Compaction Properties of L-Lysine Salts

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Received September 26, 2000; accepted December 12, 2000

Purpose. To examine the effects of salt form, i.e., different anions with a common cation (L-lysinium), on compaction properties and to identify the factors that determine the tensile strength of tablets.

Methods. L-Lysine salts with the following anions were compressed at various pressures: acetate, monochloride, dichloride, L-aspartate, L-glutamate (dihydrate), and L-lysine (zwitterionic monohydrate). The yield strength of each salt was evaluated from the "out-of-die" Heckel plot.

Results. At low compaction pressures, the tensile strength of the compacts increases linearly with increasing compaction pressure. Simultaneously, the compact tensile strength decreases exponentially with increasing yield strength of the salt. However, at high compaction pressures, the compact tensile strength is determined by the interparticulate bonding strength and not by the yield strength. The compact tensile strength, extrapolated to zero porosity, increases linearly with increasing melting temperature of the salts.

Conclusions. The counterion affects the tableting properties of L-lysine salts. The tensile strength is controlled by both the yield strength and the interparticulate interaction strength with the former predominant at low compaction pressures and the latter predominant at high compaction pressures. The melting temperature of each L-lysine salt is a good indicator of the tensile strength of its compacts at zero porosity.

KEY WORDS: L-Lysine salts; compaction; Heckel plot; tensile strength; melting temperature; interparticle bonding.

INTRODUCTION

The chemical, biological, physical, and pharmaceutical characteristics of drugs can be modified using different salt forms. Desirable properties of an acidic or basic drug are often obtained by choice of its solid salt form (1,2). Therefore, salt selection is a common preformulation step in the pharmaceutical industry (3,4). The preferred salt form of a parent compound is selected primarily on a practical basis, e.g., the cost of raw materials, ease of crystallization, and yield (1). Other important aspects are drug stability, hygroscopicity, crystallinity, purity, polymorphism/hydrate formation, and powder flowability (3,5). The salt form affects the dissolution profile and therefore the absorption of a drug (6). A suitable salt may also reduce the toxicity (7) and improve the organoleptic properties, such as bitter taste (8), of an active compound. The effects of salt form on drug stability (9), solubility (10), and dissolution rate (11) have been studied extensively. Because the physicochemical properties differ between different salts of the same parent active compound, the mechanical properties of the powder may be profoundly different. The mechanical properties of the salt may greatly influence the properties and formulation of the solid dosage form, e.g., tablet, especially when the drug load is large and direct compaction is applied. Knowledge of the effects of the counterion on the mechanical properties of an acidic or basic drug may facilitate the appropriate choice of salt form, avoid possible problems in the formulation of a drug, and therefore may expedite the process of drug development. This study aims to understand the effects of salt form on the tableting performance. A preliminary report has been presented as a poster at the AAPS National Meeting and Exposition, New Orleans, LA on November 14–18, 1999, and published as an abstract (12).

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MATERIALS AND METHODS

Materials

The following six salts of L-lysine were purchased from Sigma Chemical Co. (St. Louis, MO): L-lysine monohydrochloride (**LM**), L-lysine dihydrochloride (**LD**), L-lysine acetate (**LA**), L-lysine L-aspartate (**LS**), L-lysine L-glutamate (**LG**) and L-lysine itself (**L**). L-Lysine is a zwitterionic salt, which explains its high melting point, 229.3°C.

Sample Preparation

The salts, as purchased, displayed different crystal habits. Crystals of **LA** were plates; **LD** and **LS** were agglomerates; **LM** were pellets; **LG** and **L** were irregular fine crystals. To normalize the differences in particle size distribution and particle shape, the salts were ground and sieved. A defined particle fraction, 125–250 μm, of each salt was used for this study. The sieved fractions were allowed to relax for one month in an environmentally-controlled room at 25°C and 56% RH to reduce any grinding-induced energetic sites on the particle surfaces.

