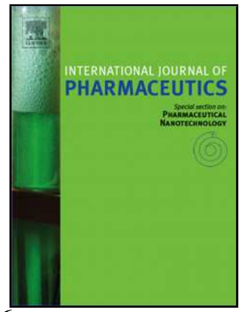

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Impact Breakage of Pharmaceutical Tablets

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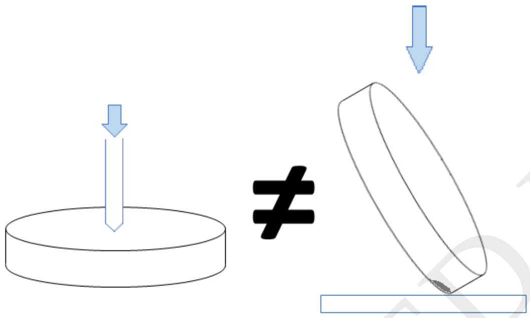
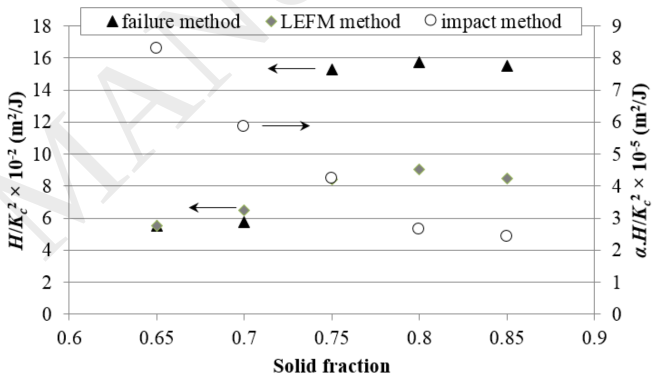
Graphical Abstract





Abstract

Tablets are the most common solid dosage form of pharmaceutical active ingredients due to their ease of use. Their dissolution behaviour depends on the particle size distribution and physicochemical properties of the formulation, and the compression process, which need to be optimised for producing consistently robust tablets, as weaker tablets are often prone to breakage during production, transport and end use. Tablet strength is typically determined by diametric compression and friability tests. The former gives rise to propagation of a crack on a plane along the compression axis, whilst the latter, carried out in a rotating drum, incurs surface damage and produces chips and debris. These tests produce different measures of strength, neither of which have been correlated with mechanical properties that are accountable for breakage, i.e. hardness, elastic modulus and fracture toughness. We propose a new method based on single tablet impact testing, following the work of Ghadiri and Zhang (2002), who analysed particle damage by propagation of sub-surface lateral cracks and identified the fundamental form accountable for impact surface damage to be a lumped parameter related to hardness and fracture toughness. Microindentation, carried out separately, to determine fracture toughness led to complete failure of the tablets, hence an unreliable measurement of fracture toughness and no correlation with the experimental trend. In addition, by assuming the fracture toughness to be proportional to the square root of Young's modulus, the indentation measurements do not correlate well with the impact breakage. The discrepancy between the impact and indentation methods is expected to be due to mechanical property variation across the tablet surface, and with strain rate. The impact method is a more suitable test to describe tablet propensity for attrition as it directly represents the failure mode tablets may experience during processing under well-defined conditions. In contrast, the friability test subjects tablets to a similar breakage mechanism but under less well-defined conditions, whilst the compression test represents a different failure mode that is not representative of stresses incurred during processing.

1. Introduction

Tablets are a very common dosage form of pharmaceutical active ingredients, due to their ease of use and rapid manufacturing route. Weak tablets are often prone to breakage during production, transportation and end use, which can result in waste that no longer meets required product specifications. Furthermore, surface damage by chipping is aesthetically undesirable and can affect content uniformity. It is therefore necessary to have reliable means of determining and predicting the extent of breakage tablets may experience during the production process.

The most common method of characterising tablet strength in industry is by diametric compression (Sinka et al., 2007), which is a standard test described by the United States Pharmacopoeia monograph 1217 (USP35/NF30, 2011) often referred to as a "hardness" test. This gives rise to propagation of a crack on a plane along the compression axis once the failure force is reached. From this test the tensile strength, σ_T, of the tablet is established following the relationship of Fell and Newton (1970):

$$\sigma_T = \frac{2F}{\pi dt} \qquad \text{(Eq. 1)}$$

where F is the breakage force and d and t are the tablet diameter and thickness, respectively. For flat, cylindrical tablets an analytical solution based on Linear Elastic Fracture Mechanics (LEFM) exists for determining tensile strength from the failure force (Timoshenko and Goodier, 1969). An empirical relationship between tensile strength and failure force which takes into account the tablet dimensions has been developed for gypsum specimens of curved cylindrical shape (Pitt et al., 1989) and elongated shape (Pitt and Heasley, 2013), whilst a modified version of this relationship was proposed for microcrystalline cellulose tablets by Shang et al. (2013). Fell and Newton (1970) determined that it is necessary to use padding between the tablet and the platens in order to minimise shear stresses at the tablet boundary, however if this padding is too soft then tensile failure may be prevented. The tensile strength of tablets typically increases with compaction pressure (Sinka et al., 2009), though at higher pressures defects may arise, such as cracking or delamination, which result in a strength reduction (Sinka et al., 2007). In addition, compression speed and dwell time influence the tablet strength (Sinka et al., 2007; Tye et al., 2005). Conflicting results have been reported on the effect of binder particle size on tensile strength: Mangal et al. (2016) and Arndt and Kleinebudde (2017) each investigated the tensile strength of paracetamol tablets of differing formulations, with the tensile strength being linearly related to binder particle size for the former work, and inversely related to the logarithm of binder particle size for the latter. In manufacturing tablets, the intention is not to maximise strength – a guide tensile strength of 1.5 – 2.5 MPa is recommended by Stricker (1987) – since this may impede disintegration in the digestive system, however it is necessary to have sufficiently robust tablets to prevent excessive attrition during handling of tablets in production and by the end user. A wide range of non-invasive techniques for analysis of tablet properties were reviewed by Dave et al. (2017), with a number of soundwave-based methods identified for characterisation of tablet mechanical properties. These methods are used in a supportive manner in some instances, however analytical efficiency and operational complexity are cited as current barriers to widespread adoption.

