasing normal stress. Shear stress is measured and plotted against the normal stress [see: <http://nordicrheologysociety.org/files/2013/10/16-Schulze-Shear-Testing-of-Powders-for-Process-Optimization.pdf>]. Cohesion is calculated from the graph when the shear stress is zero (the higher the cohesion value the higher the interparticulate forces). A study by [43] using shear test revealed that a reduction in cohesive forces upon dry coating was obtained as demonstrated by a higher shear stress value at each normal stress point for uncoated compared with dry coated particles as a result of reduced interparticulate forces.

The difference between AoR and shear testing is that AoR is carried out without subjecting the powder bed to any consolidation (zero external consolidation force) unlike the shear test where the test is carried out after initial consolidation of the powder bed [60, 61].

### **Particle size analysis/ aerosizer**

The use of particle size analyser (aerosizer) to determine the dispersibility of composite particles upon dry coating has been reported in various studies [20, 43, 61, 68]. Studying the change in particle size distribution as a function of dispersion pressure using particle size analyser with laser diffraction was employed to determine the extent of agglomeration and de-agglomeration behaviour of the powder blend after dry coating [61, 68]. The extent of dispersibility was calculated from the gradient obtained upon plotting pressure titration curve (plotting the D90 (maximum size for 90% of the sample) value

versus dispersion pressure) with low values indicating good dispersibility [64]. It was also noted that for dry coated particles the particle size (D90 value) did not reduce upon increase of dispersion pressure whereas uncoated particles showed a drastic reduction in particle size upon the increase in dispersion pressure (therefore producing higher gradient value). This difference was attributed mainly to the breakdown of agglomerates of the uncoated particles upon increase of dispersion pressure. These results provide an insight of dispersibility of the material as reduced/lowering of dispersion pressure translates into higher dispersibility underpinned by reduced cohesivity which enhances flowability. Besides, use of particle size analysis also provides vital quantitative data on the degree of particle attrition which is one of the important factors which requires optimisation in dry coating [43, 61]. Real time aerosolisation characterisation of dry coated powders using laser diffraction systems has also been used to investigate optimum coating percentage of magnesium stearate guest particles over salbutamol sulphate host particles. 2% magnesium stearate was calculated as the optimum percentage for dry coating that resulted in de-agglomeration of cohesive agglomerates causing improved aerosolisation [70].

### **Near infrared spectroscopy (NIR)**

NIR characterisation technique was introduced as a means to quantify flowability of powders. It is an in-line process based on capturing the noise from powder flowing from a funnel with the principle that less noise is produced from free flowing material. A flow intensity index is used to evaluate the consistency of powder flow (it is the inverse of the noise spectra). Consistency of powder flow was determined upon plotting the flow intensity index versus time with an aim to understand the flow properties [64] and Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011].

### **Porosity**

The measurement of porosity using gas displacement technique for dry coated powder bed was reported to provide an indication of the packing properties [68]. Results from [68] demonstrated that dry coated blends have lower porosity compared with physically mixed particles. This difference was attributed to the increase in packing of particles upon the reduction of interparticulate adhesive forces

producing more compact particles. Additionally, smaller fine particles get lodged into the pores of the host particles resulting in reduction in porosity.

### **Content uniformity and dissolution studies**

The determination of blend homogeneity for the dry coated composite particles is carried out according to the compendial requirement for actives and excipients [71, 72]. Furthermore, dissolution studies that relate to modification of drug release for model compounds upon dry coating were studied with a view to developing functionalised particles with modified release rate [19]. The methods described in compendia (USP methods using either apparatus I or II) were the most utilised techniques to study the changes in release behaviour of various functionalised particle formulations [71].

### **Crystallinity**

During dry coating, particles are exposed to high degree of compression and shear forces. Some devices produce particle attrition (e.g., high force devices like hybridizer, mechanofusion or Fluid energy mill) that might result in the formation of an amorphous form or induce polymorphic transformations of the host or guest particles [22, 29, 73]. In their research Höckerfelt and Nystorm [74] demonstrated that crystalline material subjected to mechanical force (without particle attrition or micronisation) can transform into an amorphous state which can impact on the properties of the resultant particles. The change in material crystallinity will influence its solubility, bioavailability as well as stability [22, 73]. Ishizaka [6, 29] used X-ray powder diffraction analysis (XRD) to examine crystallinity of processed material (particularly APIs). The results demonstrated a change of the API (oxyphenbutazone) from crystalline to amorphous state upon dry powder coating which further upon storage over a seven month period produced variable results (degree of crystallinity of oxyphenbutazone was reduced to 12.8% after 4 days of dry coating and was increased to 43.3% after 7 months). Furthermore, Raman spectroscopy as well as differential scanning calorimeter (DSC) were utilised to study and examine crystallinity. Using DSC, the degree of crystallinity was calculated from the ratio between heat of fusion of micronized particle and the heat of fusion of original particles [22].



