International Journal of Pharmaceutics 387 (2010) 87–92

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Blending of agglomerates into powders 1: Quantification of abrasion rate

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ARTICLE INFO

Article history:
Received 22 June 2009
Accepted 4 December 2009
Available online 14 December 2009

Keywords:
Abrasion
Dry powder
Impeller speed
Calibrated test particle
Fraction loss
Mixing time

ABSTRACT

A very common situation in the pharmaceutical arena is that a small amount of cohesive drug substance needs to be distributed in a large bulk of free-flowing filler such as lactose. The key topic of attention is that aggregates of a cohesive drug substance need to be sufficiently broken up in an acceptable time-frame. This implies that there is need for a better mechanistic understanding of the blending process and the reduction in size of the aggregates. The purpose of this study is to obtain more insight in the mechanisms that lead to the break up of assemblies of powder particles in a moving powder bed. The break up of aggregates was studied by application of so-called brittle Calibrated Test Particles (bCTPs). These are well-defined aggregates with brittle fracture properties.

The dominant mechanism of the break up of these aggregates is abrasion by multiple impacts. There is evidence of a relationship between strength (expressed as porosity) of the bCTPs and rate of abrasion. This is often a slow process and the rate is determined not only by the (mechanical) properties of the agglomerates and process conditions, but also by the particle size distribution of the bulk filler.

1. Introduction

Dry blending of powders is an extremely important unit operation in industry. In addition, academic interest led to a large amount of scientific papers discussing this topic. This interest has an obvious background because the blend uniformity is basic product quality attribute (Donald and Roseman, 1962; Das Gupta et al., 1991; Sudah et al., 2002a,b). Both the components of the blend and the applied equipment are important factors in the blending process. The properties of the components of the blend are relevant because these determine the properties such as cohesiveness of the powder (Knight et al., 1993; Nase et al., 2001; Kuwagi and Horio, 2002; McCarthy, 2003; Li and McCarthy, 2003). Here, aspects like particle size distributions play a dominant role.

Design of equipment and operating conditions also critically affects the blending process. Obvious examples are fill degree (Sudah et al., 2002a; Ng et al., 2007), operational rate (Brone et al., 1998; Sudah et al., 2002b; Ng et al., 2007) and design such as presence of baffles (Sudah et al., 2002a; Arratia et al., 2006). There are hence a large number of parameters that potentially affect the final result of the blending process. An additional challenge is that a lot of these factors show interactions. This complexity makes that there is a large interest in end-point detection using spectroscopic techniques, such as near-infrared spectroscopy or Raman spectroscopy (Hailey et al., 1996; Sekulic et al., 1998; Lyon et al., 2002; Popo et al., 2002; El-Hagrasy et al., 2006).

A frequently observed situation is that a cohesive powder needs to be blended with a free-flowing bulk powder. A typical example is a small amount of micronised drug that is blended in non-cohesive diluents such as lactose. The cohesive powder forms lumps or aggregates. These aggregates need to be broken in one way or another. Pre-screening of the aggregates is a common approach, but the cohesive properties of the powder imply the risk of re-aggregation after pre-screening but before blending. From a process quality perspective, the blending conditions need to be such that existing aggregates are broken up sufficiently and that re-formation of aggregates is prevented.

Moreover, such lumps need to disappear within a reasonable time to prevent excessively long mixing times.

Lumps consisting of a cohesive powder have a certain mechanical strength and the stresses in the blender need to be such that the lumps disappear. Tardos et al. (2004) introduced the concept of so-called calibrated test particles to measure stresses in a moving powder bed during granulation. Calibrated test particles are

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doi:10.1016/j.ijpharm.2009.12.006

plastically deforming particles with well-known strength. When test particles deform in a moving bed, the stresses in the bed acting upon these particles are larger than the yield strength of the particles itself. This concept formed the starting point for measurement of stresses in a moving powder bed presented in this paper. Adaptation of the calibrated test particle approach was necessary, however, because macroscopic deformation of the test particles did not appear to occur. Rather, the mechanisms of lumps size reduction seemed to be gradual abrasion. In order to study this type of size reduction, a new type of test particles has been developed. These are dry powder aggregates and from that perspective different from the ones discussed by Tardos et al. (2004). This paper describes these test particles and provides a proof of concept on the mechanisms of lumps size reduction in dry powder blending.

