International Journal of Pharmaceutics 172 (1998) 199–209

international journal of pharmaceutics

Disintegration of weak lactose agglomerates for inhalation applications

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Received 8 December 1997; received in revised form 9 June 1998; accepted 21 June 1998

Abstract

Inhalation is a convenient and effective method of drug delivery for a number of common illnesses, many of which affect the respiratory system, such as asthma. Lactose is a commonly used material in the pharmaceutical industry as a carrier of drugs. The use of weak lactose agglomerates in dry powder inhalers depends very much on the way the agglomerates disintegrate. The disintegration of weak agglomerates depends on the bonding mechanism and the agglomerate structure, both of which are to date poorly understood. An experimental study of the disintegration of weak lactose agglomerates is reported here. The effects of agglomerate size and ambient humidity level on the extent and mechanism of breakage are investigated using a single agglomerate impact testing technique. The extent of disintegration is shown to scale with the square of the impact velocity. The dry-kept agglomerates are shown to fail in a mode similar to the ductile failure mode of solid materials, with large overall deformation and internal shearing, without the development of a clear crack plane. Agglomerates which have been kept in a humid environment exhibit a classical semi-brittle failure mode. The experimental results of impact tests with dry-kept agglomerates compare well to the results of numerical simulations using distinct element analysis (DEA). The impact test appears to be a useful tool for the determination of the influence of material properties and structure and process conditions on the breakage behaviour.

Keywords: Inhalation; Agglomeration; Particle technology; Lactose; Breakage

1. Introduction

Inhalation is a convenient and effective way of drug delivery for many illnesses. It has many advantages over alternative methods of drug delivery, such as injection and tablets. Inhaled drugs are particularly favoured for respiratory illnesses, as they are delivered directly to their site of action. Compared to injections and oral delivery, generally smaller doses are needed, thus reducing the risk of side effects, and the action of the medication is swifter, thus making them suitable

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PII S0378-5173(98)00207-5

for treating symptoms immediately. Furthermore, the method is particularly attractive if the medication is likely to get broken down in the digestive system when using tablets.

Considerable effort is being spent to package a variety of drugs for inhalation therapy. The current technology is based mainly on 'metered-dose' inhalers using propellants. For environmental reasons, however, there are serious concerns about the use of CFC-based propellants, and the Montreal Protocol, the result of the United Nations Environment Programme (UNEP) meeting in Canada in 1987, and signed by more than 150 countries, set a world-wide goal to end CFC usage by 1 January 1996, and a specific ban on CFC in MDI by the year 2005. Since then, several CFC-free MDI propellants have been developed. However, the presence of the propellant also requires the use of additional ingredients to render the formulation of the drug successful in combination with the propellant. An additional problem is the control of the powder size during dispensing. These problems have led to the development of dry powder inhalers. In these devices, a dose of the drug is dispensed in a powdered form and the energy of the patient's breath intake is sufficient to deliver the dose. However, lack of control of the disintegration causes a significant proportion (up to 85–90%) of the drug to be deposited in the oro-pharynx (Merec Briefing, 1993). The precise delivery of the right dose in the right particle size is a challenging problem, the solution of which would make this technique suitable for use with a wide range of drugs, not only for asthma, but also for insulin for diabetes, and medication for common influenza.

A comparative study of MDI and a specific dry powder inhaler, called the Diskhaler, in asthma treatment with beclomethasone dipropionate (BDP) showed that there was a significantly larger improvement in the lung function with the Diskhaler, compared to MDI (Drepaul et al., 1989). The same study showed, moreover, that the number of patients using the Diskhaler incorrectly was significantly lower than those misusing the MDI, so that additional benefits such as efficacy, tolerability and ease of use may be achieved with dry powder inhalers.