Thermal Analysis

Thermogravimetric (TG) curves were obtained using a thermogravimetric analyzer (Du Pont, model 951, TA Instruments, New Castle, DE) linked to a data station (Thermal Analyst 2000, TA Instruments, New Castle, DE). Samples (about 8 mg) in open aluminum pans were heated to 300°C at a rate of 10°C/min under nitrogen flow at 80 mL/min.

A differential scanning calorimeter (DSC, Du Pont, model 910, TA Instruments, New Castle, DE) equipped with a data station (Thermal Analyst 2000, TA Instruments, New Castle, DE) was used to record the thermal events during heating. The temperature axis and the cell constant were calibrated with indium. Samples (about 8 mg) in crimped aluminum pans were heated to 300°C at 10°C/min under nitrogen flow at 80 mL/min.

Karl Fischer Titrimetry (KFT)

The water content of the six powders was determined by KFT using a Mitsubishi Moisture Meter (model CA-05, Mitsubishi Chemical Industries Ltd., Tokyo, Japan). Samples

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(6–7 mg) were accurately weighed and quickly transferred to a titration vessel to minimize the effect of moisture in the air.

Compaction of the Salts

Powders of suitable weight were compressed in a split die, allowing uniaxial compression and triaxial decompression (13), under a hydraulic press (Carver, model C, Menomonee, WI), to make square-faced compacts of dimension 19 mm × 19 mm × 9 mm. The punches and die were lubricated with a 5% (w/v) suspension of magnesium stearate in ethanol which was allowed to evaporate. Powder of suitable weight was then slowly poured into the lubricated die. The die was gently shaken to improve the packing of the powder bed before compaction. This procedure improves the uniformity of the tablet. The compaction pressure ranged from 6.9 MPa to 55.2 MPa and the dwell time was 1 min. All compacts were made in an identical fashion and were stored for one week in a environmentally-controlled room (25°C, 56% RH) before subsequent experiments. The dimensions were measured to ± 0.02 mm using a dial caliper (Mitutoyo Manufacturing Co., Japan). Hence, the volume of each compact was calculated.

Calculation of Compact Porosity

The true density, ρ_t, of each salt was determined in triplicate by a helium pycnometer (Micromeritics, Norcross, GA). Accurately weighed powder (2–3 g) was loaded into the sample cell which was evacuated for 3 min before measurement. The accuracy of the pycnometer was checked using a standard steel sphere at least daily and before and after measurements on a series of powders. The porosity, ε, of the compacts was calculated by equation (1):

$$\varepsilon = 1 - \rho_c/\rho_t \quad (1)$$

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

Heckel Analysis

Heckel analysis (14,15) provides one of the most useful descriptions of powder densification and is expressed as equation (2):

$$-\ln(1 - D) = K \cdot P + A \quad (2)$$

where P is the compaction pressure and D is the relativity density, ρ_c / ρ_t, of the compact. The material constant, K, is the slope of the linear portion of the Heckel plot and measures the plasticity of the material. The reciprocal of K is termed the mean yield pressure, P_y (16), which is three times the yield strength of the material. The constant A is related to the initial filling of the die and to the rearrangement of the particles in the die (14).

Historically, two types of Heckel analysis have been used, depending on the way D is measured. In the first method, termed "at-pressure" or "in-die" Heckel analysis, D is calculated from the weight and dimensions of the compacts while under the applied load (15). In this method, the relationship between D and P can be established from a single compression cycle. This method also makes it possible to analyze materials that form intact compacts with difficulty, e.g., due to capping after compaction. Although convenient, "in-die" Heckel analysis provides a K value that is affected by elastic deformation (17,18). Therefore, P_y derived from this method is the "apparent mean yield pressure". In the second method, termed "zero-pressure" or "out-of-die" Heckel analysis, D is measured on the compacts after relaxation following ejection from the die (15). P_y derived from this method is the "true mean yield pressure" of the material. However, it is more time-consuming to prepare tablets at several different pressures in order to obtain a clear relationship between D and P. The "in-die" and "out-of-die" Heckel plots are complementary and were therefore constructed in this study. The "in-die" Heckel plot was used to determine the linear region in the Heckel profile (Fig. 1). This information facilitates the appropriate choice of data points for linear regression analysis of "out-of-die" data for which fewer points are available and for which a precise choice of regression region is more difficult (Fig. 2).

