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Effect of particle properties on the flowability of ibuprofen powders

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ABSTRACT

Powder flowability is one of the key parameters in the pharmaceutical tabletting process. The flowability is affected by both the particles' properties and the tabletting equipment characteristics. Although it is generally accepted that powder flowability increases with an increase in particle size, quantitative studies and comprehensive theoretical insights into the particle property effects are still lacking. In this paper, ibuprofen, a non-steroidal drug widely used as an anti-inflammatory analgesic was chosen as a model material to assess the effect of particle properties on its flowability. Ibuprofen typically has a needle shaped morphology. The flowability of ibuprofen size fractions was studied in detail using two flow measurement methods. The separated fractions were also compared to magnesium stearate lubricated ibuprofen and its size fractions. The experimental results showed that powder flowability is significantly affected by both the particle size and size distribution. The finest size fraction that is separated from the bulk ibuprofen powder flows better than the bulk powder. For powders with narrow size distributions, the flowability increases significantly with the increase in particle size. In addition, admixing magnesium stearate to ibuprofen not only increases the flow function of the powder, but also reduces the internal friction angle. A theoretical analysis based on the limiting tensile strength of the powder bed was carried out and the flow conditions for particles of different size and shape were developed.

1. Introduction

Pharmaceutical products have very stringent requirements in terms of uniformity in content, consistency in appearance, longevity for storage, transportation and shelf life, which demands an exceptional degree of control in the manufacturing process. Direct compression is the most efficient process used in tablet manufacturing because it is fast, simple and comparatively inexpensive. Together with compression properties, the flowability of the powder mixture is one of the most important factors in this process. This is because a free flowing powder mixture can ensure a uniform feed from hoppers into the tabletting equipment so that a uniform tablet weight and drug content can be maintained (Kato et al., 2005). In addition, uneven powder flow could lead to excess entrapped air within powders, which in some high-speed tabletting conditions may promote capping or lamination (Staniforth, 2002). The flowability of the powder is affected by both the process design (including equipment characteristics) and particle properties. Particle properties that affect flowability include mean particle size, size distribution, particle shape, surface roughness and moisture content.

It is generally accepted that the larger the particles, the better the flow. Particles larger than 250 μm are usually free-flowing. As particle size falls below 100 μm, powders become cohesive and flow problems are likely to occur. Powders having a particle size less than 10 μm are usually extremely cohesive and resist flow under gravity (Staniforth, 2002). However, the effect of particle size and other properties on its flowability is also material specific and quantitative studies on the effect of particle size on powder flowability are still lacking. Köhler and Schubert (1990) studied the flow properties of fine alumina powders and found that the flow function (see Section 3.3 for definition) of the alumina is proportional to the median particle size to the power of 0.62 over the particle size range of submicron to 25 μm. Tomas (2001a,b) developed powder flow functions according to Jenike (1964) in terms of bulk powder internal friction angle, which is also a function of particle size. Li et al. (2004) proposed a flowability criterion which stated that the flowability of a powder is proportional to the particle size cubed. However, the flowability of different types of powders was compared and the effect of particle size was not verified explicitly. In the present study, a theoretical analysis on the incipient flow conditions was carried out first to explore the effect of particle size and shape on the bulk powder flow characteristics. This is followed by

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the experimental work on ibuprofen, a non-steroidal drug that is needle-shaped and widely used as an anti-inflammatory analgesic. The flowabilities of the bulk ibuprofen with and without magnesium stearate as well as different ibuprofen size fractions were studied in detail.

2. Theory

To theoretically analyze the effect of particle properties on flowability, first consider the conditions at which a powder would start to flow. Li et al. (2004) developed a quantitative model to predict the powder flowability based on the condition that the gravity of the particles for loosely packed powder exceeds its limiting tensile stress:

$$\rho_{\text{particle}} d^3 g \geq \frac{\alpha a}{\varepsilon} = \frac{\gamma^{1/3}}{\sqrt[3]{12\pi^2 h_r (1-\nu^2)^2 E^2}} \frac{a}{\varepsilon} \tag{1}$$

where ρ_{particle} is the particle density, d is the particle diameter, γ is the particle surface energy, ν is Poisson's ratio, h_r is the particle surface asperity, E is the particle Young's modulus, ε is the bulk powder bed voidage, which mainly depends on the particle size and shape, and a is the average interparticle contact surface area for each particle–particle contact. The assumption for the model is that only van der Waals and gravity forces apply to the bulk powder. As the contact area is a complex function of material properties, one cannot obtain an explicit relationship on the flow conditions.

The limiting tensile strength of a powder bed of spherical particles σ was given by Rumpf (1970):

$$\sigma = \frac{(1-\varepsilon)}{\varepsilon} \frac{F_H}{d^2} \tag{2}$$

where F_H is the particle–particle adhesion force. The average limiting tensile strength force (F_T) transmitted per particle in a bed of voidage ε, can be described (Molerus, 1982) as:

$$F_T = \frac{\pi}{6} \frac{F_H}{\varepsilon} \tag{3}$$

There are published constitutive models on the particle–particle adhesion force F_H, calculated from the van der Waals' force, such as those described by Rumpf (1990), Rabinovich et al. (2000a, b); and the JKR model (Johnson et al., 1971). However, there are various limitations on the model assumptions such as no local deformation used in the Rabinovich model. Tomas (2001a,b) developed more comprehensive models using adhesion forces including both elastic and plastic local deformation. A complete set of physical equations for steady flow, incipient yielding, powder consolidation, compressibility and flowability was also derived by including the powder's internal friction angle, the time-dependent internal friction angle and the tensile strengths of the consolidated and unconsolidated powder. However, the effect of particle size is not shown explicitly in these equations as the powder internal friction angle is a bulk material parameter and is a function of many other particle properties. We can, however, use the adhesion force model developed by Tomas to describe the incipient flow criterion based on the assumption that the gravity of the particles exceeds the total adhesive forces. The adhesion force for elastoplastic contact between two particles is (Tomas, 2001a):

$$F_H = (1+\kappa) F_{H0} + \kappa F_N \tag{4}$$

where κ is the material's contact consolidation constant and is a measure of irreversible particle contact stiffness or softness, F_N is the normal force applied to the powder and F_{H0} is the adhesion force between particles with no external normal force, which is approximately equal to $C_{H\,sls} h_r / 12 a_{F=0}^2$, where h_r is the particle surface asperity, $C_{H\,sls}$ is the Hamaker constant and $a_{F=0}$ is the inter-particle separation distance with no external forces.