In *dry powder inhalers*, the drug (in fine particulate form) is mounted/coated on the large particles of an excipient such as lactose. For the process to be effective, the drug has to be in fine particulate form, typically in the micrometre range or smaller. However, for precise dosage and ease of dispensing, the fine particulates may be agglomerated on their own or with an excipient such as lactose into much larger particles. These agglomerates should disintegrate thoroughly after dispensing, so that the fine particles can be inhaled deep into the lungs. The agglomerate must therefore be weak enough to disintegrate on a low energy impact and disperse for inhalation. On the other hand, the agglomerate should be sufficiently strong to withstand breakage during storage and transport. There is therefore a narrow window for which the strength of the agglomerate needs to be carefully tailored. A knowledge of the mechanical properties of the agglomerates, the disintegration characteristics of the agglomerate, and the environmental factors, such as humidity, is very important for reliable design and operation of dry powder inhalers. In the present study, the breakage of weak lactose agglomerates is quantified as a function of impact velocity using a single agglomerate impact testing technique. The mechanism of breakage is visualised using high-speed video recordings of the impacts and the products of the breakage are examined by scanning electron microscopy (SEM) and optical microcopy. Two different size ranges of the agglomerates are used to evaluate the effect of agglomerate size on the extent of breakage. Work by Newton and Podczeck and co-workers (see, e.g. Podczeck et al., 1996, 1997) has shown that the humidity level influences the autoadhesion forces of primary particles. Their model calculations indicated that this effect is not so much due to changes in capillary forces but more to the surface free energy and its polar component. The effect of humidity is also evaluated by testing a dry sample and a sample which has been exposed to a humid environment for a certain period of time. In the following, the test method is described first and the results are discussed and compared to numerical predictions of the breakage behaviour, obtained from distinct element analysis (DEA).

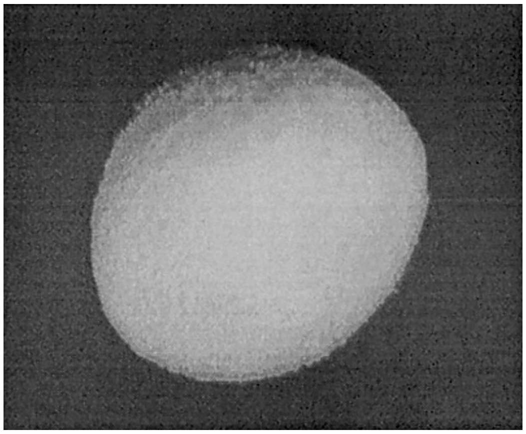


Fig. 1. A lactose agglomerate.

2. Experimental

2.1. Materials

The materials used in the test are weak agglomerates of α-lactose, formed by dry tumbling of fine powder, and were prepared by Glaxo–Wellcome R&D (Hallworth, 1995, personal communication). Fig. 1 shows an optical micrograph of an agglomerate of about 700 μm. The agglomerate has a 'fluffy' appearance because of the highly irregular surface formed by the adhesion of the primary particles, which are only a few microns in size. Fig. 2 shows loose primary particles which have detached from the agglomerate. They exhibit clear flat surfaces and high transparency. Fig. 3 shows the primary particles at the surface of the agglomerate. These primary particles are bonded by surface adhesion forces only, and no material binder is present.

Pietsch (1991) gives a number of examples of surface adhesion forces in the absence of solid or liquid bridges and binders between primaries. They can consist of molecular (Van der Waals) forces, electrostatic forces, or free chemical bonds (valences). In the case of lactose agglomerates, the adhesion forces belong to the first category, which can attain very high values at extremely short distances, but they diminish quickly with increasing distance.

The internal structure of the agglomerate is determined largely by the number and nature of the points of (near) contact or co-ordination points, and depends on the production method. The presence of humidity may cause partial dissolution at the contact points, leading to the forma-

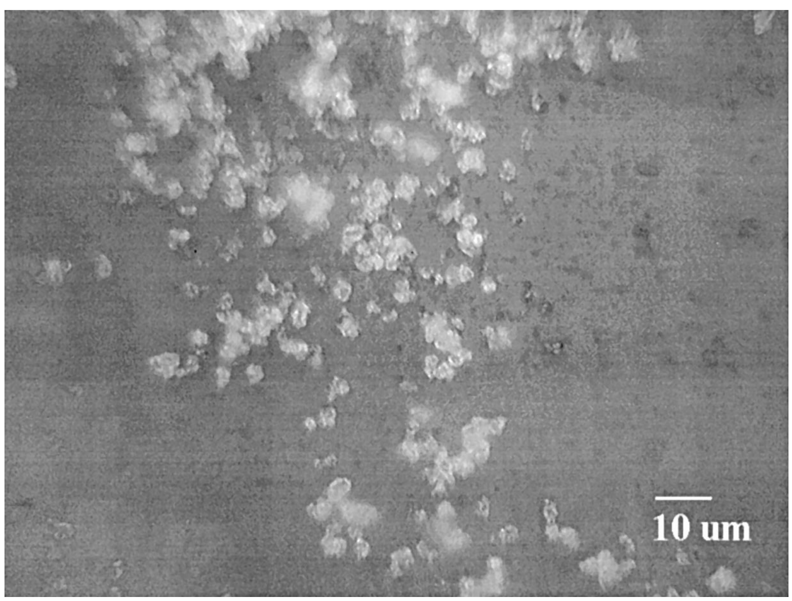


Fig. 2. Single and small clusters of primary particles.