For testing the durability of tablets, the "Roche Friabilator" was introduced by Webster and Abbé (1955). In this test, following the Method (2.9.7) of the European Pharmacopoeia (2010), 20 tablets are typically loaded into a rotating drum of 283 – 291 mm diameter and rotated at 25 rpm for four minutes. The drum contains a single curved baffle extending radially from a central shaft to the wall, which lifts the tablets and subjects them to impacts at the base of the drum. The percentage mass loss from the tablets is referred to as the friability of the tablets, with a threshold of 1% given as the upper limit. Friability has been shown to reduce with an increase in barrel temperature during tabletting (Vercruysse et al., 2012), and with an increase in relative density (Sinka et al., 2009). Sinka et al. (2009) also showed an approximately linear increase in friability of MCC tablets with rotation number, when tested beyond the standard 100 revolutions, until a weight loss of around 15%. Gong and Sun (2015) investigated a wide range of tablet 'brittleness' indices and found the strongest correlation with results of the friability test to be the reciprocal of the elastic strain to failure during diametric compression. In the review of mechanical strength of tablets given by Podczeck (2012), the recommended limit of 1% for friability is suggested to be too high for many applications. This test method aims to characterise the susceptibility of tablets to attrition. However tablet impacts are not controlled, and complex dynamic stressing conditions prevail, giving rise to a distribution of impact numbers, angles and velocities, as well as impacts being with the base and with other tablets. Furthermore, since the stresses to which tablets are exposed in processing and by patients has not been established (Podczeck, 2012), the friability test lacks the credibility of replicating these conditions.

Yüregir et al. (1986) introduced a method of subjecting single particles to impact breakage under controlled conditions of impact velocity, speed and target material. To our knowledge such an approach has not been reported for assessing breakage of tablets. Ghadiri and Zhang (2002) proposed that for particles failing in a chipping mode, the attrition propensity (% mass loss), W, is related to the particle's physical and mechanical properties and impact conditions as given by Eq 1.

$$\mathrm{W} = \alpha \frac{\rho \cdot \mathrm{D} \cdot \mathrm{H} \cdot \mathrm{V}^2}{\mathrm{K}_c^2} \qquad \text{(Eq. 1)}$$

where α is a proportionality factor which is related to the geometrical features of the shape of the chips bound by sub-surface lateral cracks and by factors accounting for energy dissipation, plastic flow and crack propagation, ρ, D, H and K_c are the particle density, characteristic length, hardness and fracture toughness, respectively, and V is the impact velocity. Zhang and Ghadiri (2002) validated the above dependency on attrition rate with material properties, particle size and impact velocity for ionic crystals of KCl, MgO and NaCl, and found α to vary from 1×10^{-4} to 8×10^{-4} for MgO and NaCl, respectively. In addition, it was shown that no breakage occurs below a threshold chipping velocity, and that the change in attrition rate with number of impacts is material specific.

In this work we propose the single impact method as a means of quantifying the attrition propensity of tablets. Furthermore, we explore the relationship between impact breakage of the tablets and their mechanical properties. It is important to note that the mechanical properties of tablets may vary from the centre to the edge (Sinka et al., 2003). Since damage due to chipping occurs at the edges, the impact method is expected to offer a more accurate prediction of attrition propensity than by mechanical property measurement.

2. Materials & methods

Cylindrical tablets of Avicel PH102 (a form of microcrystalline cellulose) with 10 mm diameter and a mass of approximately 0.29 g were produced by AbbVie to obtain solid fractions, SF, of 0.65, 0.7, 0.75, 0.8 and 0.85, and thicknesses of 2.95 – 3.89 mm (see Table 1). The tablets were produced using a Huxley Bertram ESH Tablet Press Simulator with a flat punch, using a 1% mass loading of magnesium stearate in the blend, under load control with a linear increase in compaction pressure against time. The total compression time was of the order of one second. This material is selected since it is widely used in industry and extensively reported in literature. To assess impact damage, a single tablet was dropped from the top of a vertical tube of given height to provide a single impact against a rigid stainless steel target at a speed set by the tube height. Each tablet was manually released, with its cylindrical axis aligned approximately horizontally. The impacted tablet was collected and dropped again from the top of the tube until a given tablet experienced fifty successive impacts. After each five successive impacts the tablet mass remaining was measured on a laboratory scale with a resolution of 0.1 mg. Tubes with heights of 0.85, 1.4, 4 and 5 m were used, with inner diameters of 16 and 25 mm for the shorter two tubes and the longer two tubes, respectively. The two shorter tubes were made of glass and so the absence of impacts against the tube during freefall could be confirmed. The longer two tubes were made of stainless steel, and whilst it could not be confirmed that the tablets did not impact the tubes during freefall, no impacts were audibly detected. One tablet was used for each height. The impact angle of the tablet varied between successive impacts and at different velocities, with the impact always taking place on an edge of the tablet rather than the tablet face, a typical example is shown in Figure 1. The impact velocity at each height was measured using an HG-100K Redlake high-speed camera for ten separate tablets, using the last ten frames before the tablet contacted the target. The average value for each drop height is reported.