Similar to the method used by Li et al. (2004), the incipient flow condition for each particle with diameter d in an assembly can be described using Tomas' adhesion model, Eq. (4) giving:

$$\rho_{\text{particle}} d^3 g \geq \frac{(1+\kappa) F_{H0} + \kappa F_N}{\varepsilon} \tag{5}$$

The adhesion force can be considered as a material property independent of particle size. For monosized particles, it has been shown in the literature that the packing voidage decreases with an increase in particle size (Feng and Yu, 1998; Yang et al., 2000). This relationship is found to follow the following simple relationship to relate ε to particle size d for powder of monosized spherical particles:

$$\varepsilon = -k_1 \ln(d) + k_2 \tag{6}$$

where k_1 and k_2 are empirical constants. Substituting Eq. (6) into Eq. (5), the incipient flow condition for monosized spherical particles can be described by:

$$\rho_{\text{particle}} d^3 g [-k_1 \ln(d) + k_2] = (1+\kappa) F_{H0} + \kappa F_N \tag{7}$$

Eq. (7) indicates that the net effect of particle size on a powder's incipient flow is proportional to particle size to the power of 3, albeit slightly reduced by the lower porosity value of larger size particles. This shows that the bulk powder flowability is sensitive to the particle size, as discussed by Li et al. (2004). It should be pointed out that Eqs. (5) and (7) apply for spherical particles only as the tensile strength Eqs. (2) and (3) were developed for spherical particles. In addition, Eq. (7) is only applicable to monosized spherical powders.

Now one can look at the effect of particle shape on the powder flowability. For a powder bed of non-spherical particles with a sphericity ϕ, which is defined as the ratio of the surface area of the equivalent volume sphere to the particle surface area, the limiting tensile strength can be calculated from the following equation (Shinohara et al., 1982):

$$\sigma = \frac{c\pi}{\phi} \frac{1-\varepsilon}{\varepsilon} \frac{F_H}{d_t^2} \tag{8}$$

where d_t is the single particle thickness in the direction perpendicular to tensile load and c is a proportionality constant. With uniform random packing of equal sized non-spherical particles, the average sectional area of a non-spherical particle can be approximated by its surface diameter d_{sv}. That is:

$$A_{\text{ave}} = \frac{\pi}{6} d_{sv}^2 \tag{9}$$

Similar to the method used by Molerus (1982), the average number of particles n cut by the sectional plane is:

$$n \frac{\pi d_{sv}^2}{6} = (1-\varepsilon) A_{\text{total}} \tag{10}$$

where A_{total} is the total sectional area. Therefore, the average tensile force transmitted per particle can be written as follows:

$$F_T = \frac{\sigma A_{\text{total}}}{n} = \frac{c\pi^2}{6\phi} \frac{d_{sv}^2}{d_t^2} \frac{F_H}{\varepsilon} \tag{11}$$

Similar to the case for spherical particles, we have the flow conditions for non-spherical particles:

$$\rho_{\text{particle}} d_v^3 g \geq \frac{c\pi}{\phi} \frac{d_{sv}^2}{d_t^2} \frac{(1+\kappa) F_{H0} + \kappa F_N}{\varepsilon} \tag{12}$$

The reason for using the particle equivalent volumetric size d_v on the left side of Eq. (12) is that particle gravity is directly related

to particle volume. If all the particles have the same shape, the relationship between ϕ and the particle sizes is as follows:

$$\phi = \frac{d_v^2}{d_{sv}^2} \tag{13}$$

Substituting d_{sv}^2 from Eq. (13) into Eq. (12) and assuming that the average particle thickness d_t is equal to its equivalent volume diameter d_v, one has the flow conditions for non-spherical particles:

$$\rho_{particle} d_v^3 g \geq \frac{c\pi[(1+\kappa)F_{H0} + \kappa F_N]}{\phi^2 \varepsilon} \tag{14}$$

Comparing the above equation to Eq. (5) for spherical particles, one can see that the right hand side of the equation is increased by the factor $1/\phi^2$. However, the packing voidage of a powder bed of irregular particles was found to increase exponentially with the decrease of the particle shape factor (Zou and Yu, 1996), therefore, the net particle shape effect is somewhat reduced. Nevertheless, for a certain type of powder, the less irregular the particles, the larger the minimum particle size for incipient flow. When the particle size reaches a certain value, the left hand side of Eqs. (5) and (14) is much higher than the right hand side of the equations and the powders become free-flowing.

It should be pointed out that the above theory is developed under ideal conditions. It is assumed that the particle–particle adhesion force F_{H0}, the inter-particle separation distance ($a_{F=0}$) and the particle surface asperity (h_r) are constant for a particular type of powder. For real pharmaceutical powders, these properties may vary a lot within one batch and from one batch to another. Therefore, their application may be limited by these assumptions. Nevertheless, it provides a quantitative analysis to the effect of particle size and shape on powder flowability.

3. Materials and methods

3.1. Materials

Ibuprofen USP was purchased from Professional Compounding Chemists of Australia Pty Ltd. (PCCA, Sydney). Visual observation of the powders showed that it is very cohesive and some of the particles form large but loose agglomerates. Representative samples were subsequently collected and used for particle size analysis with a Malvern Mastersizer 2000. Malvern Mastersizer measured particle size using laser diffraction technique. Particles passing through a laser beam will scatter light at an angle that is related to their size. Large particles scatter light at narrow angles with high intensity, while small particles scatter at wider angles but with low intensity. For Malvern particle size analysis, the sizes obtained are expected to represent the volumetric equivalent diameter of the particles. The size distribution of the ibuprofen measured using the Mastersizer (cumulative mass/volume percentage versus the standard size from Malvern) is shown in Fig. 1 and it had a median size $d_{[v,0.5]}$ of 70 μm. The morphology of the particles was obtained using scanning electron microscopy (SEM). The true density of the ibuprofen powder was measured using a pycnometer and was found to be 1118 kg/m^3. Magnesium stearate was supplied by Herron Pharmaceuticals Pty Ltd., Brisbane. It was used as a flow enhancing agent and had a $d_{[v,0.5]}$ of 6.5 μm.