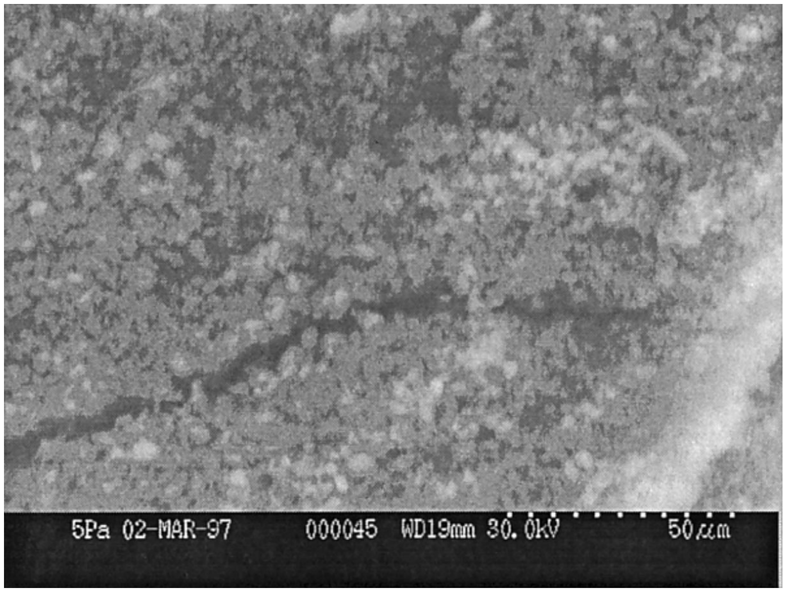


Fig. 3. Lactose agglomerate surface.

tion of liquid and solid bridges. The ambient humidity is therefore an important parameter in the breakage mechanism of weak lactose agglomerates.

Two different particle size ranges in single BS 410 sieve cuts were used, 250–355 and 600–710 μm. The samples were kept at two different humidity levels. Podczeck et al. (1997) have shown that storage of lactose assemblies at humidity levels higher than 75% results in irreversible, strong forces acting at the interface of the particles, whereas below this humidity level, capillary forces could be removed by storage at relative humidity of 5% for at least 72 h. One sample of both size ranges was kept dry in a desiccator with silica gel. Of the larger size range, one sample was kept in a humid environment. The humid environment was created in an airtight chamber, which contained a reservoir of a saturated solution of sodium carbonate monohydrate in distilled water. The temperature of the cupboard was kept at 24.5°C. At this temperature, the relative humidity reaches a value of 87% (Wexler and Wildhack, 1965). The samples were left in this environment for 72 h. The humidified samples were observed to have lost most of their 'fluffy' appearance and obtained a shiny smooth surface.

2.2. Method

A batch of agglomerates, about 2 g, is fed gently in a single array into an air eductor, shown in Fig. 4. The eductor consists of a funnel-shaped inlet section, guiding the particles into the eductor tube. Near the exit of the tube, there are two photodiodes, 16 mm apart, providing triggers for a timer for measurements of the particle velocity. After leaving the tube, the particles enter a chamber, where they impact on a sapphire target plate. The impact velocities ranged from the free fall velocity up to 10 m s^{-1}. The air used to accelerate the particles is supplied by a compressor, and is withdrawn from the collection chamber through a brass porous plate. The porous plate is covered with a paper filter (Whatman). The impacts have been recorded using a digital high-speed video camera, a Kodak HS 4540 Motion Analyzer, capable of recording rates up to 40 500 frames per second.

After impact, the products are collected from the chamber and classified using BS410 sieves. The particles are separated into two fractions. Debris is defined as the material that passes through a sieve of two standard sizes below the lower sieve size of the original material. For the two size ranges used here, 250–355 and 600–710 μm, the sieve sizes for separating the debris are 180 and 425 μm, respectively.