The mechanical properties of the tablets were measured using a Vickers indenter connected to an Instron 5566 mechanical testing machine. Each tablet was placed onto a stainless steel platen with its cylindrical axis aligned vertically, and penetrated at its centre by a Vickers indenter at a loading rate of 0.01 N/s to a maximum load of 1 N, followed by unloading at the same rate to determine hardness and Young's modulus, E. Fracture toughness, K_c, was determined using a load up to 300 N in order to generate a crack, using a loading/unloading rate of 0.5 N/s. The hardness, Young's modulus and fracture toughness are given by Eqs 2, 3 and 5, respectively.

$$H = \frac{F_{max}}{kh_c^2} \qquad \text{(Eq. 2)}$$

where F_{max} is the maximum force during loading, k is a shape factor (equal to 24.5 for a Vickers indenter) and h_c is the indentation depth after unloading (Ghadiri, 2006).

$$E_r = \frac{\sqrt{\pi}}{2}\frac{S}{\sqrt{A}} \qquad \text{(Eq. 3)}$$

where E_r is the reduced Young's modulus, S is the unloading stiffness and A is the projected area of indentation (equal to kh_c^2).

$$\frac{1}{E_r} = \frac{1-\nu_s^2}{E_s} + \frac{1-\nu_i^2}{E_i} \qquad \text{(Eq. 4)}$$

where ν is the Poisson ratio and subscripts s and i refer to the sample and indenter, respectively. Many correlations exist in the literature for determination of fracture toughness by indentation (Ponton and Rawlings, 1989). Here we use the correlation of Laugier (1987), given in Eq. 5, as it is considered to be one of the most comprehensive, since it takes into account the Young's modulus, hardness and plastic zone size.

$$K_c = 0.143\left(\frac{E}{H}\right)^{2/3}\left(\frac{a}{l}\right)^{1/2}\left(\frac{F_{max}}{c^{3/2}}\right) \qquad \text{(Eq. 5)}$$

where a is the average lateral distance from the centre to corner of the indent, l is the length of the crack from the initiating corner to its tip and c is the distance from the centre of the indent to the crack tip (equal to a + l).

3. Results & discussion

Impact breakage

The average impact velocity was measured to be 3.8, 4.0, 5.2 and 7.3 m/s for tablets dropped from heights of 0.85, 1.4, 4 and 5 m, respectively. The cumulative mass losses for tablets of each solid fraction dropped from a height of 0.85, 1.4, 4 and 5 m are shown in Figures 2a, b, c and d, respectively. In all cases the tablets failed by attrition/chipping; no fragmentation was observed. At all impact velocities the mass loss increases approximately linearly with the number of impacts, and decreases as solid fraction is increased. Minor deviations from this linearity are present, but for this material and for the range of conditions used, no significant fatigue or work-hardening effects are observed.

Figure 3 shows the cumulative mass loss after fifty successive impacts at each impact velocity for each tablet solid fraction. The mass loss increases with impact velocity, as expected and observed in Figure 2. Figure 3 clearly shows the similarity in breakage behaviour of the tablets with solid fractions of 0.8 and 0.85. For all tablets the mass loss is approximately doubled as the impact velocity is increased from 5.2 to 7.3 m/s, which represents an increase in kinetic energy at impact of 97%.

The Ghadiri & Zhang (2002) model, given by Eq. 1, can be rearranged to determine the propensity for breakage of a solid under impact conditions, as given by Eq. 6.

$$\mathrm{W} = \alpha \frac{\mathrm{H}}{\mathrm{K_c^2}} \rho \mathrm{DV^2} = \mathrm{C}\rho \mathrm{DV^2} \qquad \text{(Eq. 6)}$$

where C ($\alpha H/K_c^2$) is the material's propensity for breakage (Ali et al., 2015). By assuming the characteristic length, D, is equal to the diameter of the tablets, C is determined by the slope of the linear fit of extent of breakage after fifty impacts (W) against ρDV^2, as shown in Figure 4. The propensity for breakage (C) for tablets of each solid fraction is compared to the mechanical properties derived from indentation following determination of mechanical properties.

Hardness & Young's modulus

The mechanical properties were measured for four tablets of each solid fraction with the conditions described in the previous section. The measured load versus penetration depth for the four indents on tablets of solid fraction 0.85 are shown in Figure 5.