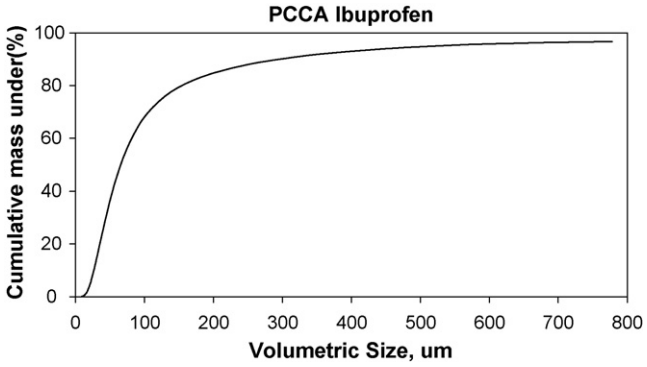

Fig. 1. The Mastersizer 2000 particle size distribution for the original ibuprofen.

To characterize the shape of individual ibuprofen particles, pictures of more than 70 particles of the representative sample of the original powder were taken using a digital camera connected to a light microscope. Digital images of the particles together with the calibration image of a 50 μm scale were taken. For each particle, the length and width were measured using ImagePro software and the aspect ratio (AR), which is defined as the ratio of width over the longest length, was calculated. The thickness of a limited number of ibuprofen crystals was also measured from the SEM images of the particles.

3.2. Preparation of narrow size fractions

To study the effect of particle size on flowability, two different types of samples were used for obtaining narrow size fraction ibuprofen. The first sample is the original ibuprofen with no lubricant. Samples were wet sieved by adding a small amount of detergent (5 ml/120 g) to wet the ibuprofen. Although the wet sieving method was able to separate the ibuprofen into narrow size fractions, the throughput of this method was very limited, hence only one batch of 50 g of ibuprofen was separated into narrow size fractions and this was used for tapping density tests only.

A Cyclosizer (Warman, Sydney), which consists of a series of five inverted hydrocyclones in series, was used to produce a larger amount of size separated ibuprofen. Water was used as the separation media and the same type of detergent was added initially to wet the sample. Once the samples for each size fraction were collected, they were filtered and dried at ambient temperature. With this method, the original ibuprofen was separated into three size fractions having sufficient quantity for shear cell testing (the quantities for other fractions were too small). It should be pointed out that the smallest size fraction is not exactly the same as that in the original bulk mixture as some fines were washed out during the separation process. Visual observation on the optical micrographs showed that the needle shape of the ibuprofen crystals is not affected by the separation process. Table 1 lists the median sizes as

Table 1
Ibuprofen size fractions without magnesium stearate (obtained from hydrocyclone separation process)

Stokes diameter d_{stokes}(μm)	$d_{[4,3]}$[a] (μm)	$D_{[v,0.5]}$ (μm)	$d_{[v,0.9]}$ (μm)	$d_{[v,0.1]}$ (μm)	Span $\frac{d_{[v,0.9]}-d_{[v,0.1]}}{d_{[v,0.5]}}$
77–110	215.2	176.2	390	88.5	1.71
50–77	123.7	105.5	207.8	54.8	1.45
<37	39.9	37.1	67.3	18.3	1.32
Bulk powder	110.9	70	195	25.3	2.43

[a] $d_{[4,3]}$ is the volumetric mean particle size and $d_{[v,0.1]}$, $d_{[v,0.5]}$ and $d_{[v,0.9]}$ are the volumetric diameters at which 10%, 50% and 90% of the particles are smaller.

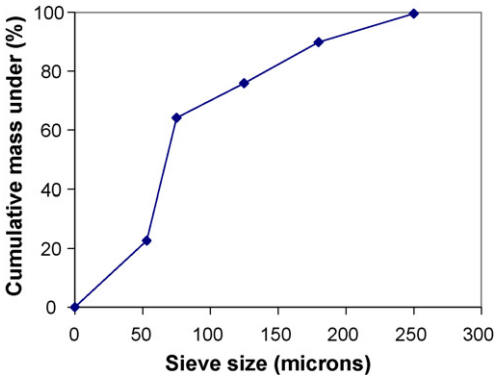

Fig. 2. Ibuprofen size distributions obtained from dry sieving analysis by adding 0.5% magnesium stearate.

well as the span of each size distribution. The data for the original ibuprofen bulk powder is also listed in Table 1 for comparison.

Since the fractionization of ibuprofen powders (both wet sieving and hydrocyclone) used water and a small amount of detergent, the process might change the flow properties of the ibuprofen size fractions. To discriminate the effect of separation process on the flow properties, one sample of the original ibuprofen was washed with water and another sample with water and a small amount of detergent water (equivalent to 120 g of ibuprofen with 5 ml of dish washing detergent). They were subsequently filtered and dried at room temperature. The flow properties of size fractions are then compared with that of the washed samples and the results are discussed in a later section of this paper.

The second type of sample was ibuprofen with 0.5% (w/w) magnesium stearate. This was obtained by mixing the original ibuprofen with 0.5% magnesium stearate in a SPEX CertiPrep 8000D mixer (SPEX CertiPrep, Inc., Metuchen) for 10 min (no grinding media was used). Due to the lubrication effect of magnesium stearate, the samples can be easily dry sieved into size fractions using sieves of 53, 75, 125, 180 and 250 μm. Fig. 2 shows the sieve analysis in terms of the cumulative mass percentage versus sieve size. As shown in Fig. 2 the majority of the particles were in the sieve size −75 to +53 μm (40%).

It should be pointed out that the particle size measures are different from different sizing methods, because the particles are non-spherical. With the Malvern particle size analysis, the size is the volume equivalent diameter; with sieve analysis, it is the screen opening size. Due to the needle shape of the ibuprofen particles, the size measured from the Malvern is much larger than the size obtained from the sieve analysis.