The extent of breakage is defined as the ratio of the mass of debris created upon impact, M_d, to the mass of agglomerates originally fed to the impact rig, M_f. Handling losses are inevitable, especially with this material in view of its high adhesivity. This leads to errors in the determination of the extent of breakage, If the handling losses are all attributed to the mother particles, a lower limit of the extent of breakage can be defined as:

$$\xi^- = \left(\frac{M_d}{M_f}\right)100\% \quad (1)$$

If, on the other hand, all losses are attributed to the mass of debris, an upper limit of the extent of breakage is defined as:

$$\xi^+ = \left(\frac{M_f - M_m}{M_f}\right)100\% \quad (2)$$

where M_m is the mass of surviving agglomerates. In practice the actual value of the extent of breakage is between these two limits, and to provide reliable data the losses have to be reduced as much as possible.

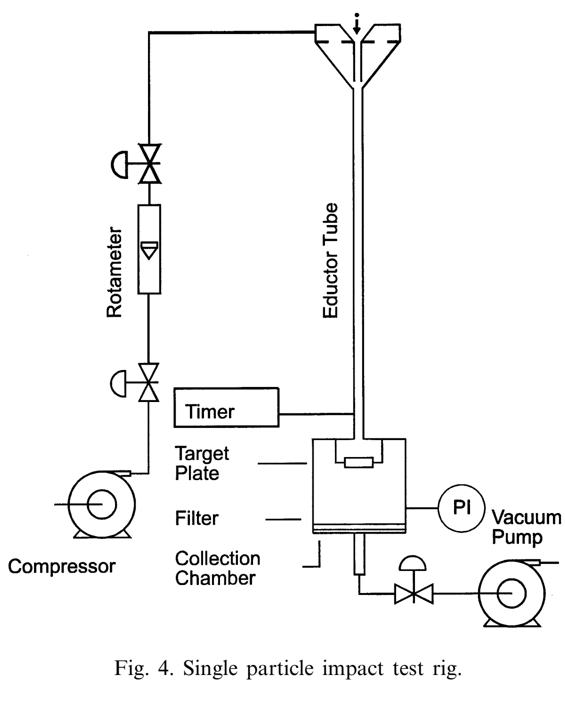


Fig. 4. Single particle impact test rig.

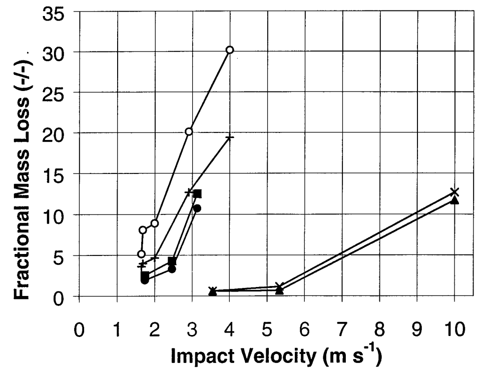


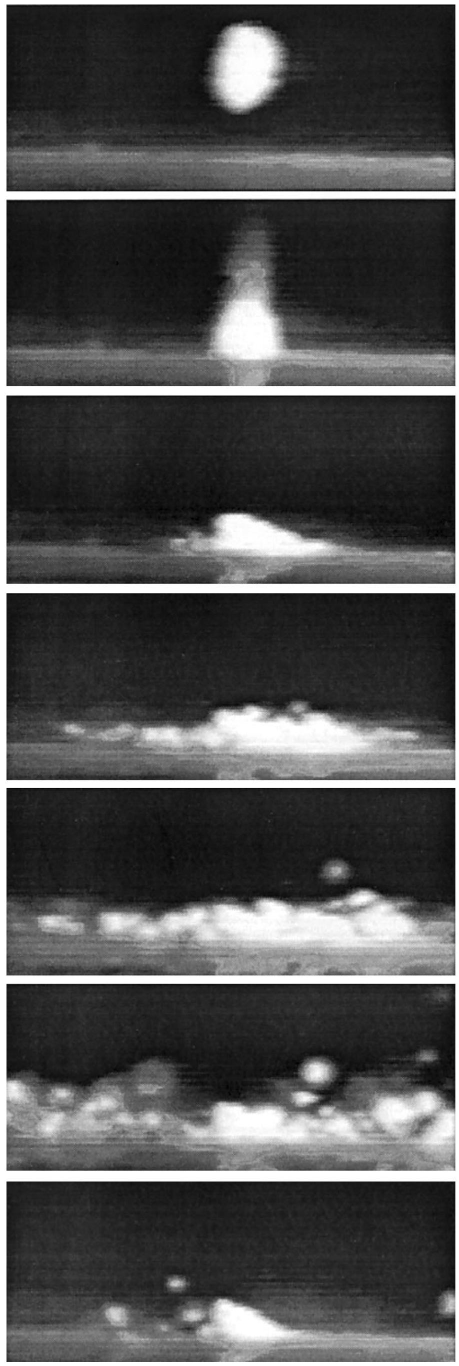
Fig. 5. Fractional mass loss as a function of impact velocity.