The unloading curve is initially close to a linear relationship, though towards the end of unloading there is a slight curvature. It is known that hardness is overestimated if the plastic depth is assumed to equal the intercept with the depth axis (Stilwell and Tabor, 1961). Here we approximate the unloading curve to be linear, and calculate the stiffness and plastic deformation using a linear fit between 50 and 95% of the maximum indentation force. Hardness and Young's modulus are calculated using Eqs. 2 and 4, respectively, and are shown in Figure 6 and Table 2 for tablets of each solid fraction. The error bars in Figure 6 indicate one standard deviation. Both hardness and Young's modulus increase with solid fraction, with the values increasing by factors of approximately 2 and 3, respectively, when solid fraction is increased from 0.65 to 0.85. The coefficient of variation is quite high for the hardness measurements, but less so for Young's modulus, with the variation being significantly higher for tablets with a solid fraction of 0.65 for both parameters.

Fracture toughness – failure method

Tablets were indented using loads of 100, 150, 200, 250 and 300 N in an attempt to generate a crack to determine fracture toughness. Indented tablets were observed using SEM to determine crack length, however no cracks were observed on any intact tablet indented at any load. At higher load the tablets failed by crack propagation from each of the four corners of the impression left by the Vickers indenter, as indicated in Figure 7. The average minimum failure force of four tablets for each solid fraction is given in Figure 8, where error bars indicate one standard deviation. The average failure force increases with solid fraction, from 143 N for a solid fraction of 0.65 to 241 N for a solid fraction of 0.85. Indents were made at a force equal to 90% of the failure force for tablets of each solid fraction, however no cracks were observed for any of the tablets when analysed under SEM.

Determination of indentation fracture toughness requires generation of a crack, we therefore analyse the fracture toughness of the tablets based on the crack length leading to failure, which is generated at the failure force. Referring to Eq. 5, the crack length, l, is assumed to be equal to the distance from the corner of the indent to the edge of the tablet, and c is equal to the tablet radius (i.e. 5 mm) as the crack reaches the edge of the tablet, whilst a is calculated from the penetration depth, h, and the Vickers indenter geometry, and l = c - a. In this method the crack length is likely to be underestimated, since were the tablet wider the crack may propagate further, and hence the fracture toughness is likely to be overestimated.

Fracture toughness – LEFM method

As an alternative method for determination of fracture toughness, we also consider Linear Elastic Fracture Mechanics (Lawn, 1993), which states

$$K_c^2 = 2E\Gamma \qquad \text{(Eq. 7)}$$

where Γ is the fracture surface energy of the material. Since all tablets considered in this work are made of Avicel and the tablet strength is attained during the compression stage through plastic flow which enlarges the interparticle contact areas, we assume the surface energy is constant and independent of the packing density. Therefore, fracture toughness is proportional to the square root of Young's modulus of the tablet. For simplicity we take the value of K_c for tablets of 0.65 solid fraction from the failure method to be correct and use the proportional change in Young's modulus to determine the fracture toughness for tablets of different solid fraction.

Fracture toughness - comparison

The fracture toughness values determined by both methods are given in Table 3, along with the values of H/K_c^2 determined by indentation by both methods, and the value of C ($\alpha H/K_c^2$) determined by impact breakage. The fracture toughness determined by the crack length at failure method is almost independent of the tablet solid fraction. This seems an unlikely trend since fracture toughness is expected to increase with solid fraction; in fact K_c for single particles is often estimated by extrapolation to zero porosity of the K_c variation with beam porosity using the fitting equations of Spriggs (1986) or Spinner et al. (1963). However since the tablets of greater solid fraction have a reduced thickness, this may have had a confounding effect on the measured fracture toughness, though it should be noted that this effect is not present in the results from the LEFM method.

Figure 9 compares the index (H/K_c^2) determined using the failure method and LEFM method, and the propensity for breakage ($\alpha H/K_c^2$) determined by impact tests. It should be noted that α is small, and therefore what is important for comparison is the trend of the data points rather than the actual values. The index (H/K_c^2) increases with solid fraction for both the failure method and LEFM method, though more substantially for the failure method. In contrast, the propensity for breakage determined by impact tests decreases with solid fraction, which is intuitively expected. A number of factors may give rise to the discrepancy in the trend between the indentation methods and the impact breakage.

1. The assumption that the crack would terminate at a distance of 5 mm (the tablet radius) from the centre of the indent, even if the tablet diameter were increased, is false.
2. LEFM method may not be applicable.
3. The Ghadiri and Zhang (2002) model is not applicable for tablets.
4. The mechanical properties of the tablet differ at the centre (measured by indentation) and the corners, where breakage occurs by chipping under impact as the solid packing density would be different.
5. The mechanical properties of the tablet may depend on the strain rate of the failure mode, hence leading to different behaviour under quasi-static indentation and dynamic impact.

The assumption that the crack would terminate at 5 mm from the indent appears to be too simplistic (despite the fact that the minimum load required to get fracture propagation was used), particularly since this leads to fracture toughness being almost independent of porosity. The variation of fracture toughness with porosity for LEFM method is more reasonable, however further work is required to characterise the variation of hardness, elastic modulus and fracture toughness from the centre to the edge. Density and hardness have been shown to exhibit variations along the radial direction under certain compaction conditions (Sinka et al., 2003). Indeed this seems the most likely reason for the discrepancy between the indentation and impact methods, along with the strong possibility of the mechanical properties changing with strain rate. However, deformations around the edges are less confined, so in addition to the solid fraction likely being lower than the centre, the edges will fail much easier by propagation of sub-surface cracks. Therefore, impact testing is a more appropriate method to assess tablet attrition/chipping due to the above two main reasons.