3.3. Flowability measurement

Two methods were used for the powder flowability measurement. The first method was the tapping density test. The ratio of the tapped bulk density, ρ_{tapped}, to its initial bulk density, ρ_{initial}, provides the Hausner ratio HR:

$$\text{HR} = \frac{\rho_{\text{tapped}}}{\rho_{\text{initial}}} \tag{15}$$

The higher the Hausner ratio, the lower the powder flowability. The tapped densities of the ibuprofen were obtained using a Quantachrome autotap machine with a 50 ml measuring cylinder and a 5 ml cylinder for the smaller amounts of sized fractions. The cylinder was filled with the desired amount of powder and then tapped for 10 min (this was the time at which the volume of the powder became a constant with further tapping).

The second method for flowability measurement was the shear cell test. A ring shear tester (Dietmar Schulze model RST-XS, Wolfenbüttel) was used. The shear tester is designed to measure shear stress τ, at different values of normal stress, σ. A Mohr diagram is constructed (Fig. 3) by plotting the shear stress as the ordinate and the normal stress as the abscissa and a yield locus is obtained by touching all of the Mohr semicircles. The yield locus is a characteristic of the powder under given conditions and several properties can be obtained from the Mohr diagram. These properties include the consolidation stress, the unconfined yield stress, the flow function FCC (defined as the ratio of consolidation stress to the unconfined yield stress), the angle of internal frication etc. A classification of powder flow behavior similar to that by Jenike (1964) has been defined by Schulze according to the FCC value; i.e., FCC < 1, not flowing; 1 < FCC < 2, very cohesive; 2 < FCC < 4, cohesive; 4 < FCC < 10, easy flowing and FCC > 10, free-flowing (Schulze, 2008). The shear tester measures the cohesive properties of the bulk powder and thus is able to give more comprehensive information on the powder flowability.

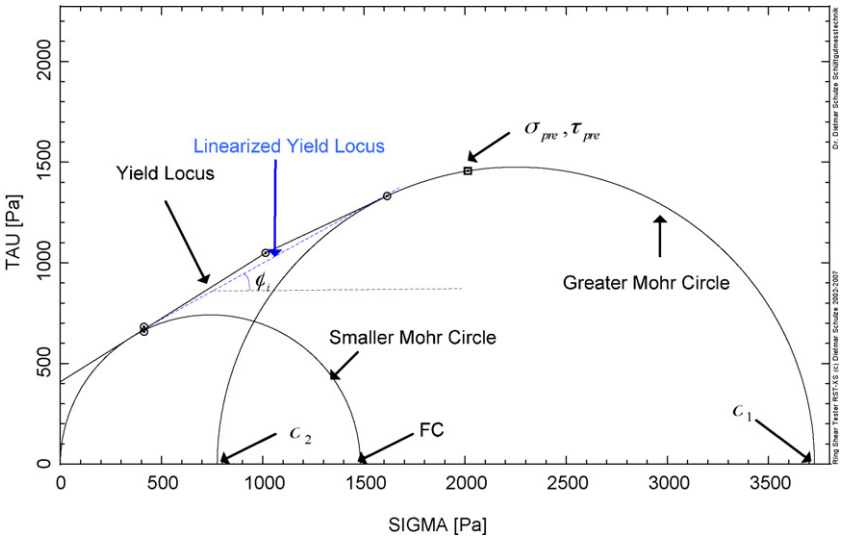

Fig. 3. An example of yield locus for ibuprofen.

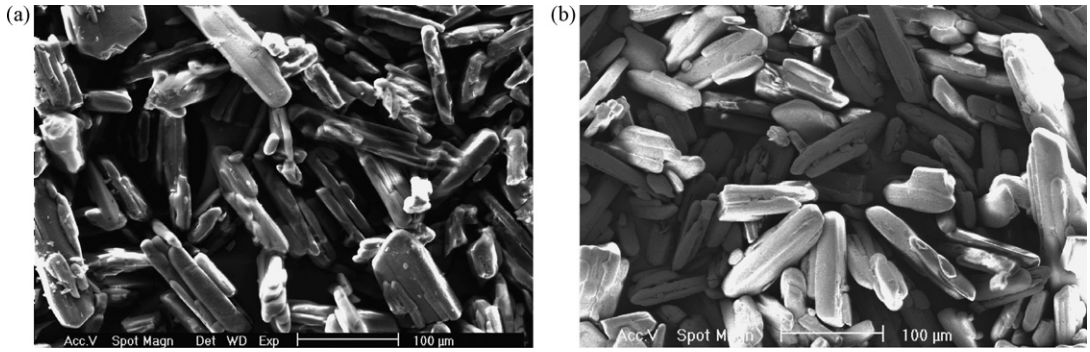

Fig. 4. SEM images of ibuprofen powder. (a) Original. (b) Original with 0.5% magnesium stearate.

4. Results and discussion

4.1. Original ibuprofen crystals with and without 0.5% magnesium stearate

4.1.1. Shape and surface morphology

A SEM image of the initial ibuprofen material is shown in Fig. 4a. As shown in the image, ibuprofen has a distinct needle shape and the surface is rough. The SEM image of ibuprofen with 0.5% magnesium stearate is shown in Fig. 4b. Magnesium stearate cannot be observed on the surface of the ibuprofen crystals, perhaps because of the small amount of lubricant added. Comparing the surface of the original ibuprofen crystals with the lubricated ibuprofen, it is seen that the demarcation lines on the crystal surface of lubricated ibuprofen are not as distinct as the original ibuprofen and the surface of the lubricated ibuprofen crystals seem to be smoother, which may be caused by the magnesium stearate thinly spreading onto the ibuprofen crystal surfaces during the mixing process.

The average aspect ratio (width to length) obtained from measuring 79 particles is 0.32 with a standard deviation of 0.12. When the aspect ratios of all the particles were plotted against their particle length (Fig. 5a), it was found that the particle aspect ratio decreased with the increase in particle length. This could be the result either of the manufacturing process or of the breakage of long crystals into the smaller ones during the powder transportation process. Limited measurements on the thickness to width aspect ratio gave an average value of 0.48. Assuming that all the particles have the same thickness to width aspect ratio of 0.48 (a reasonable assumption as particles are most likely to break along its longest direction) and also assuming that the ibuprofen particles are rectangular prisms, the particle sphericity was calculated from the aspect ratio trend line in Fig. 5a and is plotted against particle length (Fig. 5b). The particle sphericity values range from 0.48 to 0.75 and decreases with the increase in particle length which is expected.