Determination of Tensile Strength

The tensile strength of the tablets compacted at each pressure was determined in triplicate by transverse compression according to Hiestand and Poet (19). The compact was placed between a pair of platens of width 7.8 mm, about 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 stresses at the edges. A transverse load was applied to the tablets at a rate of 1.6 mm/min. An ideal tensile failure initiates from the center of the compact and propagates vertically to the platens. In this study, all the tablets were split into two halves with the fracture plane running through the center of the tablets along the loading axis, indicating tensile failure (19). Under these conditions, the tensile strength for failure, σ, is 0.16 times the mean compressive stress (19) and was calculated by equation (3):

$$\sigma = 0.16 \cdot F/(0.0078 \cdot W) \quad (3)$$

where F is the force at fracture and W is the thickness of the tablet. The width of the platens is 7.8 mm.

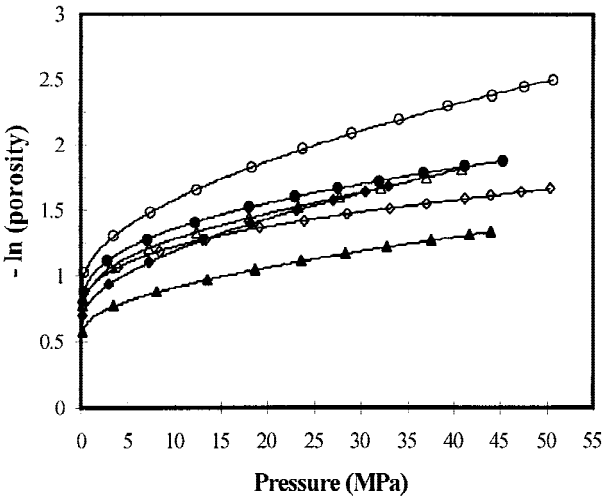

Fig. 1. "In-die" Heckel plots of six salts of L-lysine, showing the influence of salt form: (▲) **LG**; (♦) **L**; (○) **LA**; (●) **LS**; (△) **LD**; (◇) **LM**. Linear regions were observed at pressures greater than 15 MPa for all these salts.

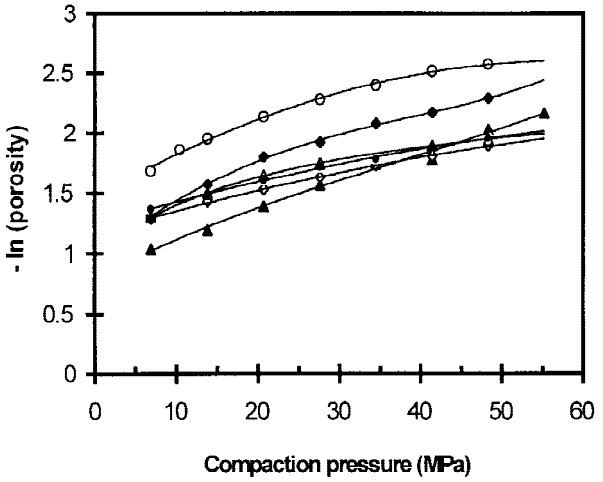

Fig. 2. "Out-of-die" Heckel plots of six salts of L-lysine (n = 3): (▲) **LG**; (♦) **L**; (○) **LA**; (●) **LS**; (△) **LD**; (◇) **LM**. For each salt, the data points at pressures greater than 20 MPa were linearly regressed to obtain the yield strength values in Table I.

RESULTS AND DISCUSSION

Physical Characterization

Powder X-ray diffractometry (PXRD) was run for each salt before and after grinding. There was no change in peak position in the PXRD pattern of all the ground salts. Therefore, no X-ray detectable solid-phase transition was induced by grinding. Also, no amorphous halo was observed for each salt after grinding and storage.