2. Materials and methods

2.1. Materials

The materials used were microcrystalline cellulose (Avicel PH-101, FMC, The Netherlands) and lactose monohydrate (Pharmatose® 100 M, Pharmatose® 450 M, from DMV Frontera, Goch, Germany). Calibrated test particles that deform plastically were made from commercially available clay based on wheat flour (Play-Doh® Hasbro Inc, Pawtucket, RI, U.S.A.). If needed, the clay was plasticized using propylene glycol (Fluka, Germany) or made more rigid by addition of iron oxide (iron(III) oxide, Sensient, Naarden, The Netherlands)

2.2. Methods

2.2.1. Powder characterization

Particle size distributions have been determined using an optical microscopy (Nikon, CFI 60 Brightfield/darkfield system) using image analysis (Morphologi G2, Malvern, UK). The true densities of the materials were determined using a gas pycnometer (AccuPyc 1330, Micromeritics, Norcross, U.S.A.) using nitrogen as test gas.

2.2.2. Plastically deforming test particles (pCTPs)

The model material to produce plastically deforming test particles was clay from Play-Doh®. Clays of different colors itself have different yield strengths. The yield strength of the clay was further reduced by addition of propylene glycol (PEG) or increased by addition of iron oxide (Fe_2O_3). The plastic test particles were prepared by extrusion through a 6.4 mm (1/4″) die and cutting the resulting strands into cylinders with a length of 8–9 mm. The yield strengths of the plastically deforming test particles were determined by compressing the sample between parallel plates in a (Lloyd LR5K-plus, Segensworth East, Fareham, UK) tensile tester. The plate movement rate was 1.67 mm/s.

Fig. 1 gives typical examples of the deformation curves of the plastically deforming test particles (pCTPs). The yield strengths of the test particles have been measured according to Tardos et al. (2004). The relative distance in Fig. 1 is equal to (Tardos et al. (2004)):

$$\text{Distance} = 1 - L = 1 - \frac{d}{h_0} \tag{1}$$

With d/h_0 the current height-to-initial height ratio of the pCTPs. The yield strength is by definition the stress (P) measured at a relative distance equal to zero.

2.2.3. Brittle test particles (model agglomerates, bCTPs)

The model material to produce well-defined brittle test particle (bCTPs) was microcrystalline cellulose. This material was selected because it is possible to produce compacts in a large porosity range in reproducible way. The model agglomerates were prepared by compressing approximately 300 mg microcrystalline cellulose into cylindrical compacts with a diameter of 11 mm using a hydraulic press (Weber, Remshalden Grunbach, Germany).

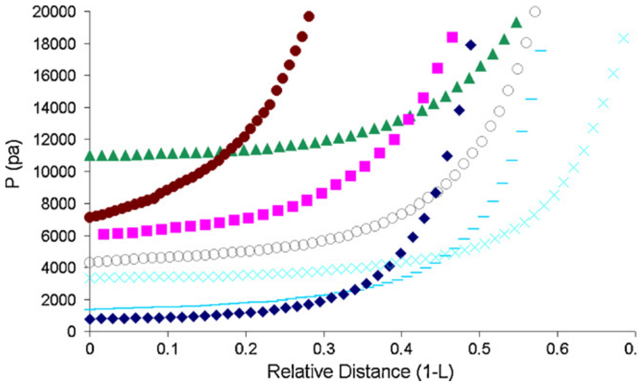

Fig. 1. Typical examples of deformation curves of plastically deforming test particles (in brackets: compound added to original pCTP). (▲) Red pCTP (9% Fe_2O_3 (m/m)), (●) red pCTP (original), (—) red pCTP (40% PEG (m/m)), (○) red pCTP (20% PEG (m/m)), (♦) yellow pCTP (40% PEG (m/m)), (■) green pCTP (original), and (×) white pCTP (original). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.).

The compression pressures varied between 0.8 and 2.6 MPa. These tablets were spheronized by placing the tablets in a vibrating sieve (Retsch AS 200, Haan, Germany) with a mesh size of 500 μm operating at amplitude 5 mm. This operation was performed until the test particle was visually spherical. A picture of typical well-defined model agglomerates is given in Fig. 2.

After the spheronization step the dimensions and weight of the test particles were determined to calculate the porosities (always assuming that the particle were spherical).