### **Wettability**

Production of dry coated composite particles with either enhanced hydrophilicity or hydrophobicity has been reported [23]. To verify the change in hydrophilic nature, wettability test was carried out using the rate penetration method. A reduction in the amount of water absorbed was noted when corn-starch (15 $\mu$ m) host particles were coated with 1% silica (0.3 $\mu$ m) using MAIC (Magnetically assisted impaction coating) dry coating. Untreated corn-starch particles absorbed almost 60% of their total weight of water, whereas dry coating dropped it to 18% of its weight [23].

### **Particle dynamics and Surface profiling characterisation for dry coating**

The movement of particles within the powder bed during mixing and dry coating process plays a fundamental role in the dynamics of mixing. Therefore, developing knowledge of the particle dynamics can enable the understanding of the dry coating mechanism and therefore, helps in enhancing the design of the dry coating device [75]. Besides, characterisation of a thin coat of the guest particles over the host is challenging due to the need for high resolution analytical techniques that can distinguish changes in surface properties [76]. Table 2 summarises the techniques that have been studied in characterisation and understanding surface coating process in dry coating.

### **Positron Emission Particle Tracking (PEPT)**

Positron Emission Particle Tracking (PEPT) has been employed to identify the mobility of dry coated versus uncoated blends [Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011]. PEPT offers thorough quantitative information on the internal flow patterns and the dynamics of the dry coating process [41]. An increase in powder flowability is related to the increase in its mobility. The test is based on the principle of tracing the movement of a single radioactive moiety as a function of time. Emission of gamma radiation from the radioactive candidate during its movement within the device can be used to track particle flow with a resolution of one tenth of a mm [41] and Beach, L., PhD Thesis, New Jersey Institute of Technology, 2011]..

Similarly radioactive particle tracking (RPT) is another technique that measures the movement of particles in circulating fluidised beds. It uses Sc46 (Scandium) as the source for gamma-ray emissions but consists of different detector system when compared to PEPT [75].

## **X-ray Photoelectron Spectroscopy (XPS)**

XPS is a characterisation technique that maps particle topography (2-10nm depth) and provides specific chemical information on coating quality of guest particles. It not only reveals the elemental composition present on the surface but also provides vital information on particle bonding. The principle is based on an x-ray beam bombarding the surface of a sample and exciting electrons that escape from the atom as portrayed in figure 5. These events are captured by electron energy analyser that produces an energy spectrum [77]. Research from [76, 78] investigated dry coating of lactose and ibuprofen particles with magnesium stearate using XPS. The elemental composition of the untreated samples did not show the presence of magnesium on the surface of lactose particles, while an increasing amount of magnesium was detected with increasing the concentration of magnesium stearate with a concomitant reduction in the intensity of oxygen atoms that represented the surface of lactose particles. Additionally, the intensity for C-C bond (characterising magnesium stearate) increased with the increase in coverage while that of C-O bond (characterising Lactose host) was reduced. It is worth mentioning that the accuracy of the