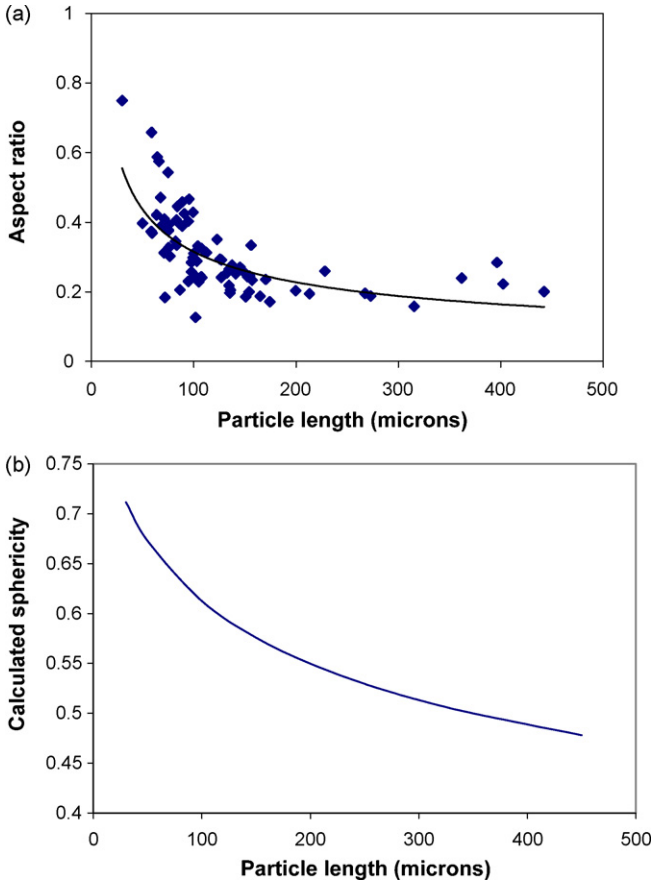

Fig. 5. (a) The aspect ratio (width over length) of the original ibuprofen particles versus particle length. (b) Calculated sphericity versus particle length.

4.1.2. Bulk density

The tapped densities and the initial powder bulk densities of ibuprofen are listed in Table 2. It is seen that, within the measurement errors, the HR value of water and detergent-washed sample are not significantly different from the original ibuprofen. Within the accuracy of the measurements, washing the samples or using detergent does not alter the Hausner ratio. However the addition of 0.5% magnesium stearate does cause significant reduction on

Table 2
Average initial and tapped densities of ibuprofen

Material	Initial bulk density (kg/m^3)	Tapped bulk density (kg/m^3)	Hausner ratio (HR)
Original ibuprofen	401 ± 21[a]	590 ± 4.0	1.47 ± 0.08
Ibuprofen washed with water	393 ± 22	593 ± 21	1.51 ± 0.06
Ibuprofen washed with detergent water	367 ± 27	570 ± 9.6	1.55 ± 0.10
Original ibuprofen with 0.5% magnesium stearate	514 ± 3.5	654 ± 10.6	1.27 ± 0.03

[a] All uncertainties are estimated standard deviations based on three measurements.

Table 3
Yield locus properties of different ibuprofen samples at preshear stress of 2 kPa

Type of ibuprofen samples	Consolidation stress σ_1 (Pa)	Unconfined yield stress FC (Pa)	Flow Function FCC	Angle of internal friction ϕ_i (°)	Bulk density from shear cell (kg/m^3) ρ_b
Original ibuprofen	3727 ± 15[a]	1482 ± 27	2.5 ± 0.1	41 ± 0.2	489 ± 5.3
Ibuprofen washed with water	3821 ± 23	1054 ± 77	3.7 ± 0.2	39 ± 1.3	496 ± 4.8
Ibuprofen washed with detergent water	3701 ± 29	1136 ± 48	3.3 ± 0.1	39 ± 0.4	498 ± 6.2
Original ibuprofen with 0.5% magnesium stearate	2664 ± 43	459 ± 7	5.8 ± 0.2	24 ± 0.6	668 ± 2.9

[a] All uncertainties are estimated standard deviations based on three measurements.

the HR value of the ibuprofen, and therefore the overall powder flowability should improve.

4.1.3. Shear cell flow properties

The flow properties of different ibuprofen samples measured with the Schulze shear tester at a standard pre-shear load 2 kPa are shown in Table 3. The results show that the bulk ibuprofen powder is very cohesive, with a flow function, FCC, of 2.5. The results from the shear tester are very reproducible and therefore produce less variability in the predictions of the powder flowability compared to flow properties assessed through density measurements. With the more sensitive measurement, we see the unconfined yield stress is reduced, the angle of internal friction reduced and the flow function increased by washing. However, within experimental error, the addition of detergent had no significant effect.

The flow properties of the ibuprofen with 0.5% magnesium stearate are also shown in Table 3. The impact of magnesium stearate addition was much greater than washing the particles. The flow function of the lubricated ibuprofen is increased to 5.8, which falls into the easy flow region. Kato et al. (2005) studied the flowability of ibuprofen with added surface-modifying agents such as anhydrous silicic acid, talc and titanium oxide and found that the increased flowability of ibuprofen is caused by the reduced adhesive force between the surface-modified ibuprofen particles. A similar interpretation can be drawn here for the magnesium stearate mixed with ibuprofen. It should be pointed out that there is a possibility of breakage during the mixing process which may enhance the powder flowability, but is not expected to be significant comparing to the effect of lubricant. In addition, the internal friction angle of the magnesium stearate lubricated ibuprofen is reduced significantly, which again could be caused by the reduced inter-particle cohesion forces.

Note that the properties measured by the shear cell can be used directly in design of hoppers and shuts using the well known Jenike design method, but for full design the flow properties need to be measured over a range of consolidation stresses for each powder of interest.