4. Conclusions

The breakage behaviour of Avicel PH102 tablets has been assessed using repeated single impacts at fixed heights. The extent of breakage increases approximately linearly with number of impacts, and the breakage propensity decreases as tablet solid fraction is increased. The extent of impact breakage correlates well with the kinetic energy of the impact. On this basis the propensity for breakage, represented by the lumped parameter $\alpha H/K_c^2$, has been determined using the model of Ghadiri and Zhang (2002). The Young's modulus, hardness and fracture toughness of the tablets were determined independently by (quasistatic) microindentation, and the index (H/K_c^2) calculated for comparison with impact tests. Fracture toughness could not be measured reliably since generated cracks led to complete failure of the tablets. The index H/K_c^2 determined in this way did not correlate well with the propensity for breakage, nor did applying the LEFM approach, i.e. Kc being correlated with Young's modulus. Tablet attrition and chipping occur at edges, where the solid fraction is likely to be different from the internal regions (Sinka et al., 2003). This feature together with deformation being less confined at the edges and its possible strain rate sensitivity will make the quasi-static characterisation of tablet damage mechanics challenging. Therefore impact testing and damage analysis by the use of Ghadiri and Zhang (2002) model may provide a quicker and easier way to assess tablet impact damage, as it better represents the dynamic mechanical properties.

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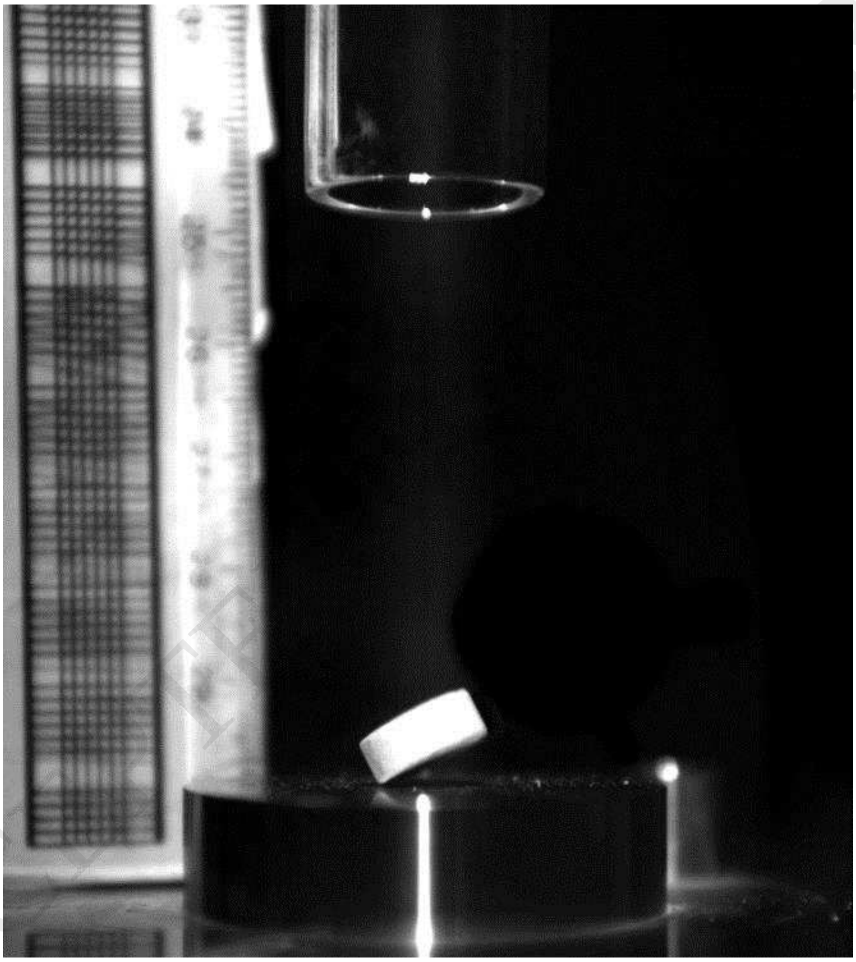

Figure 1. Tablet impact test setup

(b)