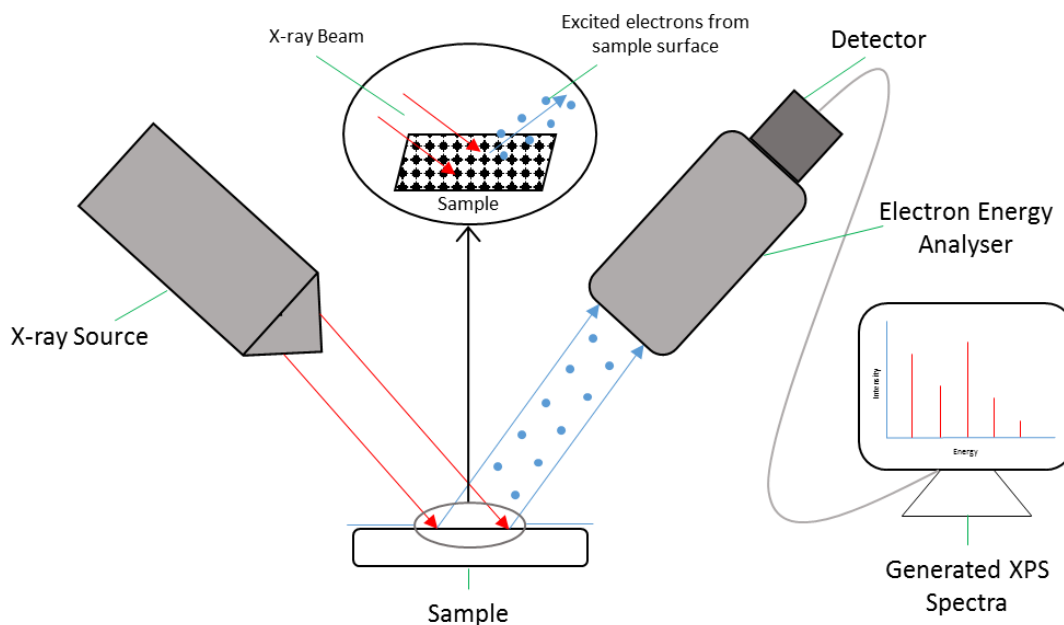


Figure 5: Schematic diagram showing the XPS process, whereby the sample surface is bombarded with an x-ray beam resulting in the excitation of electrons from the atom. The electron energies are detected and converted to an XPS spectrum for the sample.

technique is limited since the guest particles occupy up to 2nm of the guest surface whereas the surface mapping penetrates up to 10nm of the particle surface. Nevertheless, this technique can be used to distinguish changes in surface morphology upon dry coating and provides a reasonable quantitative estimate of surface loading of the guest particles [77, 78].

### **Time- of -flight secondary ion mass spectrometry (TOF-SIMS)**

TOF-SIMS is an analytical method that is used for surface profiling and provides chemical information pertinent to elemental, isotopic and molecular structure of the first 1-2 monolayers of small particles [76]. The basic principle of TOF-SIMS is based on energy rich ion beam bombarding the primary targeted atom that generates a secondary ion on the surface of the sample which in turn is detected by a mass spectrometer [79]. TOF-SIMS signal mapping for both lactose (host) and functionalised lactose (with magnesium stearate) upon dry coating was investigated by [76]. Initial experiments focused on extracting individual mass spectra for both the host as well as the guest

particles (for e.g.,  $C_6H_{11}O_5$  ring to represent lactose and magnesium signals to represent magnesium stearate). Uncoated lactose particle signal map revealed the ring ( $C_6H_{11}O_5$ ) for lactose, however, when magnesium stearate was adsorbed to the surface of lactose by dry coating, the signal map showed an increase in the density of magnesium signal with increase in the concentration of magnesium stearate (with a concurrent reduction in the density of signal for  $C_6H_{11}O_5$ ). One of the key outcomes from these studies was the application of TOF-SIMS to quantify the percentage of guest material that provides optimal surface coverage thereby significantly influencing the resultant functionality of the dry coated particles [76]. Additionally, TOF-SIMS was investigated to profile surface coating of ibuprofen host particles with magnesium stearate that was used to improve lubrication, compressibility and flowability of cohesive ibuprofen [78].

### **Scanning Electron Microscopy (SEM)**

SEM can be used to qualitatively determine particle morphology as well as the quality and extent of dry coating. It enables the investigation of the changes in particle size and shape which provides vital information on the suitability of processing technology (particle attrition – major or minor) as well as quality of the final finished product. SEM has been extensively utilised in multiple studies to evaluate the morphology of dry coated particles [19, 24, 29, 43, 61, 80]. SEM coupled with energy dispersive X-ray analysis (EDX) has been used for qualitative evaluation of coating efficiency [19, 61, 68]. The work from [61] using SEM to demonstrate the change in cohesiveness of powder upon dry coating revealed that the coating of fine particles over the host particles reduces particle agglomeration. Elemental mapping using SEM-EDX confirmed the deposition of fine leucine particles over potassium chloride host particles which were used as the basis for elucidating the enhancement of flowability of the resultant dry coated particles.

### **Fourier transform infrared spectroscopy (FTIR)**

FTIR spectrum usually represents the fingerprints of materials where absorption peaks represent the frequency of vibrations between the bonds within the molecule. Each spectrum is formed when the energy absorbed from a particular frequency of infrared radiation leads to the excitation of a specific

bond within the molecule to a higher state of vibration by stretching or bending. Specific bonds can easily be identified at different spectral regions and the peak size in each spectrum is a direct indication of the amount of material available within the sample [81, 82] [29, 83]. Pfeffer and co-worker [23] used FTIR spectrum to identify the chemical reaction upon dry coating using MAIC where model host (corn-starch or cellulose) and guest (silica) particles upon dry coating resulted in the reduction of the intensity of FTIR spectra of OH group. This reduction in surface OH group intensity was attributed to the reaction between acidic silanol group (-Si(OH)-) on the surface of silica and the neutral hydroxyl groups on corn-starch/cellulose surfaces forming hydrophobic (-O-) groups with a release of water molecule.