3. Experimental results

Fig. 5 shows the extent of breakage, expressed as the fractional mass loss defined by Eqs. (1) and (2), versus the impact velocity. The fractional mass loss is larger for the smaller agglomerates when compared to both wet and dry of the larger agglomerates. The extent of breakage of the smaller sample is about twice that of the larger dry sample. The sample that has been exposed to a humid environment appears to be far more resistant to breakage than the dry sample of the same size range, 600–710 μm.

Inspection of the debris of the dry impacted agglomerates using optical microscopy showed that the debris mainly consists of single primary particles and small clusters of only a few primary particles. Cleaver et al. (1993) have shown that the extent of breakage (Eqs. (1) and (2)) is insensitive to the criterion of the debris sieve size if the debris is much smaller than the original particles. The debris of the wet agglomerates consists of small flakes, well below the size of the mother agglomerates.

Fig. 6 shows a sequence of high-speed images captured from the impact of a dry agglomerate at 10 m s^{-1}. The agglomerate is shown to deform strongly upon impact during the first stages of the



(a) 28.5 μs before impact;

(b) t = 20.77 μs;

(c) t = 131.8 μs;

(d) t = 353.8 μs;

(e) t = 612.8 μs;

(f) t = 1.427 ms;

(g) t = 6.387 ms.

Fig. 6. A sequence of images captured by high-speed digital video recording at 27000 frames s^{-1} of an agglomerate impact at a velocity of 10.0 m s^{-1}. Time is relative to first contact between agglomerate and target.

impact. As the impact progresses, a large number of small fragments, consisting of small clusters and single primaries, detach from the agglomerate and disperse into the surrounding air flow. The way the impact progresses for a wet agglomerate is very different from this. The agglomerate shows much less deformation, and a few chips, flaky pieces, detach from the agglomerate rather than numerous small clusters and single primaries. This is illustrated in Fig. 7, which shows an impacted wet agglomerate at 3.96 ms after the first contact with the target plate. A similar difference in behaviour between dry and wet agglomerates is also illustrated by the behaviour at free fall impact velocity. The dry agglomerate already loses a considerable amount of primary particles at the lowest impact velocities, whereas the wet agglomerate was seen to bounce off the plate without incurring significant damage. The surface adhesion forces bonding the primary particles of the dry agglomerate are of the order of 10^{-11} N, i.e. some six orders of magnitude smaller than the strength of the liquid and solid bridges that sustain the wet agglomerate structure (Podczeck et al., 1997).

4. Comparison with DEA

The DEA, first developed by Cundall (1971, 1988), presents a convenient way to obtain insight into the behaviour of particle systems and provides fundamental information such as microscopic structure, interparticle forces, particle velocities, etc. Most importantly, this method makes it possible to relate the bulk mechanical behaviour of the assembly to individual particle properties. A detailed examination of the micromechanics, which

Fig. 7. Impact of a wet agglomerate at 8 m s^{-1} at 3.96 ms after the impact.

