

Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder

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Abstract

L-lysine monohydrochloride (LMH) dihydrate was crystallized and the resulting powder was sieved to obtain various size fractions. The influence of other factors, such as crystallinity and crystal shape, was minimized by using the same batch of crystals. Compression of smaller particles at low compaction pressures resulted in tablets of greater porosity. The differences in porosity decreased with increasing compaction pressure. At the same compaction pressure, smaller particles formed tablets of greater tensile strength. However, fragmentation of the larger particles tended to equalize the particle size and reduce its influence. The differences were reduced for particles larger than 710 μm . For crystals of all size fractions, tensile strength increased with increasing compaction pressure. The tensile strength increased more rapidly for smaller crystals. Tensile strength decreased exponentially with increasing porosity for all fractions. The dependence of tensile strength on porosity is explained in term of tablet structure. Yield strength, calculated from 'out-of-die' Heckel analysis, increased with increasing particle size. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: L-lysine monohydrochloride dihydrate; Particle size; Tableting; Tensile strength; Yield strength; Particle fragmentation

1. Introduction

The importance of the initial size of the particles constituting a powder in determining compaction behavior has long been recognized (Hersey et al., 1967). However, the influences are often conflicting. For most powdered pharmaceuticals, compaction of smaller particles results in

stronger tablets because the smaller particles provide a larger total area for bonding than larger particles. However, the effects of the initial particle size on the strength of tablets depend on the mechanical properties of the materials. For example, dicalcium phosphate and sucrose undergo extensive fragmentation under pressure, and their tablet strength is independent of variations in particle size (Alderborn and Nyström, 1982). For sodium chloride, tablet strength increases with increasing particle size because of the formation of strong bonds in the form of solid bridges (Alderborn and Nyström, 1982).

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Compaction speed has also been found to play an important role in determining the effects of initial particle size on tensile strength. At lower compaction speeds, larger sodium chloride particles lead to higher tensile strength. However, when the compaction speed is increased, the tensile strength of the larger particles is lower than that of the smaller particles (Sheikh-Salem and Fell, 1982). For lactose, differences in tensile strength due to differences in initial particle size are reduced as the compaction speed is increased, because the more extensive particle fragmentation of the starting material minimizes the initial differences in particle size (Sheikh-Salem and Fell, 1982).

Milling and sieving are the most common methods for obtaining particles of different sizes. However, smaller particles obtained by milling and sieving contain more defects, corresponding to a lower crystallinity. Crystallinity influences the tableting behavior of powders, as explained by the 'activation theory' (Hüttenrauch, 1983). Generally, lower crystallinity improves the binding properties of a powder because the greater plastic flow at the points of contact increases the bonding area and results in stronger tablets.

Crystal shape may significantly affect tablet strength (Bandyopadhyay, 1998; Sun and Grant, 1999; Wong and Pilpel, 1990). Bandyopadhyay (1998) and Sun and Grant (1999) found that the different orientations of slip planes in tablets are responsible for the different tensile strengths of tablets formed from differently-shaped crystals, i.e. prisms and plates, of L-lysine monohydrochloride (LMH) dihydrate.

The aim of this study is to investigate the influence of the initial particle size of crystals constituting a powder of LMH dihydrate on its tableting behavior, while minimizing the effects of other factors, e.g. crystallinity and crystal shape.

2. Materials and methods

2.1. Materials

Short prism-shaped crystals of LMH dihydrate were crystallized from ethanol + water (1:1, v:v, $a_w = 0.80$, Göllés, 1962) as described previously (Sun and Grant, 1999). The crystals were then sieved using standard sieves. Six fractions (< 150, 150–250, 250–355, 355–595, 710–850, and 850–1000 μm) were collected and stored over a saturated aqueous solution of sodium chloride (75% RH) at 25°C before compaction studies. Because all the crystals were crystallized in the same batch, and because they were not milled, differences in crystallinity and crystal shape among the sieve fractions were minimal. This assumption is supported by the constancy of the differential scanning calorimetric (DSC) measurements of the enthalpy of dehydration (Table 1). Furthermore, Table 1 shows that the water content of the various sieve fractions is constant, does not increase with decreasing particle size (i.e. increasing specific surface area), and is close to the theoretical water content of LMH dihydrate (16.4% w/w). Hence, storage of the crystals at 75% RH and at 25°C causes very little adsorption of surface moisture.