### **Specific surface area**

Determination of specific surface area of powder is carried out according to USP <846> using gas (nitrogen) adsorption followed by quantitative analysis of the amount of adsorbed gas using BET theory (Brunauer, Emmett and Teller) [60]. Dry coating of particles results in changes in particle surface characteristics which in turn influences the total surface area [76]. A study evaluating the reduction in specific surface area upon mechanofusion of lactose host particles with (0.5% and 1% ) magnesium stearate was attributed to the reduction in surface asperities (irregularities) of lactose where magnesium stearate (guest) fills the gap producing a smoother surface for the resultant composite particles (also supported by SEM images). The reduction in specific surface area varied according to the percentage of added magnesium stearate (MS); untreated (1.079 m<sup>2</sup>/g), at 0.5% MS (0.826); 1% MS, (0.77) and at 5% MS (0.913). This technique also enabled the determination of the optimal percentage of MS to produce complete coverage. An increase in specific surface area with 5% MS indicated that the amount of MS was greater than that was needed for complete surface coverage of the host [76].

### **Surface free energy**

The total surface energy is the sum of dispersive and specific surface energies with the former related to van der Waals forces that are universally to all particles surfaces. The specific surface energy on

the other hand relates to the interactions including polar, acid-base, hydrogen or ionic bonding. Inverse Gas Chromatography (IGC) was used to study the changes in surface energy of dry coated particles [11, 80]. It enabled the evaluation of changes in surface energy upon dry coating and its resultant effect on particle functionality such as enhancement of flowability [80]. The method developed by [80] using IGC was used to compare dry coated lactose (with magnesium stearate) using mechanofusion with regular mixing in turbula blender. Heptane, octane and nonane were used to determine the non-polar (dispersive) surface energy whereas dichloromethane and ethylacetate were used as solvents to evaluate the polar (specific) surface energy. The results revealed that the total surface energy of lactose with 5% magnesium stearate was significantly lower following dry coating compared with conventional mixing which provided the evidence for the enhancement of flowability and dispersibility of dry coated mixture compared to conventionally mixed powder blend. Additionally, AFM (atomic force microscopy) and contact angle methods were used to determine the free surface energy [80]. The use of atomic force microscopy (AFM) to study particle properties such as surface roughness provided the evidence for flowability enhancement as dry coating of sub-micron particles with nano particles showed an increase in roughness which reduced the contact area between particles [11, 24, 65]. Chen and colleagues [11] used images from AFM to estimate the interparticulate adhesion. Saharan [54] reported the use of AFM to investigate the increase in affinity of guest API (zanamivir) to Lactose (host) when the molecular arrangement in zanamivir changed from crystalline to amorphous form.

### **Numerical Simulation using DEM (Discrete Element Method)**

Numerical simulation of dry powder coating devices has been reported [23, 84, 85]. Chen and co-workers [84] conducted numerical simulation for mechanofusion using DEM to visualise air flow pattern and dynamics of the systems, and offered an understanding of the influence of various operating parameters on the resultant particle characteristics. Similarly, a three-dimensional DEM was used to study the compression and shear forces involved in theta composer [27]. It was found that the shear force and hence coating is proportional to the speed of the rotor tip and mixing time but inversely proportional to the distance between the rotor and the wall. In another study by Nakamura

and colleagues [86] numerical simulation of dry coating in RFB (rotating fluidised bed) using DEM-CFD (Discrete Elemental Modelling coupled with Computational Fluid Dynamics) enabled the researchers to simulate the three-dimensional fluidization of particles within the system. Mass distribution was visualised and the effect of different processing parameters were also investigated. The results were used to provide additional evidence of the coating process using RFB compared with conventional fluidised bed. Recently [87] a hybrid DEM with PBM (population balanced modelling) was employed to develop a better understanding of the mixing process using conventional mixers. DEM simulation provides information at particle level including its velocity, while PBM is a reflection of blending dynamics affecting the mixing process which includes RSD (relative standard deviation) and blend composition.