Table 1
Material properties used in the simulations

	Lactose crystals	Stainless steel
Young's modulus (GPa)	3.2	215
Poisson's ratio	0.3	0.3
Density (kg m^{-3})	1550	7800
Yield stress (GPa)	0.21	3.04
Friction	0.35	0.35
Fracture toughness (kPa $m^{-1/2}$)	41.9	NA

determine the bond breaking and the internal microstructural deformation, can therefore be provided. Simulations of impact fracture of agglomerates have been reported by Thornton et al. (1996) for two-dimensional agglomerates (2D) and by Kafui and Thornton (1993, 1994) for three-dimensional agglomerates (3D). In the latter, a monodispersed spherical agglomerate consisting of 8000 primary particles in face-centred cubic arrangement was impacted against a wall. In order to analyse some of the above experimental results, Ning et al. (1997) have recently carried out distinct element simulations of impacts of weak dry lactose agglomerates, using the code as developed by Thornton and co-workers (Thornton, 1991; Thornton and Yin, 1991; Ning, 1995). The model of Johnson et al. (1971) was used for calculation of the interparticle forces in a dry agglomerate system. For the simulations, the mechanical properties of the constituent particles were assumed to be the same as those of lactose crystals. For the latter, the material properties have been characterised by the use of nano-indentation techniques (Arteaga, 1995, University of Surrey, private communication) and are summarised in Table 1. Roberts (1991) summarised reported values of the interface energy of lactose crystals, which varied from 0.2 to 42 J m^{-2}! This variation is considered to be due mainly to differences in material properties such as Young's modulus and porosity, as well as the test methods used. The agglomerate used in the simulation has an overall size of 300 μm and consists of 2000 particles of 10 μm, with a solids fraction of 0.522 and an interface energy of 0.5 J m^{-2}. The method of preparation of the agglomerate has been de-

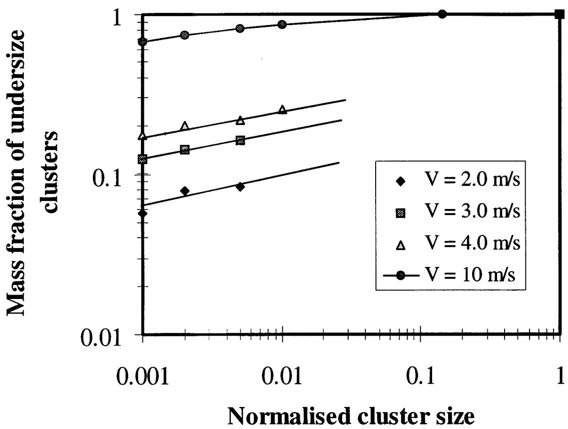


Fig. 8. Fragment size distribution.

scribed in detail by Ning et al. (1997), and further details of the input parameters for the simulations may be found there.

Fig. 8 shows the fragment size distribution upon impact. The impact damage results in several relatively small clusters of up to a few tens of particles, and one residual cluster of much larger size. An interesting point to note here is the self-similarity of the size distributions of the complement for different impact velocities, i.e. having similar slopes of the trend lines when plotted on a log–log scale. For comparison with the experimental data of impacts of dry agglomerates of 250–355 μm (Fig. 5), the total mass of the small clusters is defined as debris, and in this way the

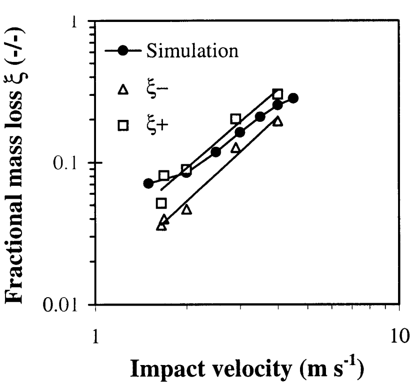


Fig. 9. Comparison of simulation of 300 μm agglomerate impact with experimental results for 250–355 μm agglomerate impacts.