Table 1

Differential scanning calorimetric (DSC) and thermogravimetric (TG) data of different size fractions of LMH dihydrate crystals previously stored at 75% RH and at 25°C for at least 1 week^a

Sieve fractions (μm) ^b	<75	125–150	300–355	500–595	600–710
ΔH , ^c J/g (S.D. $n \geq 3$)	471.1 (2.3)	471.9 (4.2)	469.3 (4.4)	469.2 (1.3)	– ^e
Weight lost ^d (% , $n = 1$)	16.55	– ^e	16.80	16.67	16.43

^a These thermal analytical methods are described by Sun and Grant (2000).

^b Because each DSC and TG run requires only a few milligrams of sample, sieve fractions of narrower particle size were employed. These crystals were sampled from the same batch as those for the tableting study.

^c ΔH is the enthalpy of dehydration of LMH dihydrate and was measured using DSC (Sun and Grant, 2000).

^d The weight lost was measured by TG (Sun and Grant, 2000). The theoretical water content for LMH dihydrate is 16.4% (w/w).

^e Data are not available.

2.2. Methods

2.2.1. Compaction of crystals

Powders of suitable weights were compressed in a split die, which allowed uniaxial compression and triaxial decompression, under a hydraulic press (Carver, model C, Menomonee, WI) to make tablets of dimensions, 19 mm × 19 mm × 9 mm. The compaction pressures ranged from 6.9 to 55.2 MPa, which were conveniently accessible to the Carver press, and the dwell time was 1 min. The tablets were then stored for 4 days in a chamber containing a saturated aqueous solution of sodium chloride (75% RH) at 25°C before subsequent experiments. The linear dimensions of the tablets were measured to ±0.02 mm using a dial caliper (Mitutoyo, Manufacturing Co., Japan). For each dimension, the mean of four measurements was used to calculate the volume of each tablet.

2.2.2. Determination of true density and compact porosity

The true density, ρ_t , of the crystals was determined in triplicate by a helium pycnometer (Micromeritics, Norcross, GA). The porosity, ϵ , of the compacts was calculated by the following equation:

$$\epsilon = 100(1 - \rho_c/\rho_t), \quad (1)$$

where ρ_c is the density of the resulting compact which was calculated from the weight and volume of the compact.

2.2.3. Calculation of the yield strength

The densification data were analyzed by the Heckel, 1961a,b equation, thus:

$$-\ln(1 - D) = KP + A, \quad (2)$$

where P is the compaction pressure, D is the relative density, ρ_c/ρ_t , of the compact, K is the slope of the linear portion of the Heckel plot that measures the plasticity of the material, and A is the intercept of the linear portion when P is zero. The constant A is related to the initial filling of the die, and to the rearrangement of the particles in the die. The yield strength, σ_y , is equal to one third of the reciprocal of K , which is termed the

mean yield pressure, P_y , (Hersey and Rees, 1970) thus:

$$\sigma_y = P_y/3 = 1/3K. \quad (3)$$

‘Out-of-die’ Heckel analysis was used to calculate the yield strengths of the powders. Because D of the compacts is measured after relaxation following ejection from the die, the effect of elastic deformation of the powder on the Heckel analysis was absent. In Heckel analysis, each measurement was performed in triplicate. The slope of the line was obtained by least squares linear regression analysis.

2.2.4. Determination of tensile strength

The tensile strength of the compacts was determined by transverse compression according to a procedure described by Hiestand and Smith (1984). The compact was placed between a pair of platens of width 7.8 mm, 0.4 times the width of the square-faced tablet. The platens were padded with four layers of filter paper fixed by four layers of double-sided adhesive tape to ensure good contact and to reduce shearing stress at the edges. A transverse load was applied to the tablets at a rate of 1.6 mm/min. In this study, all the tablets split into two halves with the fracture plane running through the center of the tablets along the loading axis, indicating ideal tensile failure (Hiestand and Smith, 1984). Under these conditions, the failure tensile strength is 0.16 times the mean compressive stress (Hiestand and Smith, 1984). The tensile strength was determined in triplicate.