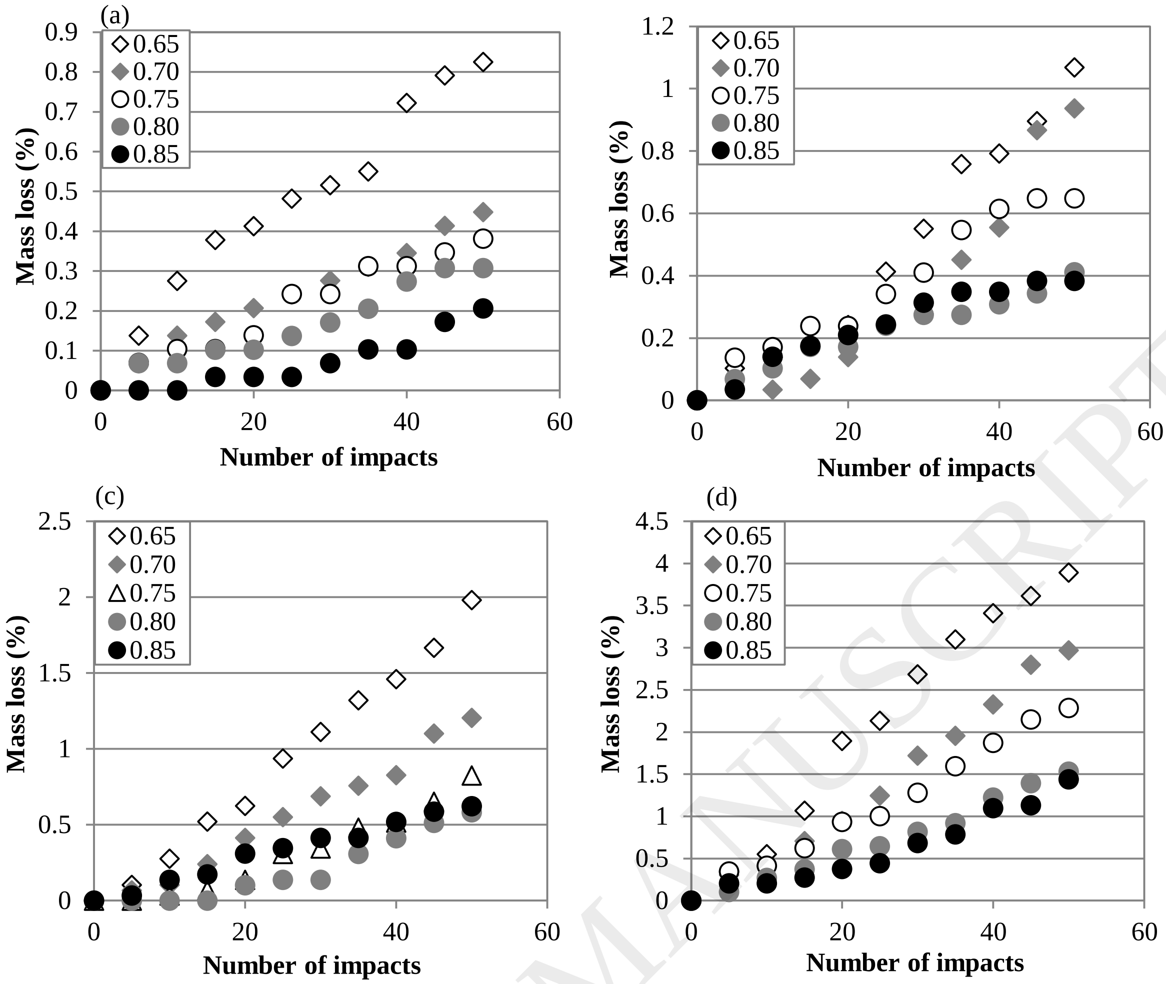

Figure 2. Cumulative mass loss due to impact for Solid fractions (SF) of 0.65, 0.70, 0.75, 0.80 and 0.85 at impact velocities (a): 3.8 m/s; (b): 4.0 m/s; (c): 5.2 m/s; (d): 7.3 m/s