4.2. Ibuprofen of different size fractions

The different size fraction samples used for tap density tests are from the wet sieving process. Due to the small amount of powders obtained from the sieving, a 5 ml cylinder was used for the measurement of tapping density. Fig. 6a shows the tapped densities of different size fractions versus its average particle (sieve) size. The corresponding Hausner ratios are plotted in Fig. 6b. The error bars are the standard deviation.

Fig. 6a shows that both the initial bulk density and the tapped density increase with the increase in particle size. All the three larger size fractions have a loose bulk density around 440 kg/m^3 while the three smaller size fractions have a loose bulk density around 350 kg/m^3. The tap density of the bulk mixture (~590 kg/m^3 from Table 2) is closer to that of the larger size fractions.

The Hausner ratio, which reflects the powder flowability, is approximately 1.39 for the three smaller size fractions but then decreases with increasing size at the larger size ranges (Fig. 6b), i.e., the powder flowability increases with the increase in particle size. It is also noted from Fig. 6b that even the smallest size fraction has a Hausner ratio smaller than that for the bulk powder. Visual observation by tilting the powder of the separated size fractions held in a container showed that the powders were less cohesive than the original bulk material.

As mentioned previously, shear tests on the unlubricated ibuprofen size fractions were carried out with samples separated using the hydrocyclone. Table 4 shows the flowability data measured using the Schulze tester. A standard preshear load of 2 kPa was used for all the tests. The data presented are the average of two separate measurements.

Table 4 shows that the flow functions of all the size fractions are higher than for the bulk powder (Table 3) and they all fall into the easy flow region with flow functions ranging from 5 to 11. The unconfined yield stress decreases and the flow function increases

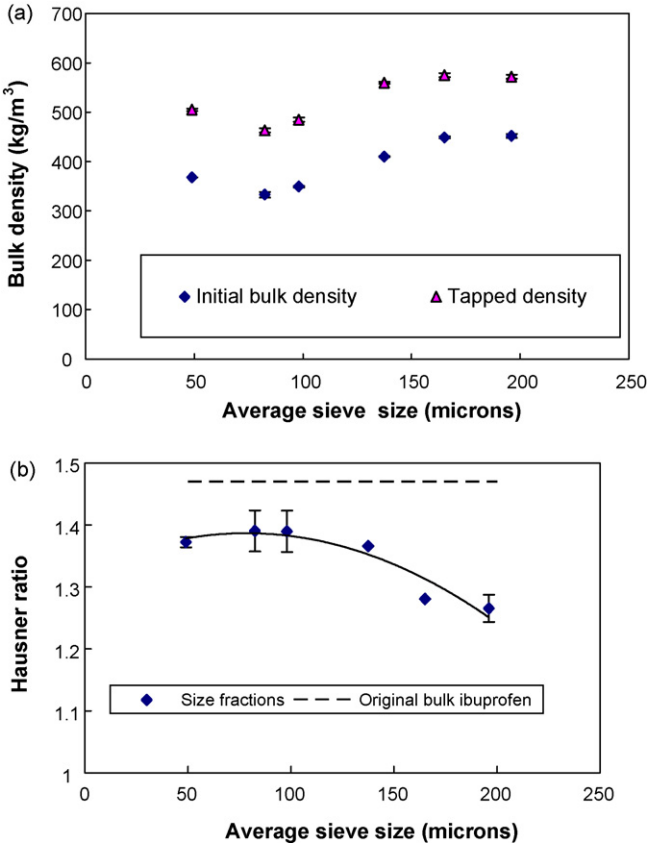

Fig. 6. Tapping density results of different size fractions. (a) The initial bulk and tap densities. (b) Hausner ratio.

Table 4
Yield locus results of different size fractions from hydrocyclone at preshear stress of 2 kPa

$d_{[v,0.5]}$ of the different size fractions (μm)	Consolidation stress σ_1 (Pa)	Unconfined yield stress FC (Pa)	Flow Function FCC	Angle of internal friction ϕ_i (°)	Bulk density from shear cell ρ_b (kg/m^3)
215.2	4529 ± 176	435 ± 7	10.5 ± 0.7	41 ± 0.4	518 ± 11
123.8	4696 ± 156	534 ± 25	8.8 ± 0.4	42 ± 0.8	509 ± 18
39.9	4213 ± 280	802 ± 76	5.3 ± 0.2	41 ± 2.0	453 ± 23

with increasing particle size. That is, the flowability of particles improves with the increasing particle size. However, even the finest size fraction flows better than the original bulk mixture, which is consistent with the tapped density results. As mentioned previously, the finest size fraction tested here is not exactly the same as that in the bulk mixture as some fines were lost during the separation process. However, this size fraction still has a smaller volume median particle size than the bulk which elucidates that not only the mean particle size of the powder, but also the spread of the particle size play a major role in powder flowability. A bulk mixture with a smaller mean size but narrow size distribution may flow better than a coarser mixture with a wider size distribution with larger mean particle size. The internal friction angles which measure the powder's ability to maintain a steady flow, however, change very little with particle size.

4.3. Flowability of magnesium stearate lubricated ibuprofen size fractions

Fig. 7a shows the initial bulk densities and the tapped densities of each size fraction versus the average sieve size and Fig. 7b shows