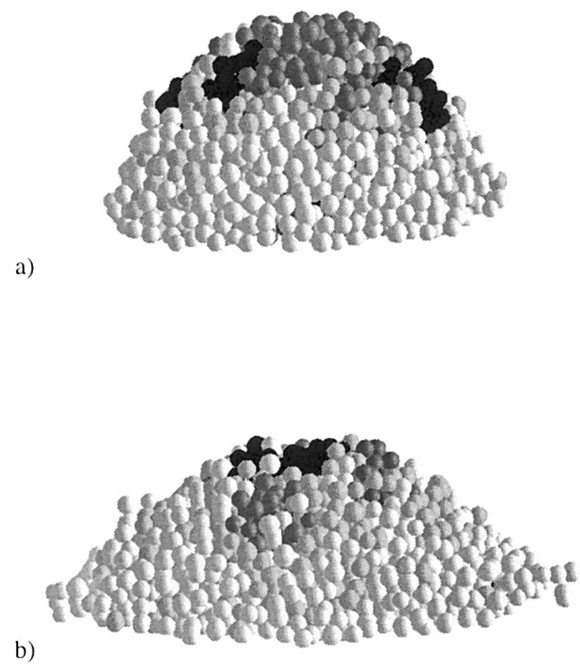


Fig. 10. Simulation of an impact of an agglomerate at 10.0 m s^{-1} at (a) $t = 10.6$ μs and (b) $t = 17.7$ μs after contact. Colour coding: white, singlets; light grey, clusters containing two to ten particles; black, clusters containing 11–30 particles; dark grey, residual cluster.

extent of breakage is calculated, as shown in Fig. 9. A good agreement between the predictions of the simulation and the experimental results is found. Fig. 10 shows the simulated agglomerate at two stages during an impact at 10 m s^{-1}. The agglomerate has deformed and disintegrated. The appearance is very similar to the later stages of the impact recorded in Fig. 6.

5. Discussion

5.1. Breakage mechanism of dry and wet agglomerates

Breakage of particulate solids is broadly classified in terms of brittle, semi-brittle and ductile failure, depending on the deformation mode (Puttick, 1980; Shipway and Hutchings, 1993). Brittle failure is caused by fracture with little or no plastic deformation. Impact under this failure mode usually produces diametrical cracks, splitting the particle into fragments, as the diametrical plane is under the greatest tensile stress (Shipway and Hutchings, 1993). If plastic flow precedes the fracture, the process is termed semi-brittle. The plastic zone produces compressive radial stresses and tensile hoop stresses. The latter type of stress propagates radial and median cracks, initiated from the plastic zone. When the load is removed, the residual tensile stresses, formed after the elastic unloading process, generate sub-surface lateral cracks. The characteristics of the semi-brittle failure mode are particle fragmentation due to the formation of median and radial cracks, and chipping due to the formation of lateral cracks (Puttick, 1980; Ghadiri and Zhang, 1992; Papadopoulos and Ghadiri, 1996). Ductile flow is dominated by extensive plastic flow which is responsible for the rupture of the material. Ploughing and cutting are the two main mechanisms of material removal for this failure mode (Hutchings, 1992).

On the basis of a linear elastic fracture mechanics analysis of semi-brittle failure, Ghadiri and Zhang (1992) showed that the impact breakage should scale with the square of the impact velocity. Indeed, the slope of the trend lines of the fractional mass loss versus impact velocity shown in Fig. 9 is 2. The breakage mode of dry agglomerates, however, is not comparable to a semi-brittle failure mode for a solid particle. The dry agglomerates deform considerably upon impact and the debris created consists mainly of single primary particles and small clusters of a few primaries. Wet agglomerates on the other hand, appear to break in a mode which is more similar to that of a semi-brittle solid, with the formation of flaky chips from the agglomerate surface, but considerable plastic deformation is still observed.

Duo et al. (1996) have shown that even the breakage of very tough agglomerates with a porous structure (fluid cracking catalyst) exhibits a square dependence on the impact velocity. Papadopoulos and Ghadiri (1996) have shown that many different materials with widely different structures exhibit the same tendency. From this, it may be inferred that the amount of breakage scales with the kinetic energy upon impact, regardless of the material structure.

5.2. Effect of agglomerate size

When comparing the extent of breakage of the small and large dry agglomerates, it is evident from Fig. 5 that the extent of breakage is larger for the smaller particles. This is in contrast to the observed trends for solid particulates for which the extent of breakage increases with particle size. The model of Ghadiri and Zhang (1992) for semi-brittle particulates predicts a linear dependence of the extent of breakage on the particle size. Duo et al. (1996) have verified this experimentally for fluid cracking catalyst particles. For the brittle failure mode, Kendall (1978) relates the increased breakage propensity of larger solid particulates to an increase in the size and density of the pre-existing flaws. The present agglomerates exhibit a higher resistance to breakage with an increase in size. However, bearing in mind that these agglomerates do not fail in a brittle mode, it is most likely that the structure of the agglomerates is different between the two sizes. As the agglomerates are dry tumbled, the agglomerate growth is by layer-wise adhesion of the primary particles. Consequently, the core can get more compacted, resulting in a stronger agglomerate with an internally non-uniform but distributed porosity. The analysis of agglomerate strength by Kendall (1988) shows that both the fracture toughness and the bending strength of agglomerated materials increase strongly with a decrease in void fraction. In his comprehensive review of the dependence of fracture energy and toughness on grain size and porosity, Rice (1996) shows that the Young's modulus, tensile strength and fracture toughness all increase with a decrease in porosity. This aspect has important implications on the manufacturing procedure. A tight control of the particle size distribution is required to prevent large differences in mechanical properties within a single batch of agglomerates.