2.2.5. Environment scanning electron microscopy (ESEM)

ESEM enables the image of the natural state of the specimen to be revealed without subjecting it to extreme conditions, such as a high vacuum. Accordingly, ESEM was used for image analysis of the fracture face of a tablet of LMH dihydrate compressed at 55.2 MPa. The humidity in the sample chamber was maintained at 50% to prevent dehydration of the sample. The working voltage of the electron gun was 10 kV, and the gun-anode spacing was 3 mm.

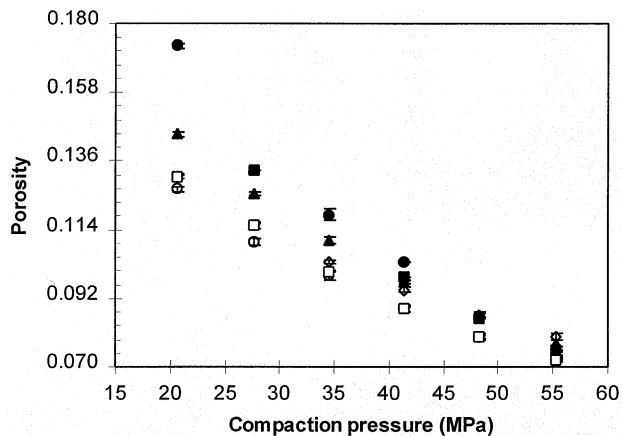


Fig. 1. Effects of particle size on the relationship between tablet porosity and compaction pressure. Larger particles lead to a lower porosity at the same pressure. The differences decrease with increasing compaction pressure. \bullet $< 150 \mu\text{m}$; \blacksquare $150\text{--}250 \mu\text{m}$; \blacktriangle $250\text{--}355 \mu\text{m}$; \square $355\text{--}595 \mu\text{m}$; \diamond $710\text{--}850 \mu\text{m}$; \circ $850\text{--}1000 \mu\text{m}$.

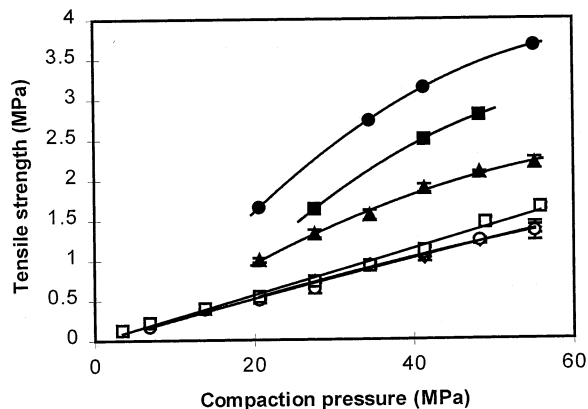


Fig. 2. Relationship between tensile strength of the tablets and compaction pressure for different fractions of crystals. For each fraction of crystals, the tensile strength increases with increasing compaction pressure. The tensile strength is greater for tablets of smaller particles. \bullet $< 150 \mu\text{m}$; \blacksquare $150\text{--}250 \mu\text{m}$; \blacktriangle $250\text{--}355 \mu\text{m}$; \square $355\text{--}595 \mu\text{m}$; \diamond $710\text{--}850 \mu\text{m}$; \circ $850\text{--}1000 \mu\text{m}$.

3. Results and discussion

3.1. Effects of particle size on volume reduction of powders

The larger crystals appear to be more easily

compressed at pressures lower than 35 MPa. Tablets prepared by compacting larger crystals showed lower porosities than the tablets prepared by compacting smaller crystals (Fig. 1). However, the difference in porosity is less at higher pressures. At 55.2 MPa, the smallest crystals, $< 150 \mu\text{m}$, achieve a lower porosity than that of the larger crystals, because they pack more efficiently.