2.2.4. Blending tests

The blending experiments reported in this study were performed in a convective mixer with a bowl volume of 25 L (Fukae Powtec model FS-GS-25J, Co., Japan). The chopper was not installed and the impeller rotated at rates between 100 and 400 rpm corre-

Fig. 2. Typical example of a brittle test particle (diameter of test particle 8.6 mm).

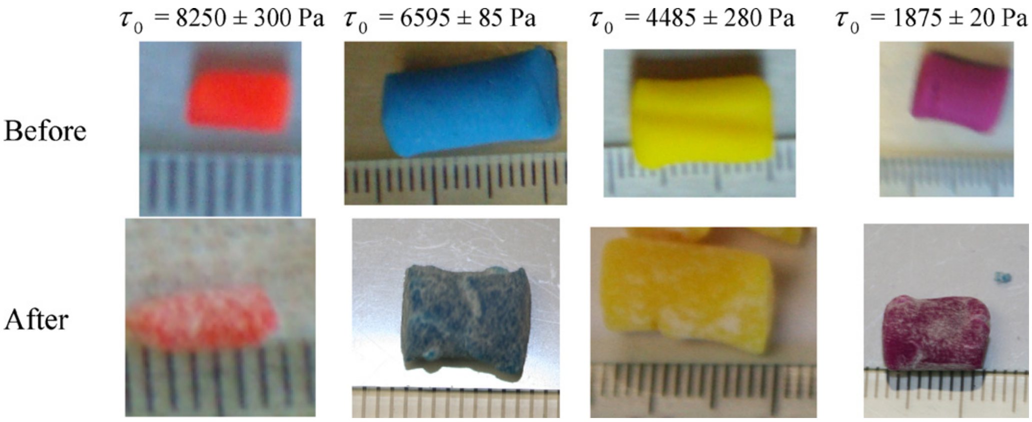

Fig. 3. Plastically deforming test particles with different yield strengths (top row) before a blend test (middle row) and after the blend test (bottom row). The blending test was performed at an impeller rate of 400 rpm.

sponding with tip speeds between 2.09 and 8.37 m/s. The fill degree at each experiment was 4 kg blend.

A test was started by adding selected test particles to a powder sample of lactose 100 M. This mixture was placed in the blender. After a given blending time, the test sample was sieved over a 500 μm sieve to collect the test particles. For the plastically deforming test particles, the shape of the particles was visually assessed. Specific attention was given to deformation and fracture. The weights and dimensions of the brittle test particles were determined as a function of blending time.

3. Results and discussion

3.1.1. Plastically deforming test particles

To assess the (shear) stresses in the blender, plastically deforming test particles were added to the diluent and a blending test was performed. Fig. 3 shows photos of plastically deforming test particles of different strengths before and after a blending test.

The figure shows that no deformation of plastic test particles was observed. Even the weakest test particle with yield strength of 1875 ± 20 Pa at the highest impeller rate (400 rpm) was not deformed. Therefore, it is plausible to assume that shear forces are not the dominant mechanism in dry mixing under these conditions, even not under vigorous blending conditions. In practice, aggregates and lumps reduce in size during blending; therefore another fracture mechanism is likely to play a role.

3.1.2. Brittle test particles

Brittle test particles were added to diluents and a blending test was performed at predefined conditions. Fig. 4 gives a typical example of the evolution of the test particle size in time during such a blending test. The figures displays that the particles reduce in size, but do not visually change in shape during mixing. The particle does not break; therefore abrasion is most likely to be the dominant mechanism of volume reduction, although it is possible that consolidation (i.e. densification) of the test particle might also occur.

Fig. 4 gives examples of the relative changes in volume and in mass of the brittle test particles with different porosities over time in a set of typical experiments. Visually the curves are similar which indicates that the changes in volume and mass in time follow the same patterns in a blending test.

In order to make a better comparison between the mass and volume change rates, Fig. 5 compares the change in mass and the change in volume of the test particles shown in Fig. 6.