Table 2: Summary of particle dynamics and surface profiling techniques for dry coated composite particles highlighting the used techniques, their advantages and limitations

Technique	Advantages	Limitations	Reference
PEPT	<ul style="list-style-type: none"> <li>Quantitative analysis of dynamics of the particles within the dry coating device.</li> <li>Can be used for opaque devices entailing metals with multiphase components</li> </ul>	<ul style="list-style-type: none"> <li>High cost tag</li> <li>Could not fit all dry coating devices</li> <li>Requires specialised personnel</li> </ul>	[88]
RPT	<ul style="list-style-type: none"> <li>Quantitative analysis of dynamics of the particles within the dry coating device.</li> </ul>		[75]
XPS	<ul style="list-style-type: none"> <li>Elemental analysis of upper most layer 2-10nm</li> <li>High accuracy and specificity</li> </ul>	<ul style="list-style-type: none"> <li>The depth up to 10nm allows for lower layer to be detected therefore no precise quantification</li> <li>Distinctive differences in elemental composition between guest and host is prerequisite to enable the identification of the coat</li> <li>High cost tag</li> <li>Requires specialised personnel</li> <li>Not suitable for thermolabile material</li> <li>Slight contaminations might alter the results</li> </ul>	[77, 78, 89]
TOF-SIMS	<ul style="list-style-type: none"> <li>Elemental analysis and quantification of upper most layer 2-5nm</li> <li>Ultrahigh sensitivity and specificity</li> <li>Very small sample size</li> </ul>	<ul style="list-style-type: none"> <li>High cost tag</li> <li>Requires specialised personnel particularly for interpretation and analysis of data</li> <li>Slight contaminations might alter the results</li> </ul>	[78, 79, 89]
SEM	<ul style="list-style-type: none"> <li>Qualitative analysis of the extent of coating</li> <li>Particle attrition could be detected.</li> <li>Simple techniques when compared to XPS and TOF-SIMS</li> <li>Very small sample size</li> </ul>	<ul style="list-style-type: none"> <li>Requires conditioning for the sample by coating to enhance the conductivity.</li> </ul>	[61]
FTIR	<ul style="list-style-type: none"> <li>Identify physical or chemical bonding between host and guest particles by changes in the intensity of specific spectra</li> </ul>	<ul style="list-style-type: none"> <li>Requires specialised personnel to analyse spectra</li> </ul>	[29, 83]
BET	<ul style="list-style-type: none"> <li>Identify the reduction in specific surface area upon coating. Used to identify optimum percentage of guest material to produce complete coverage.</li> </ul>	<ul style="list-style-type: none"> <li>Not suitable for thermolabile material.</li> <li>Require conditioning for the sample</li> </ul>	[60]
IGC	<ul style="list-style-type: none"> <li>Identify the change in surface energy (dispersive and specific) upon coating.</li> <li>Good for thermolabile material</li> </ul>	<ul style="list-style-type: none"> <li>Requires specialised personnel to analyse results</li> <li>High price tag</li> </ul>	[11, 80]
AFM	<ul style="list-style-type: none"> <li>Determine surface roughness at submicron level.</li> <li>Can be used to determine surface energy, enhancement in flowability and particle affinity.</li> </ul>	<ul style="list-style-type: none"> <li>Requires specialised personnel to analyse results</li> <li>Only for small particle size (submicron host and nano scale guest)</li> <li>High price tag</li> </ul>	[11, 54]
DEM	<ul style="list-style-type: none"> <li>Numerical simulation of particles within the device to understand the dynamics of the</li> </ul>	<ul style="list-style-type: none"> <li>Requires specialised personnel</li> <li>Extensive research owing to the big difference between guests to host particles</li> </ul>	[23, 84, 85]



	system	size.	
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## **Conclusion**

Dry powder coating is an emerging technique in pharmaceutical and chemical industries with diverse applications. A one step process produces composite particles with improved functionalities. The gap in this domain is due to the lack of user friendly processing equipment and characterisation techniques that enable understanding of the process and evaluation of the resultant functionalities. In this review, key characterisation techniques were addressed and adapted to understand particle functionalities to discuss coating performance. The knowledge of characterisation technique will enable formulators and researchers to select the optimal method for their formulation. The use of commonly employed flowability characterisation techniques like angle of repose, bulk and tapped densities are still of value for screening changes in flowability. However, emerging techniques such as aeration, shear cell test and particle size analyses for dispersibility provide an added value of enabling the quantitative analysis of the extent of dry coating necessary to achieve the target functionality. Complete coverage may not be required for specific functionalities as in the case such as flowability, dispersibility, and fluidisability. Hence correlating functionality assessment with the degree of coating should be targeted in formulation optimisation. Also, processing conditions could vary according to the desired functionality and physical properties of components. Therefore, advanced surface profiling techniques like XPS, TOF-SEMS, AFM, BET and SEM contribute to better understanding of the mechanism of coating. Evaluating the changes in surface energy, area and elemental analysis will facilitate formulation and device performance optimisation.

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