Pharmaceutical Research, Vol. 14, No. 4, 1997 Report

Effect of Compaction Temperature on Consolidation of Amorphous Copolymers with Different Glass Transition Temperatures

K. Van der Voort Maarschalk,[1,4] K. Zuurman,[1]
M. J. Van Steenbergen,[2] W. E. Hennink,[2]
H. Vromans,[3] G. K. Bolhuis,[1] and C. F. Lerk[1]

Received September 10, 1996, accepted January 30, 1997

Purpose. The purpose of this study was to relate the combination of glass transition temperature (T_g) and temperature of measurement with the mechanical and compaction properties of some test materials.

Methods. Copolymers with different T_g's were synthesised by free radical copolymerisation of methyl methacrylate with lauryl methacrylate. Elastic moduli were measured by dynamic mechanical analysis at different strain rates and temperatures. Compaction experiments were performed at different compaction speeds and temperatures.

Results. The difference between temperature of measurement and T_g appears to determine both elastic modulus and yield strength completely. They both decrease with decreasing difference between temperature of measurement and T_g and increase with strain rate. At temperatures of measurement higher than the T_g, the elastic modulus is extremely low because the materials behave as rubbers. Consequently, the amount of energy stored during compaction decreases when the compaction temperature approaches the T_g and increases with strain rate. When the compaction temperature is higher than the T_g, the amount of stored energy is extremely large. The compaction experiments show that the final tablet porosity is completely determined by stress relaxation phenomena. Consequently, the final tablet porosity follows exactly the same relation as that of stored energy.

Conclusions. The final tablet porosity is unequivocally determined by the amount of stored energy. This implies that tablet production at a temperature of about 20 K under the glass transition temperature of the material yields tablets with minimum porosity.

KEY WORDS: tablet; copolymer; glass transition temperature; porosity; viscoelasticity.

INTRODUCTION

A coherent tablet is the result of deformation of powder particles and bonding between the particles. Both deformation and bonding are important topics in tabletting research. Materials are generally classified as either brittle or ductile, depending on the predominant deformation properties of the particles. Amorphous and partially crystalline polymers form an important group of ductile materials. These materials receive a lot of attention in pharmaceutical research because they suffer from problems like strain rate sensitivity (1) and extreme sensitivity to water content (2,3,4).

In tabletting science, it is known that there is an intimate relation between physico-mechanical properties of the excipients and the properties of the resulting tablets (5). The glass transition temperature of amorphous materials appears to be a critical parameter with respect to mechanical properties of amorphous materials (6). From this, it is evident that the glass transition temperature of amorphous materials affects compaction properties of these materials.

The aim of this paper was to study the effect of the difference between temperature of measurement and glass transition temperature on mechanical properties of a model excipient with different glass transition temperatures. Mechanical properties were related with the consolidation of the powdered materials. Excipients with different glass transition temperatures were produced by synthesis of copolymers with varying amounts of monomer with plasticising properties. This method was chosen rather than addition of a plasticiser to an existing polymer (like water in starch), because the latter sometimes suffers from problems like phase separation at high plasticiser contents, evaporation of plasticiser and effects of plasticiser on bonding properties (4). For this reason, it was chosen to copolymerise methyl methacrylate with lauryl methacrylate.

THEORETICAL BACKGROUND

The glass transition temperature of a random copolymer with two monomer types can be calculated with the Fox-equation (7):

$$\frac{1}{T_g} = \frac{\nu_1}{T_{g,1}} + \frac{\nu_2}{T_{g,2}} \qquad (1)$$

with T_g the glass transition temperature of the copolymer, ν_1 and ν_2 the weight fractions of the monomers 1 and 2, and $T_{g,1}$ and $T_{g,2}$ the glass transition temperatures of homopolymer 1 and 2, respectively.