5.3. Effect of humidity

From Fig. 5, it is evident that the agglomerates which have been kept in a humid environment have a far lower breakage propensity. The most likely reason is the transformation of amorphous lactose, produced during the milling operation, into a lactose monohydrate which could cause the solidification of interparticle contacts. Amorphous lactose is highly hygroscopic. This could lead to surface adsorption, particularly at the contact points, resulting in the formation of solid bridges of the monohydrate form of lactose crystals. The structure of the agglomerate becomes more rigid and thus brittle, as the primaries are no longer capable of sliding along each other, but are fixed in their place by the bridges. This is confirmed by the formation of flaky chips upon impact, instead of the detachment of small clusters and single primaries from the agglomerate. The formation of crack planes in the former is similar to those found in semi-brittle failure of non-porous particulates (Ghadiri and Zhang, 1992) and brittle spheres (Arbiter et al., 1969). Sebhatu et al. (1994) found that moisture uptake causes an amorphous–crystalline transition in spray-dried (15% amorphous) lactose powder. They postulated that moisture is adsorbed preferentially in the amorphous regions, setting up conditions for crystallisation, resulting in a higher compact strength.

5.4. Self-similarity of fragment size distribution

For brittle spheres, Arbiter et al. (1969) showed that the fragment size distribution can be represented by a set of three straight lines on a logarithmic coordinate system, one for each of the three categories: coarse fragments (residual, or mother particle), fine fragments (complement) and dust. Fig. 8 shows that the slope of the complement size distribution is the same for all the impact velocities. Arbiter et al. (1969) observed the same phenomenon with sand–cement spheres. Impact studies of PMMA particles by Papadopoulos (1998) and distinct element simulations of agglomerate impacts by Thornton et al. (1997) show the same as well. This suggests that the characteristics of the size distribution are insensitive to changes in the impact velocity.

6. Conclusions

Breakage of weak lactose agglomerates has been investigated using a single particle impact test method. The breakage mode was identified using high-speed digital video recordings, and was found to be very different from that of non-porous particulates reported so far, i.e. extensive deformation takes place which resembles that of highly ductile solids. A strong effect of humidity on the extent of breakage was found, which is attributed to the change of interparticle bonding mechanism. A comparison of impact breakage of large and small agglomerates showed that large agglomerates are less prone to breakage than smaller agglomerates. This behaviour is in contradiction with that of the solids reported so far, and is considered to have arisen from the difference in the structure of the agglomerate, evolving as a result of the preparation procedure.

A good agreement was found between the experimental results and simulations of impact of small and dry lactose agglomerates using DEA. Both experiments and simulations show that the impact breakage of dry agglomerates is a function of the square of the impact velocity. This is in agreement with the behaviour of other types of particulates and with the model of Ghadiri and Zhang (1992) for semi-brittle failure. However, the present agglomerates fail in a mode which is more similar to ductile failure of non-porous particulates. The fragment size distribution obtained from the simulations shows self-similar trends which are in good agreement with results reported in the literature for other materials. DEA appears to be a useful tool for providing insight into the internal mechanism of breakage of weak dry agglomerates.

7. Nomenclature

M_d mass of debris (g)
M_f mass of particles fed (g)
M_m mass of surviving agglomerates (g)
ξ^+ upper limit of breakage (Eq. (1)) (–/–)
ξ^- lower limit of breakage (Eq. (2)) (–/–)

Acknowledgements

The authors wish to express their gratitude to Dr G.W. Hallworth of Glaxo–Wellcome Research and Development for preparing the lactose agglomerates. The authors acknowledge support from the Engineering and Physical Sciences Research Council for the purchase of the Kodak High Speed Motion Analyser used in this work. The authors are grateful to Mr. Pedro Arteaga for providing data on some of the mechanical properties of lactose crystals, measured by nano-indentation and used in the DEA simulations.

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