3.2. Effects of particle size on tensile strength

For tablets prepared by compaction of crystals of each of the six size fractions, their tensile strength increases with increasing compaction pressure (Fig. 2). A linear relationship between tensile strength and compaction pressure is apparent for crystals of size greater than $355 \mu\text{m}$. However, curvature is observed for crystals smaller than $355 \mu\text{m}$ (Fig. 2). Therefore, the tensile strength of tablets prepared by compacting smaller crystals reaches its plateau value at a lower compaction pressure than for larger crystals because of the greater compressibility of the smaller crystals, as suggested by the lower yield strength of smaller crystals calculated from the Heckel plots (Section 3.3). At any given pressure, larger crystals tend to form tablets of lower tensile strength (Fig. 3). However, the effects of particle size on tensile strength appear less significant when the particle size is greater than $595 \mu\text{m}$ (Fig. 2). In explanation, the fragmentation of larger crystals under pressure reduces the effects of differences in initial particle size.

For crystals of each size fraction, the tensile strength decreases exponentially with increasing porosity (Fig. 4). This relationship can be expressed by Eq. (4), as suggested previously (Ryshkewitch, 1953).

$$\ln \sigma = \ln \sigma_0 - b\varepsilon, \quad (4)$$

where b is related to the pore distribution in the tablets and σ_0 represents the tensile strength at zero porosity. A higher value of b indicates higher yield stresses or anisotropic deformation (Robert et al., 1995).

The values of b and σ_0 are listed in Table 2. With decreasing initial particle size, b tends to decrease and levels off at median particle size greater than 500 μm , indicating more homogeneous distribution of pores in tablets of smaller particles. The improved homogeneity of pore size distribution of smaller particles may be related to the ease of plastic deformation, i.e. the easier the

plastic deformation the more homogeneous is the pore distribution. Robert et al., (1995) found that the value of b varies from 3.529 for caffeine to 10.924 for anhydrous β -lactose. In the present study, b values are close to the upper end of this range, from 8.143 to 18.288. However, σ_0 tends to decrease with increasing initial particle size, indicating weaker bonding for larger crystals.

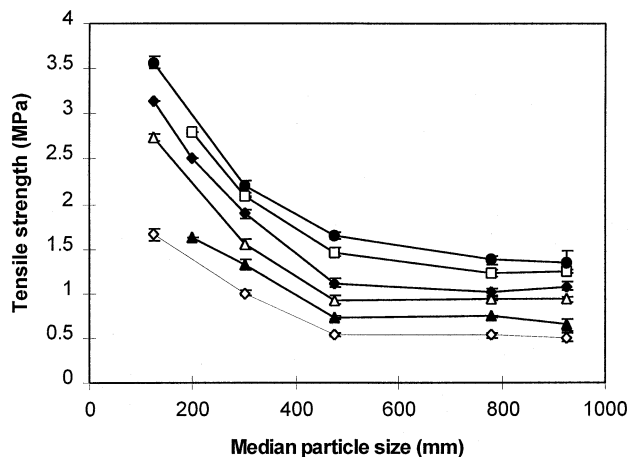


Fig. 3. Effects of the initial particle size on tensile strength of tablets. Tensile strength decreases with increasing particle size at a given compaction pressure. ● 55.2 MPa; □ 48.3 MPa; ◆ 41.4 MPa; △ 34.5 MPa; ▲ 27.6 MPa; ◇ 20.7 MPa.