In order to produce copolymers with well-defined glass transition temperatures, it is necessary to produce random copolymers and prevent production of blocks rich in one of the monomers in the copolymers. Calculation of the copolymer reactivity ratios enables to predict the possibility of block formation (6). The copolymer reactivity ratios (r_1, r_2) can be calculated with:

$$r_1 = \frac{Q_1}{Q_2} \cdot e^{-e_1\cdot(e_1-e_2)} \qquad (2)$$

and

$$r_2 = \frac{Q_2}{Q_1} \cdot e^{-e_2\cdot(e_2-e_1)} \qquad (3)$$

---

[1] Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV, Groningen, The Netherlands.

[2] Department of Pharmaceutics, University of Utrecht, The Netherlands.

[3] N.V. Organon, Oss, The Netherlands.

[4] To whom correspondence should be addressed.

ABBREVIATIONS: A_{comp}, penetration depth; E, elastic modulus; e_1, e_2, polarity (of monomer 1 and 2, respectively); f, angular frequency F, f, molar fraction in feed and polymer, respectively; M_n, molecular weight on number basis; M_w, molecular weight on weight basis; Q_1, Q_2, reactivity (of monomer 1 and 2, respectively); r_1, r_2, copolymer reactivity ratio (of monomer 1 and 2, respectively); T_g, glass transition temperature of copolymer; $T_{g,1}$ $T_{g,2}$, glass transition temperature (of homopolymer 1 and 2, respectively); T_m, temperature of measurement; v, compaction speed; W_{rev}, stored energy; ΔT, temperature difference; ν_1, ν_2, weight fraction (monomer 1 and 2, respectively); σ_c, yield strength; $\rho_{compact}$, compact density; ρ_t, true density.

where Q_1 and Q_2 are representations of the reactivity of monomers 1 and 2 and e_1 and e_2 are measures of the polarity of the monomers, respectively. Values of Q and e can be found in literature. The copolymerisation behaves ideally if the product of the reactivity ratios equals 1. This means that a random distribution of the monomers can be expected in the polymer chain.

Mechanical properties of viscoelastic materials can be characterised by stress-strain relations (8). For an elastic solid, stress is directly proportional to deformation (strain). The proportionality constant (E) is called the Young's or elastic modulus. It is a measure of the rigidity or resistance to deformation. The material behaves predominantly elastic up to a yield point, where the stress is called yield stress (σ_c). Beyond that point the material behaves as a plastic, rather than as an elastic solid; it flows under practically constant stress. A simplified stress-deformation curve can be derived by plotting a linear portion with tangent E up to the yield stress (σ_c), followed by a horizontal portion from a point of 'critical deformation' where yielding starts (4). Consequently, it is possible to calculate the stored elastic energy (W_{rev}) in the deformed material as a function of the deformation rate by:

$$W_{\text{rev}} = \frac{1}{2} \cdot \frac{\sigma_c^2}{E} \tag{4}$$

Equation (4) assumes that all material is forced to yield and the equation is consequently only valid at high pressures.

A previous study indicates that the amount of stored energy is the driving force for stress relaxation of tablets. The expression of stress relaxation of tablets is an increase in porosity after compression (9).

MATERIALS AND METHODS

Materials

Methyl methacrylate (MMA), lauryl methacrylate (LMA) and 2, 2′-azobisisobutyronitril (AIBN) were from Fluka (Buchs, Switzerland) and used as received. Toluene was from Baker (Deventer, The Netherlands).

Synthesis and Characterisation of Copolymers

Poly(methyl methacrylate-co-lauryl methacrylate) copolymers were synthesized by solution free radical copolymerization of methyl methacrylate (MMA) and lauryl methacrylate (LMA) using AIBN as initiator. The desired amount of monomers was weighed (total amount around 100 g) and 1 L of toluene was added. This solution was heated to 333 K, flushed with argon after which the initiator (AIBN) was added (M:I = 250 mol·mol^{-1}). After a polymerization time of 22 hours, part of the toluene was evaporated under reduced pressure and the remaining viscous solution was added dropwise in petroleum either 40–60 (polymers with high MMA content) or methanol (polymers with high LMA content) to precipitate the polymer. The precipitate was collected by filtration and vacuum dried until constant weight at 323 K.