The water content of **LG** and **L** was 9.6% (w/w) and 10.3% (w/w), respectively, by KFT (Table I). TG analysis showed that 9.6% of the weight was lost at 50–100°C from **LG** powder, whereas 10.2% of the weight was lost at 40–50°C from **L** powder, matching well with the KFT results. These two values match the theoretical water content of **LG** dihydrate (10.93%) and **L** monohydrate (10.96%), respectively. Because PXRD indicated high crystallinities of these salts, the water content is mainly lattice water. For the other four salts, only a small amount, <0.4%, of water was found (Table I), suggesting surface adsorption.

From DSC, a high melting temperature, with decomposition, was observed for each salt. Therefore, the melting temperature was read from the leading intercept of the first fusion peak not from the peak temperature. Sharp dehydration endotherms for **LG** and **L** were observed at about 110°C and 60°C, respectively, corresponding to the weight loss in TG. The dehydration temperatures appeared higher in a crimped pan in DSC than in an open pan in TG, because the escape of water is postponed in a crimped pan.

The "in-die" Heckel plots of the six salts (Fig. 1) appeared linear at pressure greater than 15 MPa, a relatively low pressure. Because initial nonlinearity of a Heckel profile normally represents rearrangement and fragmentation of the particles (14,15), this linearity may be attributed to the prior particle size reduction by grinding, leading to denser packing of the particles prior to compaction and to reduced fragmentation during compaction. Data points at pressures greater than 20 MPa were then used for least-squares linear regression analysis of each "out-of-die" Heckel plot of these six salts (Fig. 2). The yield strengths, listed in Table 1, were calculated from the slopes of the lines.

Definition of Terms

To describe the tableting performance of powders, the terms defined by Joiris et al. (20) are used and are summarized below.

Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure and is represented by a plot of tablet porosity against compaction pressure (20).

Compactibility is the ability of a material to produce tablets with sufficient strength under the effect of densification and is represented by a plot of tablet tensile strength against tablet porosity (20).

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure and is represented by a plot of tablet tensile strength against compaction pressure (20).

Compressibility of the Salts

Compressiblity affects the compact strength. The more compressible the powder, i.e., the smaller the porosity, the larger the interparticulate bonding area and the stronger the

Table I. Physical Characterization of the Six Salts of L-Lysine (Standard Deviations in Parentheses)

Salt	T_m (°C)[a] (leading intercept)	Measured[b] water (% w/w) (n = 5)	Theoretical water (% w/w)	Yield[c] strength (MPa)	σ_0 (MPa)[d] (n = 3)
L-lysine L-glutamate dihydrate (LG)	179.7	9.59 (0.19)	10.93	12.0	6.52 (0.21)
L-lysine acetate (LA)	192.7	0.32 (0.08)	0.0	23.0	10.07 (0.40)
L-lysine dihydrochloride (LD)	200.2	0.33 (0.07)	0.0	33.7	10.33 (0.88)
L-lysine L-aspartate (LS)	219.6	0.28 (0.024)	0.0	26.3	14.36 (1.37)
L-lysine monohydrate (L)	229.3	10.3 (0.4)	10.96	19.2	15.90 (1.32)
L-lysine monohydrochloride (LM)	258.0	0.40 (0.03)	0.0	26.7	21.92 (1.44)

[a] Melting temperatures were determined by DSC.
[b] Water content was measured by KFT.
[c] Yield strength was calculated by Heckel analysis, Eqn. (2).
[d] σ_0 is the tensile strength extrapolated to zero porosity. The extrapolated mean and standard error were obtained using a statistical program (SigmaPlot 4.0, SPSS Inc., Chicago, IL).

compact, provided that the interparticulate interaction strength is the same. When compressed under the same compaction conditions, **LA** compacts have the lowest porosity, i.e., **LA** is the most compressible among the six salts. **L** is the second most compressible salt. The porosity of **LG** has the greatest dependence on the compaction pressure. When the compaction pressure increases, the porosity decreases most rapidly for **LG** (Fig. 3). This result is attributed to the greater plasticity of **LG**, as indicated by its low yield strength (Table I).