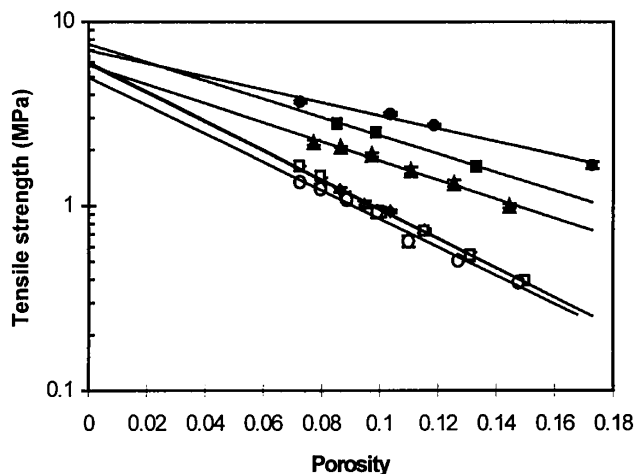


Fig. 4. Logarithmic relationship between tensile strength and porosity of tablets for different size fractions of compacted crystals. Greater dependence of tensile strength on porosity is observed for larger crystals. ● <150 μm ; ■ 150–250 μm ; ▲ 250–355 μm ; □ 355–595 μm ; ◇ 710–850 μm ; ○ 850–1000 μm .

Table 2
Parameters describing tableting properties of different size fractions^a

Particle size (μm)	Parameters in Eq. (4)			Yield strength	
	b	σ_0 (MPa)	R^2	P_y (MPa)	R^2
< 150	8.143	6.968	0.981	13.39	0.998
150–250	11.380	7.547	0.994	15.95	0.999
250–355	11.923	6.387	0.988	18.42	0.999
355–595	18.288	5.996	0.995	19.16	0.996
710–850	18.189	5.893	0.993	20.83	0.996
850–1000	17.620	4.966	0.983	23.47	0.994

^a b and σ_0 , are constants in Eq. (4). Smaller b is related to more homogeneous pore distribution in tablets. Tensile strength extrapolated to zero porosity, σ_0 , indicates bonding strength of a powder. P_y is yield strength calculated from Heckel plot. R^2 is the coefficient of determination.

3.3. Effects of particle size on yield strength

'Out-of-die' Heckel analysis of compaction data of the six fractions is shown in Fig. 5. As observed previously (Sun and Grant, 1999, 2000), the 'out-of-die' Heckel plot of LMH dihydrate appears linear at pressures greater than 20 MPa. Linear regression was performed on data points in that region to calculate the yield strength for all six fractions of crystals (Table 2). Yield strength increases with increasing particle size (Fig. 6). Similar observations were made on α -lactose monohydrate, chloroquine diphosphate, and calcium carbonate (York, 1978). The relationship between yield strength and initial particle size may be attributed to the effects of the initial particle size on the volume reduction of the powder bed under pressure. In the tablets prepared from larger crystals, the pores are also larger than those from smaller particles. The reduction of the size of the pores by plastic deformation will also be less efficient for larger particles. The rate of volume reduction of larger particles is slower under the same pressure. Therefore, $-\ln \varepsilon$ increases more slowly with increasing pressure. Consequently, the linear portion of the Heckel plot has a lower slope and therefore the yield strength calculated from Eq. (4) is greater for larger crystals. The different observed yield strengths between crystals of different sizes may also reflect the true differences between them, because defect concentration within crystals of different sizes

may differ even in the same batch of crystallization.

Interpretation of the results of the previous paragraph is also complicated by the fact that the initial particles fragment under pressure. The fracture surface of a tablet, formed by compressing the 355–595 μm sieve fraction of LMH dihydrate crystals at 55.2 MPa, was examined by ESEM. This technique showed that much smaller particles, 1–10 μm , fill the spaces between the larger crystals, indicating fragmentation of the initial crystals (Fig. 7). Because a larger mean compress-