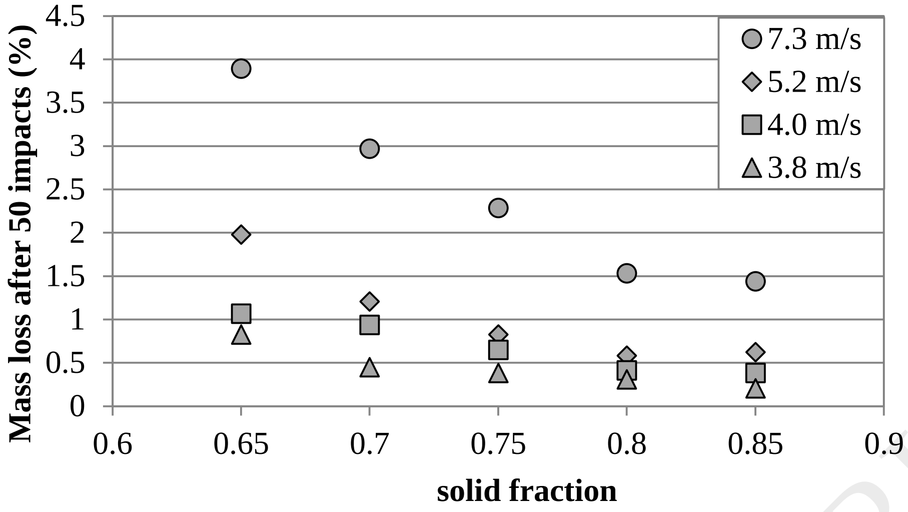

Figure 3. Total mass loss after 50 impacts at different impact velocities

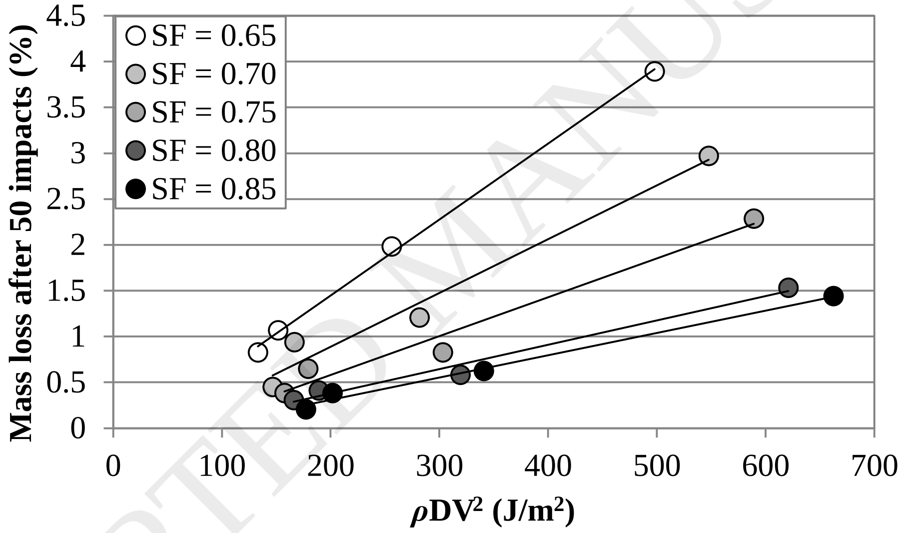

Figure 4. Impact breakage propensity of the tablets

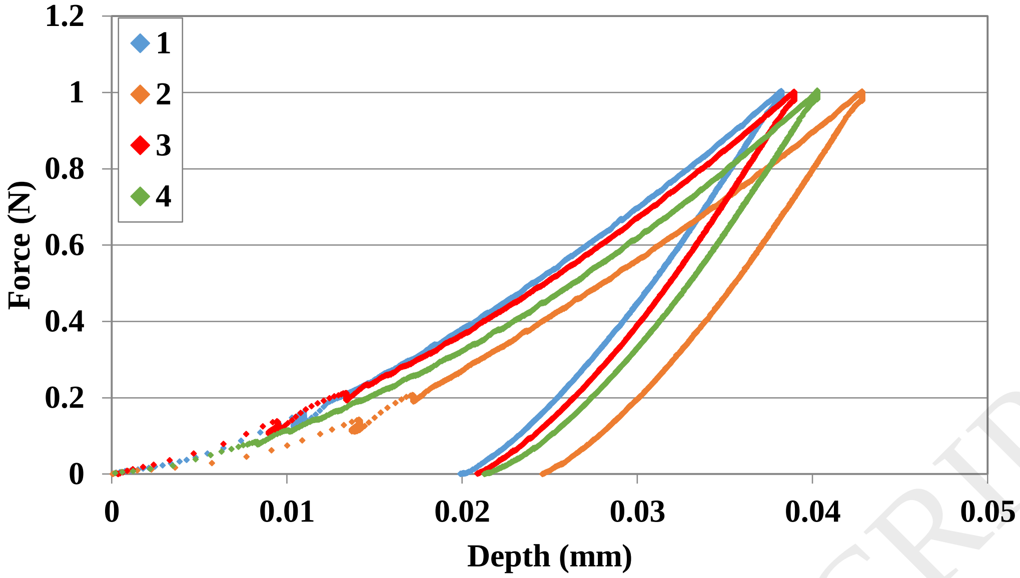

Figure 5. Indentation profiles on Avicel tablets of 0.85 solid fraction

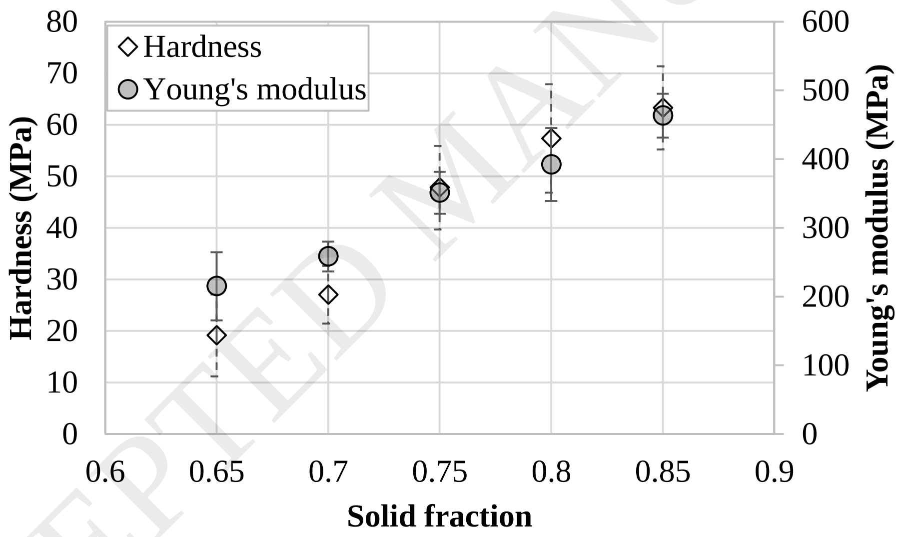

Figure 6. Hardness and Young's modulus of Avicel tablets

Figure 7. Crack propagation at failure force

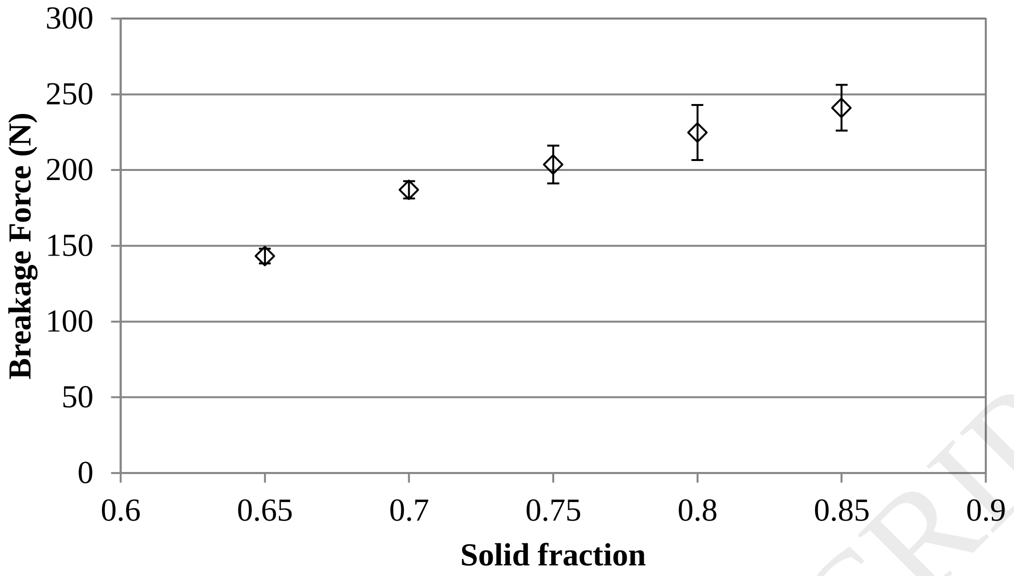

Figure 8. Failure force of the Avicel tablets as a function of solid packing density

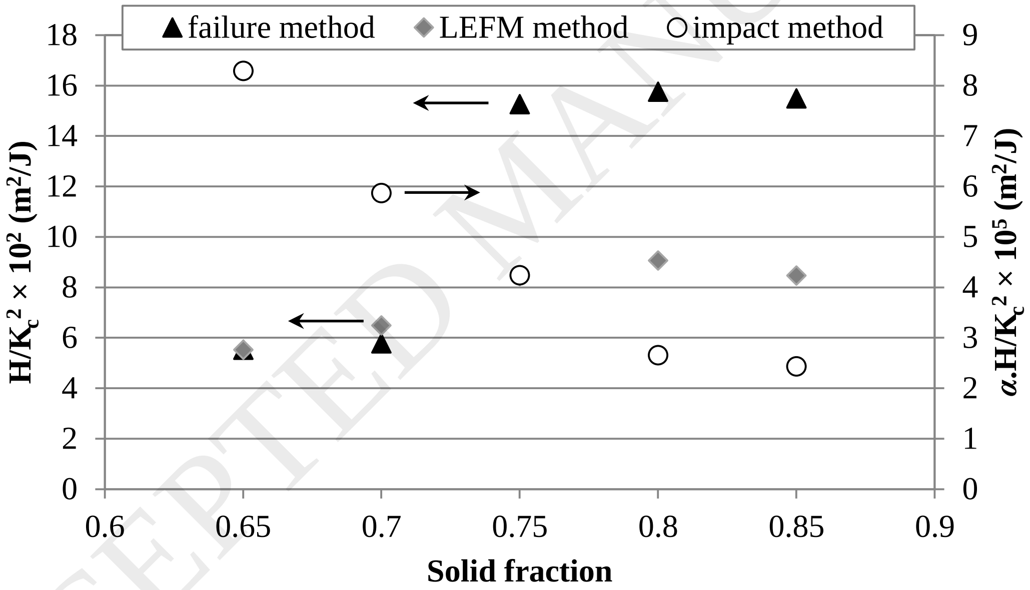

Figure 9. Comparison of brittleness index and propensity for breakage

Table 1. Tablet dimensions and density

Solid fraction	Diameter (mm)	Average thickness (mm)	Average mass (g)	Density (kg/m^3)
0.65	10	3.89	0.2896	947
0.70		3.55	0.2908	1042
0.75		3.34	0.2938	1121
0.80		3.16	0.2932	1181
0.85		2.95	0.292	1260

Table 2. Hardness and Young's modulus of Avicel tablets