Compactibility of the Salts

An exponential relationship between tensile strength and porosity was suggested by Ryshkewitch (21), thus:

$$\sigma = \sigma_o e^{-b\varepsilon} \quad (4)$$

The tensile strength at zero porosity, σ_o, has often been obtained by fitting equation (4) to the data, followed by extrapolation (22,23). All the six salts except **LG** follow the exponential relationship described by equation (4). However, a strong linear relationship between σ and ε was observed (R^2 = 0.992) only for **LG** (Fig. 4). Therefore, the σ_o of **LG** was obtained by linear extrapolation while σ_o of the other five salts was obtained by exponential extrapolation. The unique behavior of **LG** is still unclear.

Tabletability of the Salts

Among the tabletability plots, a linear relationship between tensile strength and compaction pressure was observed for **LG** at relatively low compaction pressures and for each of the other five salts over the range of compaction pressures studied (Fig. 5).

The tabletability of the salts follows the rank order, **LG** > **L** > **LA** ≈ **LM** >**LS** > **LD**, and is determined by both the compressibility, therefore the bonding area, and the compactibility, therefore the bonding strength, of the salts. For example, the similar tabletability of **LM** and **LA** is a result of the mutual compensation of compressibility and compactibility. **LA** is more compressible, with a lower porosity at the same compaction pressure, than **LM** (Fig. 3). Therefore, the interparticulate bonding area within **LA** tablets is greater than that within **LM** tablets. However, the tablet strength is also determined by the bonding strength per unit bonding area, which is indicated by the tablet tensile strength at zero porosity. The tensile strength of **LM** is greater than that of **LA** at the same porosity (Fig. 4), canceling out the effect of the smaller interparticulate bonding area of **LM**. Two similar tabletability curves are therefore obtained. At higher compaction pressures where most of pores have been eliminated, the difference in interparticulate bonding area will be small and the bonding strength per unit bonding area will be the decisive factor in controlling compact strength. Consequently, the two tabletability curves will diverge and **LM** will show a greater tabletability at a higher compaction pressure.

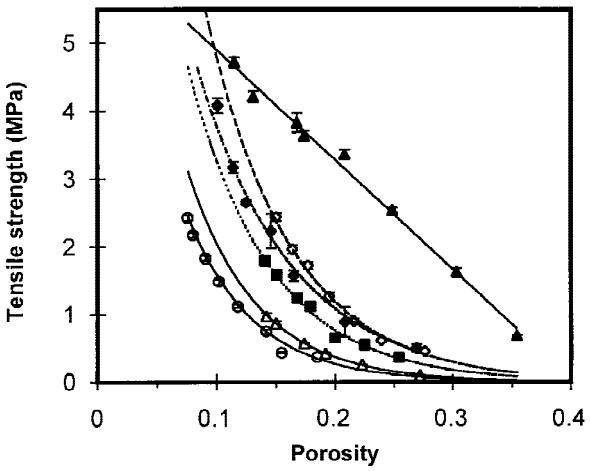

Fig. 4. Plots of tensile strength against porosity, showing the compactibility of six salts of L-lysine (n = 3): (▲) **LG**; (♦) **L**; (○) **LA**; (●) **LS**; (Δ) **LD**; (◇) **LM**.

Relationship Between Tensile Strength and Yield Strength

The yield strengths of the six salts were calculated from "out-of-die" Heckel plots (Fig. 2) and are listed in Table I. When compacted at a low pressure, the tensile strength of the compact of each salt decreases exponentially with increasing yield strength of each salt (Fig. 6). In explanation, at a low compaction pressure, the contact area can vary greatly among