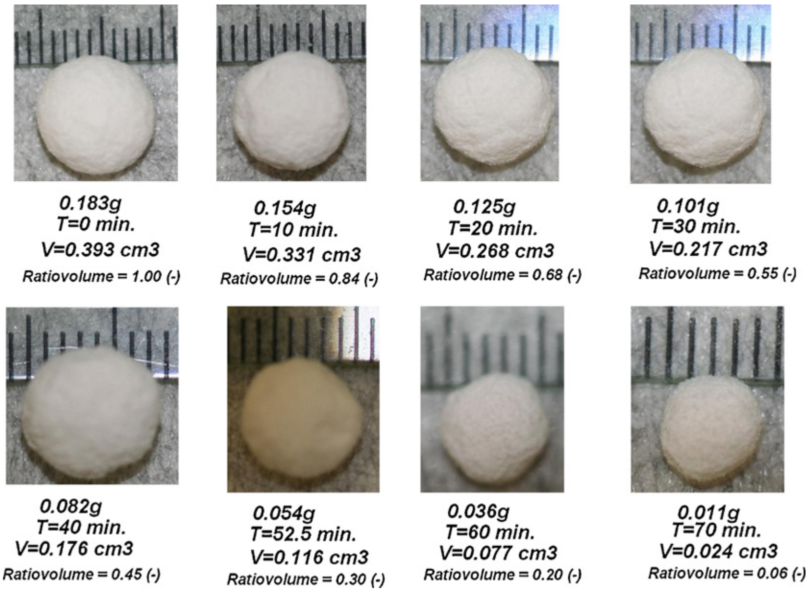

Fig. 4. Evolution of the size of a brittle test particle during a blending test using lactose M100 as diluent (impeller rate 400 rpm and fill degree of 4 kg).

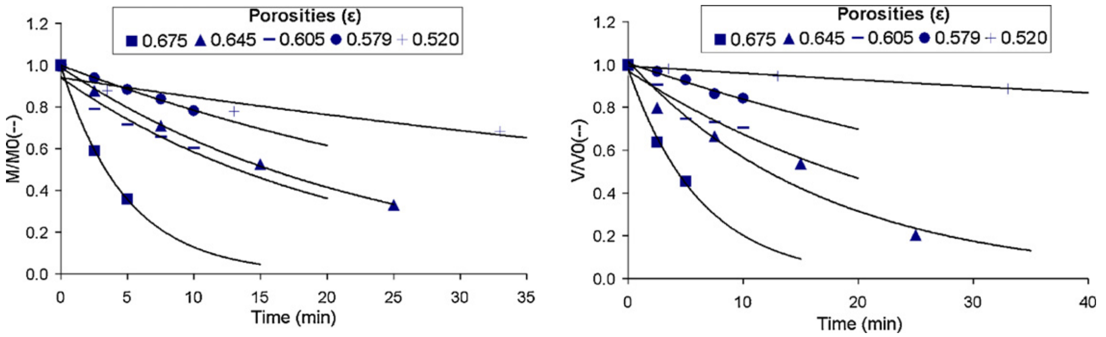

Fig. 5. Relative volume and mass reduction versus time profile of test particles with different porosities.

The diagonal line in Fig. 6 depicts exactly equal abrasion rates. The figure shows that the volume and mass based abrasion rates are very similar. Only when there is a lot of mass or volume reduction a tendency seems to exist that the mass reduction is larger than the volume reduction. This large abrasion corresponds with abrasion of porous test particles. Such test particles are porous that tend to be less spherical than the denser ones. This introduces relatively large errors in the volume test and such calibrated test particles may suffer from some fracture too (which explains lower sphericity of the particles).

The observation that the volume and mass based abrasion rates are very similar shows that no densification of the test particles occurs in time. This means that the test particles do not reduce in size as an effect of (isotropic) compression of the test particles, but by gradual removal of debris from the surfaces of the test particles. It supports the hypothesis that size reduction during dry blending is the result of abrasion rather than of shear stresses leading to deformation and fracture of the bCTPs.

The observation that no significant densification occurs during an abrasion test means that the mechanical properties of the test particle do not change during a test. This is because the porosity of a body determines a lot of mechanical properties (Mashadi and Newton, 1987a,b; Yashima et al., 1987; Roberts et al., 1991, 1995).

Because there are no alterations in mechanical properties of the test particle during a test, it is plausible that the relative abrasion rate of a test particle will have a fixed value. This makes that the relative volume change in time can be described by a first-order approximation:

$$V_{\mathrm{rel}} = \frac{V(t)}{V_0} = e^{-\xi_v * t} \tag{2}$$

with $V(t)$ the volume after blending time t, V_0 the initial volume at time 0, and therefore ξ_v is the (volume based) abrasion rate constant. It is possible to follow exactly the same considerations for the mass change in time. This leads to the mass based abrasion rate (ξ_{m}).