Property	Solid fraction	Average value	Standard deviation	Coefficient of variation (%)
Hardness (MPa)	0.65	19.1	7.9	41.5
	0.70	27.0	5.6	20.7
	0.75	47.8	8.1	16.9
	0.80	57.3	10.5	18.4
	0.85	63.3	8.1	12.8
Young's modulus (MPa)	0.65	215	49	23.0
	0.70	258	22	8.4
	0.75	351	31	8.7
	0.80	392	53	13.5
	0.85	463	32	6.9

Table 3. Fracture toughness and breakage propensity of Avicel tablets

Solid fraction	0.65	0.70	0.75	0.80	0.85
H (MPa)	19.1	27.0	47.8	57.3	63.3
E (MPa)	215	258	351	392	463
K_c – failure method ($kPa.m^{1/2}$)	18.6	21.6	17.7	19.1	20.2
K_c – LEFM method ($kPa.m^{1/2}$)	18.6	20.4	23.8	25.2	27.3

H/K_c^2 – failure method (m^2/J)	5.52×10^{-2}	5.77×10^{-2}	1.53×10^{-2}	1.58×10^{-1}	1.55×10^{-1}
H/K_c^2 – LEFM method (m^2/J)	5.52×10^{-2}	6.48×10^{-2}	8.44×10^{-2}	9.06×10^{-2}	8.47×10^{-2}
$\alpha H/K_c^2$ – impact method (m^2/J)	8.29×10^{-5}	5.87×10^{-5}	4.24×10^{-5}	2.65×10^{-5}	2.43×10^{-5}

*please note the uncertainty in the accuracy of these values, as detailed below