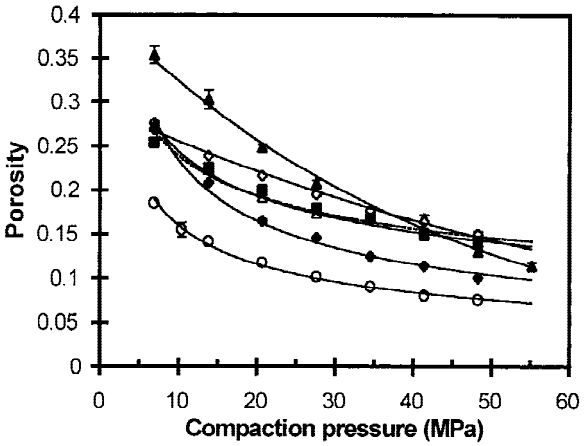

Fig. 3. Plots of tablet porosity against compaction pressure, showing the compressibility of six salts of L-lysine (n = 3): (▲) **LG**; (♦) **L**; (○) **LA**; (●) **LS**; (Δ) **LD**; (◇) **LM**.

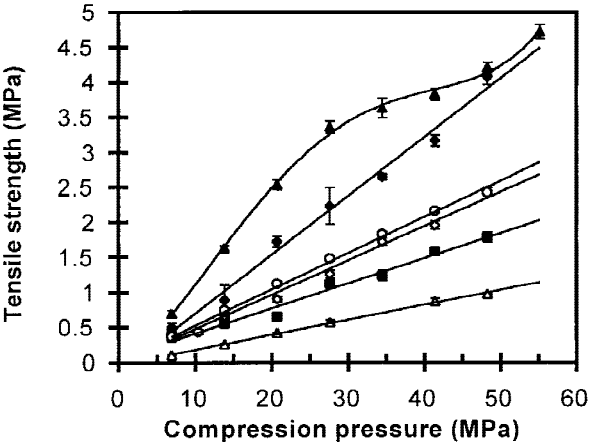

Fig. 5. Plots of tensile strength against compaction pressure, showing the tabletability of six salts of L-lysine (n = 3): (▲) **LG**; (♦) **L**; (○) **LA**; (●) **LS**; (Δ) **LD**; (◇) **LM**.

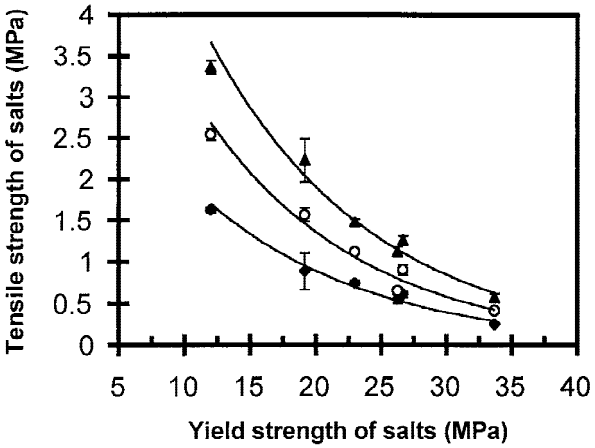

Fig. 6. Tensile strength (n = 3) at constant low compaction pressures: (♦) 13.8 MPa; (○) 20.7 MPa; (▲) 27.6 MPa; decreases exponentially with increasing yield strength of the salts, indicating that the greater the plastic deformation of the salt, the stronger the tablets at a defined pressure.

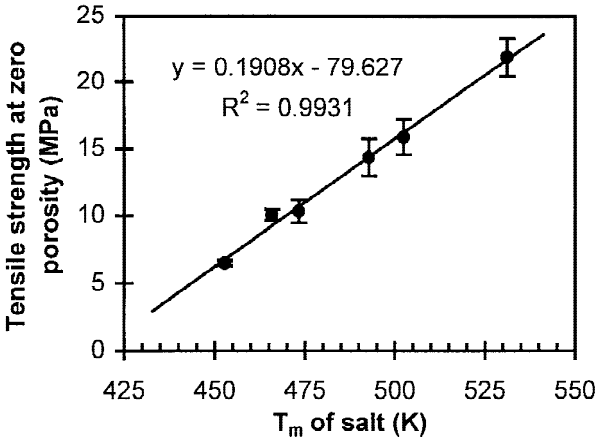

Fig. 7. The tensile strength at zero porosity increases linearly with increasing melting temperature of the six salts of L-lysine.

materials depending on their yield strength. When a material is more plastic, i.e., has a lower yield strength, a larger interparticulate contact area is developed during compaction and a higher fraction of the bonding area will survive the elastic recovery of particles during the decompression phase. In this situation, the interparticulate bonding area outweighs the effects of bonding strength and is the predominant factor controlling the tensile strength of the compact.