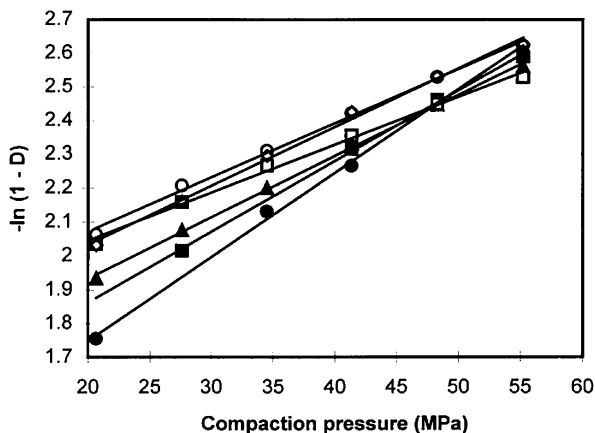


Fig. 5. 'Out-of-die' Heckel plots for different size fractions of crystals. Linear plots are observed at pressures greater than 20 MPa for all fractions. ● < 150 μm ; ■ 150–250 μm ; ▲ 250–355 μm ; □ 355–595 μm ; ◇ 710–850 μm ; ○ 850–1000 μm .

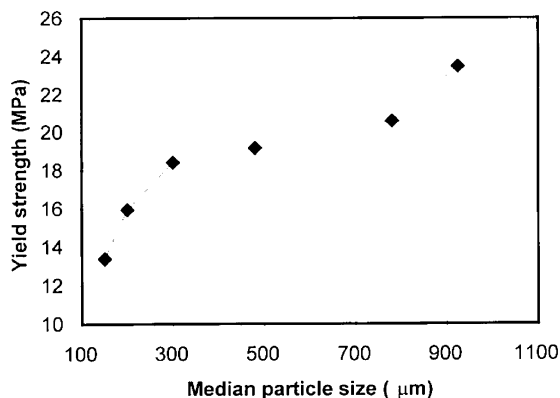


Fig. 6. Effects of particle size on the yield strength of LMH dihydrate. The yield strength of the compacts increases with increasing particle size.

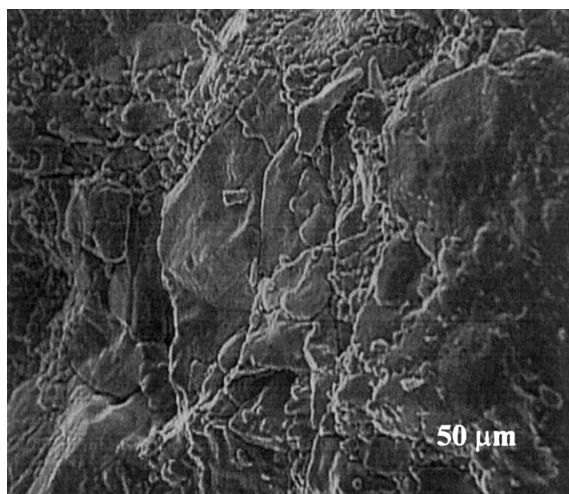


Fig. 7. ESEM photograph of a fracture surface of a tablet formed by compressing the 355–595 µm sieve fraction of LMH dihydrate at 55.2 MPa. Much smaller particles, 1–10 µm, fill the spaces between the larger crystals, indicating fragmentation of the initial crystals.

sive stress is needed to crack a smaller particle of the same substance (Kendall, 1978), the fragmentation properties of crystals of different sizes may be different. The different fragmentation of crystals of different initial sizes may cause different shapes and distributions of pores in the tablets. The effects of both plastic deformation and fragmentation of the initial crystals are reflected in the Heckel analysis. Therefore, for meaningful com-

parisons of yield properties between different materials using Heckel analysis, initial particle size should be carefully controlled.

4. Conclusions

Larger crystals pack more efficiently, giving lower porosities at low compaction pressures. However, volume reduction due to pressure is more rapid for smaller crystals. Consequently, the porosities of compacts prepared from crystals of different sizes approach each other at higher pressures. The tensile strength of tablets increased with decreasing particle size due to a larger number of contact points between smaller crystals. However, the tensile strength of compacts from crystals larger than 710 µm approached each other due to fragmentation of the initial crystals. Smaller crystals tend to form tablets with a more homogeneous distribution of pores. Increasing yield strength with increasing particle size indicates greater apparent plasticity of the smaller particles, which is also responsible for a more homogeneous pore distribution in tablets of smaller crystals. Fragmentation of the initial particles should be considered in order to understand the effects of particle size of pharmaceutical powders on their tableting properties.

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