Molecular weights (M_n and M_w) of the different copolymers were determined by gel permeation chromatography. Shodex columns were used with $CHCl_3$ as mobile phase. The columns were calibrated using polystyrene standards of known weight.

The glass transition temperature (T_g) of different copolymers was determined by differential scanning calorimetry (DSC) analysis using a TA 2920 MDSC (TA Instruments, Gent, Belgium). Samples of about 10 mg in aluminium pans, were heated to 373 K and subsequently cooled to 173 K. After 5 minutes of equilibration at this temperature, the sample was heated to 423 K (average heating rate 2.0 K·min^{-1}; modulation: ±0.318 K·min^{-1}). T_g was taken as the midpoint of the transition.

The copolymer composition (ratio MMA:LMA) was established by ^{1}H-NMR analysis. NMR spectra were recorded in $CDCl_3$ with a Gemini 300 Mhz spectrometer (Varian Associates Inc. NMR Instruments, Palo Alto, CA). The molar ratio MMA:LMA in the copolymers was calculated by comparing the integrated intensity of the resonance at δ 3.6 (assigned to the -O-CH_3 protons of the methyl methacrylate group) with that at δ 3.9 (assigned to the -O-CH_2-protons of the lauryl methacrylate group.

Preparation of a Sieve Fraction of the Different Copolymer Powders

Quantities of about 5 gram of the material were milled (Moulinex MCU1H, France) for a period of less than 10 s. A sieve fraction of the milled materials was obtained with USA standard testing sieves (W.B. Tyler inc. Mentor, OH, USA). All experiments were performed with a sieve fraction of 106–212 μm. True density of the copolymers was measured with a helium pycnometer (Quantachrome, Syosset, USA).

Dynamic Mechanical Analysis Experiments

Dynamic mechanical analysis was performed at several temperatures on a Rheometrics Solids Analyzer (Piscataway, NJ, USA), using the dual cantilever method. Non-porous strips of the test materials were produced in order to measure properties of the material and prevent complicating effects of particle interactions on viscoelastic properties (9). Strips with a size of about 60 · 6 · 1 mm were prepared by heating the material until the temperature was equal to the glass transition temperature of the test material. The warm material was than compressed at a pressure of about 100 MPa. The measurements were preformed as previously described (10).

Compaction Experiments

Flat-faced compacts of 500 mg and a diameter of 13 mm were prepared on a high speed compaction simulator (ESH, Brierley Hill, UK) at various temperatures. It appeared to be impossible to evaluate the effect of the compaction process at high speeds on the temperature of the material. The tabletting procedure was described previously (9). As sinusoidal profiles were used, a complete profile involves π rad. Knowing both the compression speed (v) and the penetration depth (A_{comp}), it is possible to calculate the angular frequency of the compression (f):

$$f = \frac{\pi \cdot v}{2 \cdot A_{\text{comp}}} \tag{5}$$

which makes it possible to correlate dynamic mechanical to compaction experiments. The average compaction speeds were

3, 30 and 300 mm·s^{-1}. These values fall within the range of strain rates as applied in dynamic mechanical analysis.

The yield strength of the test materials was measured according to Heckel (9,10). Linear interpolation was performed in the porosity range between 35% and 8%. After a relaxation period of at least 16 hours, tablet dimensions were measured with the micrometer and the tablet was weighed on an analytical balance.

RESULTS AND DISCUSSION

Polymer Characterisation and Deformation

Table I summarises the conditions of the copolymerisations and the characteristics of the copolymers prepared. The Q and e values for MMA and LMA have been published in literature (13). The product of the reactivity ratios ($r_1 \cdot r_2$, based on Q and e values, according to eq. 2 and eq. 3) equals 1, which demonstrates that the copolymerisation behaves ideally. This indicates a random distribution of the monomers in the polymer chain.

For random copolymers, the T_g value depends upon the copolymers composition according to eq. 1. The glass transition temperature of PMMA was determined using DSC analysis (391 K, Table I); the glass transition temperature of PLMA was calculated using the approach described by Van Krevelen (7) and amounted 237 K. Table I presents both calculated and measured values of the glass transition temperature. The table shows a good correlation between the observed and the calculated T_g values. This again demonstrates that the monomers are randomly distributed in the copolymers. Effects of LMA on deformation and tabletting properties will consequently be a result of this plasticiser on the polymer chains and not an effect of the presence of LMA rich blocks.