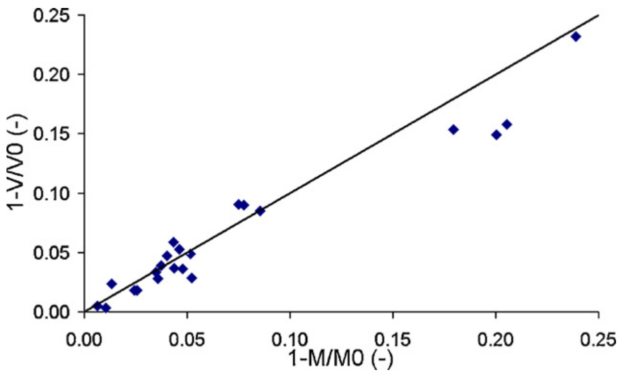

Fig. 6. Volume based abrasion rates versus mass based abrasion rates.

The abrasion rate constants from the tests as depicted in Fig. 5 are shown in Fig. 7. A high porosity results in a high abrasion rate. Clearly, the mechanical properties of the test particles play a large role and strong aggregates lead to impractically long blending times.

It can be seen from Fig. 7 that the rate of abrasion increases with the speed of the impeller. Under these circumstances the centrifugal movement is induced by the impact of the impeller causing the excipients to move, subsequently colliding with the bCTPs on their way (Ramaker, 2001). The abrasion is most likely caused by the impacts when excipients collide with the bCTPs. As a consequence the number of impacts on the bCTPs determines the rate of abrasion. This implies that the abrasion per revolution of the bCTPs should be comparable at each impeller speed. Fig. 8 shows the abrasion per revolution. This figure supports that the number of impacts determines the total abrasion.

In extreme conditions, i.e. when impeller tip speeds are very high or aggregates are very porous, other fracture mechanisms will start to dominate over the abrasion mechanism. There is some experimental evidence for that because the sphericity of the very porous bCTPs was sometimes visually reduced during a test when the impeller speeds are high.

It is obvious that the mechanical properties of aggregates determine the break up rate during blending. Figs. 7 and 8 also illustrate that at low porosities the abrasion rates are very low and less significant compared to the abrasion rates found at higher porosities.

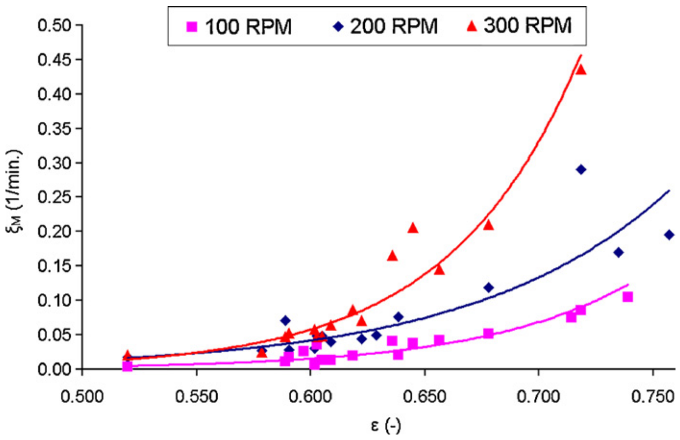

Fig. 7. Mass based abrasion rate constant as a function of porosities of calibrated test particles using lactose M100 as diluent with a blender running at rates of 100 rpm (■), 200 rpm (♦), and 300 rpm (▲).

Based on previous papers (Yashima et al., 1987; Mashadi and Newton, 1988; Roberts and Rowe, 1989; York et al., 1990; Roberts

Table 1
Properties of excipients ($n = 3$).

Diluent type	Particle size (CE diameter)				
	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Mean CE diameter (μm)	Mean circularity (–)
Lactose 100 M	67	115	226	133	0.79
Lactose 450 M	22	32	56	36	0.78

The particle properties were measured by an Image Analysis System with the Morphologi G2 microscope (Morphologi G2, Malvern, UK).

et al., 1991, 1993b; Ramaker, 2001), porosity has been selected to quantify these properties.

The abrasion rate is not only a function of the mechanical properties of the aggregate, but also of the blending conditions. Tip speeds and mixing times are generally accepted parameters that influence the results of the blend. Figs. 7 and 8 show that the abrasion rate of the test particles heavily depends on porosity. The discussion so far gave evidence that the mechanism of aggregate destruction is abrasion. Abrasion is a function of the number of impacts by the excipients. Fig. 8 shows that the abrasion rate is basically determined by the number of impacts.