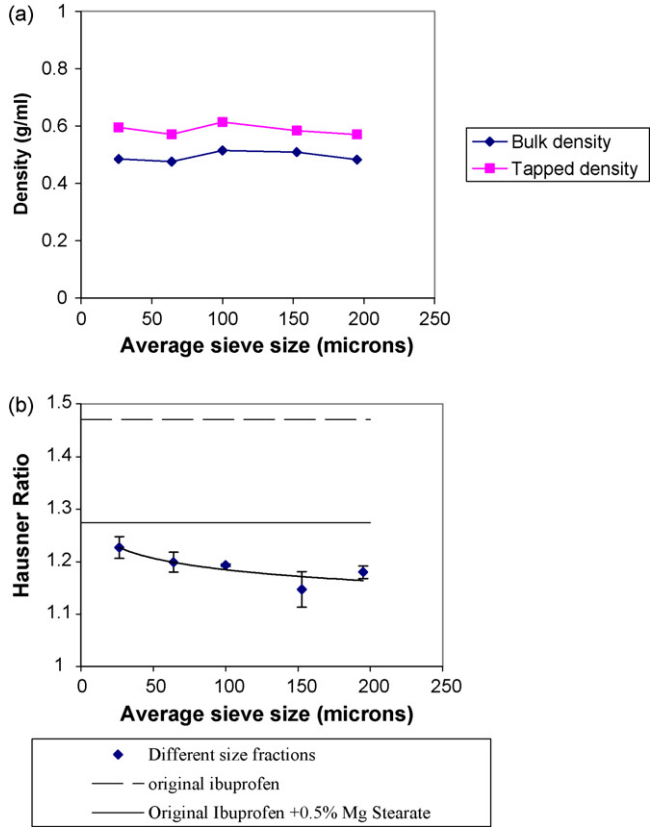

Fig. 7. Tap density results of different size fractions of ibuprofen with 0.5% added magnesium stearate (a) Bulk and tapped densities. (b) Hausner ratio. (The error bars are the standard deviation based on two measurements.)

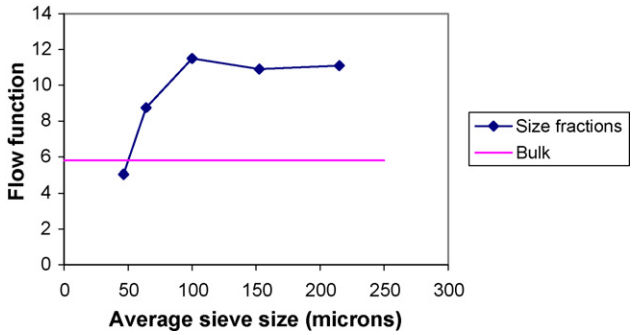

Fig. 8. The flow functions of magnesium stearate lubricated ibuprofen fractions.

the corresponding Hausner ratios (HR), together with the HR value of the original bulk mixtures.

Fig. 7 shows that the HR values of all the different size fractions from the sieved 0.5% magnesium stearate added ibuprofen are lower than the bulk mixture (solid line) and much lower than that without magnesium stearate. However, the effect of particle size on HR value and hence flowability is much less significant than that without magnesium stearate (Fig. 6). Except for the two small size fractions, the HR value is almost independent of particle size. This can be explained in terms of the lubricating effect of the flow agents. For a cohesive bulk sample such as ibuprofen, the cohesiveness is mainly caused by the smaller particles in the mixture. Once a flow agent is added, the lubricant will coat the surface of the particles and improve the overall flowability. In essence, the flowability of smaller particles after adding lubricants is improved as larger particles flow well irrespective of the presence of flow agents. This explains why the flowability of the smaller size fractions increased whereas the flowability of the larger particles is similar to those without the flow agent.

Table 5 lists the shear test results of different size fractions with 0.5% added magnesium stearate. To show the effect of particle size more clearly, the flow function and the internal friction angle of the different size fractions are shown in Figs. 8 and 9.

Fig. 8 shows that the flow functions of lubricated samples (ranging from 5 to 11) all fall into the easy flow region. For different

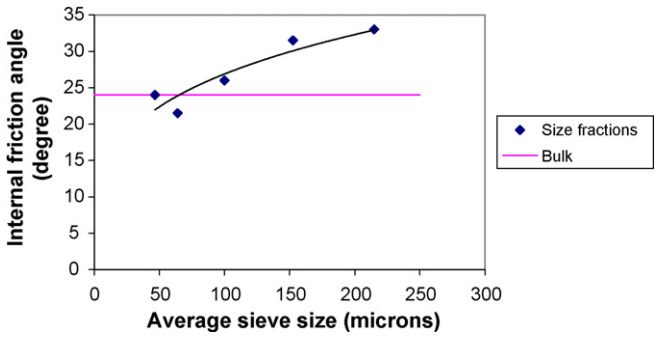

Fig. 9. The internal friction angles of magnesium stearate lubricated ibuprofen fractions.

Table 5
Yield locus results of ibuprofen with 0.5% magnesium stearate at a preshear stress of 2 kPa

Sample size (μm)	Average sieve size (μm)	Consolidation stress σ_1 (Pa)	Unconfined yield stress FC (Pa)	Flow function[a] FCC	Angle of internal friction ϕ_i (°)	Bulk density from shear cell ρ_b (kg/m^3)
−250 + 180	215	3863	344	11.1	33	507
−180 + 125	153	3514	336	10.9	32	500
−125 + 75	100	3095	293	11.5	26	538
−75 + 53	64	2687	310	8.8	22	571
−53	46	2720	685	5.1	24	595

[a] The average flow function of two measurements, not the ratio of average consolidation stress over the average unconfined yield stress.

sized ibuprofen, the FCC value initially increases with the increase in particle size and then levels off. This matches the packing density results. The smallest size fraction (−53 μm) has a flow function slightly lower than the bulk mixture but all the rest are above.

The internal friction angle results shown in Fig. 9 are interesting. Firstly, the lubricated samples including all the size fractions have a much lower internal friction angle than the original material without the magnesium stearate (42°), which indicates that the powder internal friction during steady flow is much smaller (or in other words, the lubricated samples are more able to maintain constant volume flow). Secondly, the internal friction angle of the size frictions increases with the increase in particle size. This can be postulated that the magnesium stearate is more prevalent on the smaller particles due to their larger surface area which subsequently reduced the internal friction angles of smaller size fractions. Thirdly, if one compares the flowability data for the magnesium stearate lubricated mixture with that of the larger size fractions from the hydrocyclone, it is noticed that, although the flow function of the large un-lubricated ibuprofen particles have a higher flow function, their internal friction angles are hardly changed compared to the bulk mixture. This may be explained by the postulate that the internal friction of the bulk powders are more affected by the particles surface friction whereas the incipient flow is more affected by the interlocking of the powder assemblies.

Particle shape may also play a role in the measured internal friction angle. The sphericity of the particles decreases with increasing particle size (see Fig. 5). The larger needle like particles will have greater contact area with other particles and need to dilate more to flow. Thus, the level of friction during flow, as measured by the internal friction angle is expected to be larger for the most non-spherical particles.