The elastic modulus quantifies mechanical properties of materials at small strains. Figure 1 depicts the relation between the elastic modulus, measured by dynamic mechanical analysis, and the difference between temperature of measurement (T_m) and glass transition temperature (T_g), called temperature difference (ΔT):

$$\Delta T = T_m - T_g \tag{6}$$

The figure shows decreasing elastic moduli when the temperature of measurement approaches the glass transition temperature. Measurements at different temperatures on materials with a fixed glass transition temperature give exactly the same relation as measurements at a fixed temperature but on materials with different glass transition temperatures. So there is a unique relation between the temperature difference and the elastic modulus.

Table 1. Copolymerisation of MMA with LMA Carried out in Toluene at 333 K Using AIBN as Initiator (M:I = 250 mol·mol^{-1})

MMA: LMA (kg:kg)	F^a	f^a	M_n (g·mol^{-1})	M_w (g·mol^{-1})	T_g calc. (K)	T_g meas. (K)	ρ_t (gr·ml^{-1})
100:0	1.00	1.00	18 400	53 100	391	391	1.173
83:17	0.91	0.92	18 800	60 400	352	350	1.137
72:28	0.84	0.87	14 600	67 000	331	326	1.114
64:36	0.79	0.82	19 300	67 100	317	319	1.100

[a] F and f are the molar fractions of MMA in the feed and the copolymer, respectively.

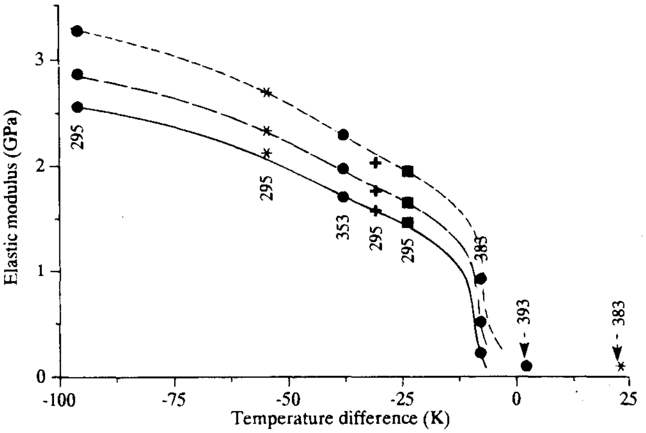

Fig. 1. Elastic modulus of the (co-)polymers as a function of the difference between the temperature of measurement and the glass transition temperature, expressed as temperature difference, at three rates of strain. The arrows with the dashed lines indicate that the elastic modulus is under 0.1 GPa and the given numbers refer to the temperature of measurement. Symbols: T_g = 391 K (●), T_g = 350 K (*), T_g = 326 K (+), T_g = 319 K (■).

If the temperature of measurement is approximately equal to the glass transition temperature, the elastic modulus starts to decrease dramatically, which is evidently a result of the glass transition temperature of the material: the materials comes in the rubbery state, causing completely other mechanical properties of the material (6). According to eq. 5 compaction speed (tabletting) and angular frequency (dynamic mechanical analysis) are interrelated. Figure 1 shows increasing Young's modulus with strain rate, which is also observed in a previous publication (8).

The dynamic mechanical analysis experiments presented here, yield the elastic modulus in plain tension. However, it can be assumed that particle deformation in tabletting is a complex result of tension, shear and compression. The different moduli (elastic modulus, shear modulus and bulk modulus, respectively) are proportionally related (6). This paper reports the elastic modulus only. This may introduce numerical errors in further calculations, the rank order remains constant, however.