These findings imply that the properties of the excipient particles are a significant factor determining the abrasion rate. Hence, the rate of abrasion is not only influenced by mechanical material properties of the aggregates or bCTPs and the operating conditions, but also influenced by the formulation properties, specifically, size of the excipient particles. Table 1 illustrates the aspect ratios and other properties of the excipient primary powders from image analysis. The effect of the excipient particle size is illustrated in Fig. 9 that correlates the abrasion rate constants with the porosity of bCTPs using lactose of different particle sizes as filler. There is a strong effect of excipient particle size.

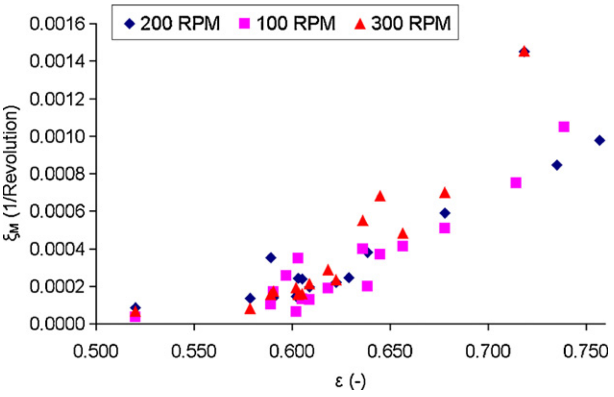

Fig. 8. The mass based abrasion rate per revolution.

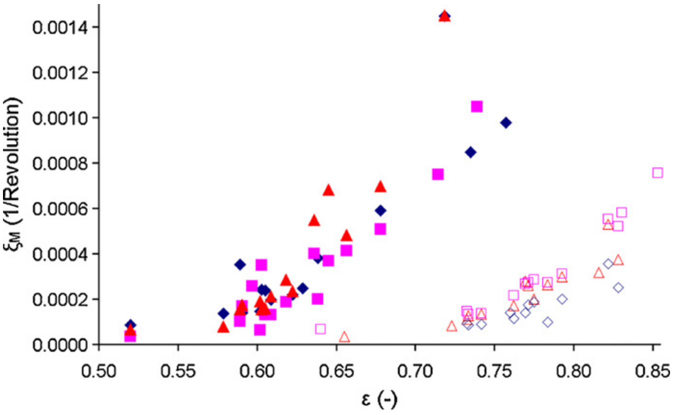

Fig. 9. The effect of excipient particle size on the mass based abrasion rate constant (filled symbols are from lactose 100 M; empty symbols are from lactose 450 M). (■, □) 100 rpm; (♦, ◇) 200 rpm; (▲, △) 300 rpm.

Larger particles generate higher impact force removing the material surface quicker and producing a heavier texture. Excipient particle shape also plays a role (Oka and Yoshida, 2005).

Fig. 9 depicts that the impact of moving excipient particles increases with particle size. For that reason it is assumable that the impacts of the lactose 100 M particles are higher when the assumption is that the impeller in the blender totally determines the linear velocity of the lactose particles. This relatively large difference in impact could very well explain the relatively large difference in abrasion rate of bCTPs of equal porosities, hence mechanical material properties.

4. Conclusion

Many powder blends contain of small amount of cohesive material distributed in a large bulk of an excipient. To evenly distribute the cohesive powder into the bulk the conditions must be capable of breaking up the aggregates of the cohesive particles. In practice we observe that agglomerates and lumps of a cohesive component reduce in size during dry blending.

The study with the pCTPs showed that the stresses (shear) acting upon particles in a dry powder blend are very low. This result implies that fracture is not the dominating mechanism of size reduction of aggregates.

In this paper we provide for the first time a mechanistic model to quantify the abrasion rates of agglomerates during a dry powder blending. Tests using bCTPs reveal that abrasion is the dominating size reduction mechanism of aggregates. Furthermore there is evidence of a relationship between strength (expressed as porosity) of the bCTPs and rate of abrasion. Obviously the speed of the impeller in the blender is also a dominant parameter. Finally, it can be argued that a coarse excipient will lead to faster abrasion (and shorter mixing times) and this has experimentally been confirmed.

Acknowledgement

This study was performed within the framework of Top Institute Pharma project number D6-203.

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