However, when the compaction pressure is high, i.e., when the compact porosity is low, the difference in interparticulate bonding area is reduced. At the extreme, i.e., at zero porosity, the interparticulate bonding area is determined only by the geometry of the compact and is not material-dependent. Therefore, the interparticulate bonding mechanism, determined by the intermolecular bonding strength, is the decisive factor in controlling compact tensile strength at or near zero porosity. Hence, the σ_o may not decrease with increasing yield strength. This speculation is supported by the plot of σ_o against yield strength of each salt, in which yield strength does not appear to be the factor controlling the strength of the tablet at zero porosity. The points on the plot are scattered, the determination coefficient of linear regression, R^2, being 0.157.

Tensile Strength–Melting Point Relationship

Because the interparticulate bonding area at zero porosity is normalized for all salts, the tensile strength at zero porosity, σ_0, should be related only to the bonding mechanism. Because a higher melting point indicates stronger intermolecular and interionic interactions in the crystals, the tensile strengths at zero porosity might be related to the melting points of the six salts. This concept is supported by the observation that σ_o increases linearly with increasing melting point (Fig. 7). A similar observation was reported by Jaffe and Fosse (24) in which the hardness of the tablets of a series of inorganic salt increases with increasing boiling temperature, indicating a higher cohesive affinity, of the salts. In this study, the relationship between σ_o and the enthalpy of fusion could not be determined because all six salts decompose at their melting temperatures. Moreover, because dehydration of **LG** dihydrate and **L** monohydrate took place prior to melting, only the melting temperature of anhydrous **LG** and **L** were obtained and were used to approximate the cohesive affinity of their hydrates. We recognize that the water of crystallization may profoundly affect the compaction behavior of a compound because plasticity and other mechanical properties could have been changed following a change in crystal structure. However, it is also possible that the difference in σ_o between a hydrate and anhydrate of a salt may not be significant, because the contribution of the water of crystallization to the overall lattice energy should be relatively low in comparison with the strong interaction between the ions.

CONCLUSIONS

The yield strength is the dominant factor that determines the tensile strength of compacts of the six salts compressed at pressures from 6.9 MPa to 27.6 MPa. For all the salts except **LG**, the tensile strength decreases exponentially with increasing porosity, while the tensile strength of **LG** decreases linearly with increasing porosity.

The strength of the intermolecular and interionic interactions is the dominant factor that controls the tensile strength of the compacts at or near zero porosity, at which the bonding area is similar among compacts of different salts. Higher melting point indicates greater strengths of the intermolecular and interionic interactions and greater σ_o. The tensile strength of compacts that are compressed at medium compaction pressures is controlled by both plasticity and the strength of the intermolecular and interionic interactions, i.e., bonding strength.

This study confirms that the compact tensile strength is determined by both the total interparticulate bonding area and the bonding strength. Under moderate compaction pressures, the interparticulate bonding area is determined by the deformability, i.e., yield strength, of the salt. For a salt of lower yield strength, a larger bonding area is formed under the same conditions of compaction. Hence, a stronger compact is formed. When the porosity is low or zero, the total bonding area is determined only by the geometry of the compact and not by the deformability of the salts. Therefore, the compact strength at low porosity should be determined by the

bonding strength, i.e., by the strength of the intermolecular and interionic interactions, of the salts. Although these conclusions are derived from experiments on salts, they may be also applicable to molecular crystals.

ACKNOWLEDGMENTS

We thank the American Foundation for Pharmaceutical Education (AFPE) for a Pre-doctoral Fellowship for C.S. and Pfizer Central Research for partial financial support.

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