International Journal of Pharmaceutics 362 (2008) 109–117

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Effect of particle properties on the flowability of ibuprofen powders

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ARTICLE INFO

Article history:
Received 1 May 2008
Received in revised form 19 June 2008
Accepted 19 June 2008
Available online 4 July 2008

Keywords:
Ibuprofen
Flowability
Particle size
Hausner ratio
Shear cell tester

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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doi:10.1016/j.ijpharm.2008.06.023

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:

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

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

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

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

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

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