4.4. Comparison with theory

The experimental results can now be compared with the theory in Section 2. The different ibuprofen size fractions vary in their particle size, shape and the packing density, but the adhesion force between the particles are likely to be the same (the different crystal faces are ignored here). Since the initial packing porosity can be calculated directly from the bulk density values from the shear cell measurement, one can obtain $\rho_{particle} d_v^3 g\phi^2\varepsilon$ (Eq. (14)) directly for these powders. Note that for a powder with a wide size distribution, the minimum particle size $d_{v\,min}$ should be used to replace d_v in Eq. (14). This is because the flow conditions for smaller particles should be satisfied since they are more stringent than the larger particles. To simplify the calculations, $d_{[v,0.1]}$, the volumetric size at which 10% of the particles are smaller was used as $d_{v\,min}$. The reason for using $d_{[v,0.1]}$ is that one can obtain $d_{[v,0.1]}$ automatically from a Malvern Mastersizer and it is the most commonly used parameter for representing the smallest size of a powder. The $d_{[v,0.1]}$ value of the smallest size fraction was used for the original bulk powder. Since there is no explicit relationship between the volumetric diameters from the Malvern Mastersizer to particle length, one cannot obtain the accurate sphericity values from Fig. 5b for the size fractions. Therefore, the sphericity values were approximated from Fig. 5b and were assumed to be 0.55, 0.60 and 0.65 for the size fractions with $d_{[v,0.5]}$ of 215.2 μm, 123.7 and 39.9 μm, respectively. The sphericity value of the smallest size fraction was used for the bulk powder as the smaller particles determine the flow. Table 6 lists the values of $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ for the different size fractions from the hydrocyclone and the original bulk mixture. It clearly shows why the finest fraction that was separated from the bulk mixture flows better than the bulk mixture as the porosity of the finest size fraction is higher than the bulk and hence the higher $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ value shown in Table 6.

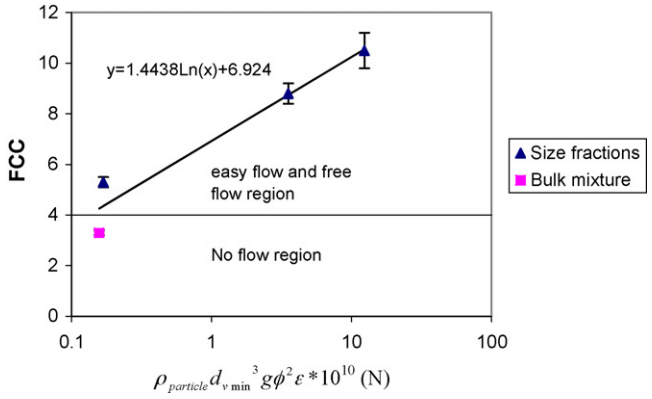

Fig. 10. Relationship between the flow functions and $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ values for the original ibuprofen and its fractions.

Fig. 10 plots the measured flow function (FCC) values versus the $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ values for all the powders in Table 6. The best-fit curve between the flow functions and the $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ values is also plotted. It is interesting to note that linear relationship between the flow function and $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ (logarithmic scale) exists, which shows that the powder flow function is proportional to $\ln(d_{min})$. However, the relationship between FCC value

Table 6
Theoretical analysis for the hydrocyclone fractions

Sample	ε	ϕ	$\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon \times 10^{10}$(N)	F_H	Measured flow function (FCC)
Size fraction with $d_{[v,0.5]}$ 215.2 μm	0.54	0.55	12.33	Constant	10.5
Size fraction with $d_{[v,0.5]}$ 123.7 μm	0.54	0.60	3.54	Constant	8.8
Size fraction with $d_{[v,0.5]}$ 39.9 μm	0.59	0.65	0.169	Constant	5.3
Original ibuprofen	0.55	0.55	0.157	Constant	3.3

and a powder's $d_{v\,min}$ is more complicated as the porosity of the powder is also a function of particle size as shown in Eq. (7).

With the addition of lubricants such as magnesium stearate into a powder, the major effect is the reduction of the particle–particle adhesion force, which makes the value of the right hand side of Eq. (8) smaller and thus it is much easier to satisfy the flow condition. The exact effect will depend on the type of lubricant and the amount of lubricant added. This explains why the lubricated samples flow much better. As for the lubricated size fractions tested here, it is possible that the smaller size fractions of the magnesium stearate lubricated ibuprofen have higher amount of magnesium stearate. One cannot compare their $\rho_{particle} d_{v\,min}^3 g\phi^2\varepsilon$ values alone as the particle–particle adhesion force for different size fractions could be different due to the possibly increased amount of magnesium stearate caused by the sieving process for the finer fractions.

Both experimental results and the theoretical analysis confirm that increasing particle size and adding lubricant will increase the powder flowability. The ultimate choice will depend on the process requirements. In direct compression process, adding a lubricant would reduce the bond strength and hence reduces the tablet strength, which was verified by a separate study. In this case, increasing particle size and sphericity are preferred to adding a lubricant.

5. Conclusions

The flow properties of ibuprofen and ibuprofen size fractions were studied. The tap density and Hausner ratio method is simple and in general gave a good indication of the powder flowability, particularly for powders with narrow size distributions. Shear tests gave more comprehensive flow information and greater sensitivity and reproducibility but a relatively larger quantity of material is required for each test.

It has been demonstrated both experimentally and theoretically that powder flowability is significantly affected by the particle size and the size distribution. Theoretical analysis has also shown why particles with irregular shape have poorer powder flowability. The original ibuprofen bulk powder is very cohesive and does not flow but the finest size fraction separated from the bulk powder flows better than the bulk powder. For powders with narrow size distributions, the flowability increases significantly with the increase in particle size. For powders with the same median size, the narrower the size distribution, the better the flowability.

The flowability of ibuprofen powder was improved substantially by adding a lubricant. The advantage of adding a lubricant compared to increasing the particle size is that the lubricant also acts to reduce the internal friction angle of the bulk powder whereas increasing particle size makes little change to the powder internal friction angle. However, adding a lubricant will undoubtedly reduce the ibuprofen particle–particle bond strength and possibly reduce the tablet strength. The ultimate objective is to produce particles that will not only flow better but also compact well.

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