Measurements of elastic moduli are measurements at small strains, causing predominantly elastic deformations, whereas consolidation experiments force the materials to yield. Figure 2 shows that yield strength of the materials (derived from consolidation experiments) decreases when the temperature of measurement approaches the glass transition temperature of the material. Just as has been found in measurements of elastic modulus, the temperature difference appears to be the central parameter in yield strength measurements too. Again, an increase in temperature has the same effect on yield strength as a decrease in glass transition temperature by incorporation of a monomer with plasticising properties.

Mechanical properties of materials may change on heating and subsequent cooling. Some random checks pointed to small effects of heating and cooling on both Young's modulus and yield strength. These effects were assumed to be negligible.

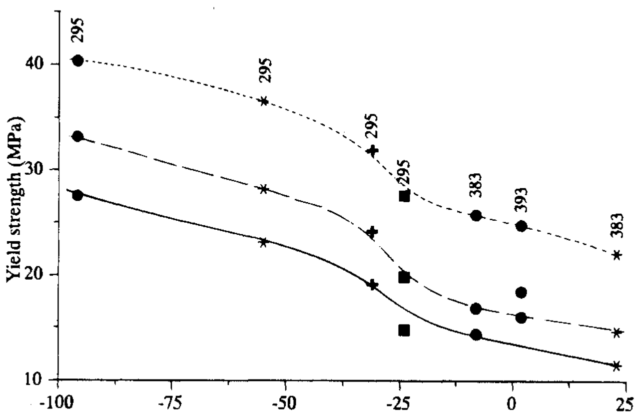

Fig. 2. Yield strength of the (co-) polymers as a function of the temperature difference. Symbols as in Figure 1.

Assuming that all material yields and that no additional energy is stored in the yielded material, the simplified stress-strain relation enables to calculate the amount of energy that is stored during compression. Figure 3 shows the stored energy (eq. 4) as a function of temperature difference at three different rates of compaction. At compaction temperatures less than 20 K under glass transition temperature of the material or at compaction temperatures higher than it, there is a rapid increase in stored energy with increasing temperature difference, pointing to larger stress relaxation propensity of materials in the rubbery state. However, it is noted that the polymers come in the rubbery state at these temperature differences; it is than hard to define a yield pressure and quantifications of stored energy may than be difficult. When the temperature difference is less than −30 K (i.e. glass transition temperature more than 30 K higher than temperature of measurement), the amount of stored energy appears to increase slightly with decreasing temperature difference, which is primarily a result of the increase in yield strength with decreasing temperature difference. The amount of stored energy also increases with compaction speed, which is in accordance with previous papers (4,11).

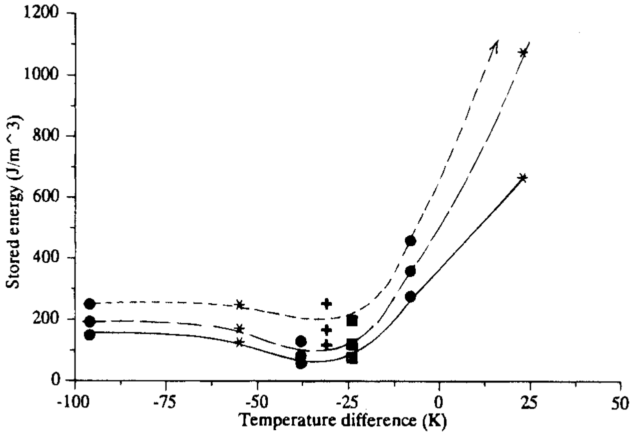

Fig. 3. Stored energy as a function of temperature difference of the (co-) polymers. Symbols as in Figure 1.

Compacts Produced from the Polymers

Tablets were compressed from the copolymer powders at different compaction speeds and temperatures. Figure 4a shows the relation between compact density after relaxation of the tablets and compaction pressure of the material with 36% LMA (T_g = 319 K) at different compaction speeds and a temperature of 293 K. The figure also gives the compact density under pressure at a compaction speed of 3 mm·s^{-1}. The figure indicates material compression under pressure as the compact density reaches higher values than true density. Besides, the figure shows that the final tablet density is the result of relaxation phenomena occurring after compression: the density of the final tablet is much lower than under pressure. Finally, there is an effect of compaction speed on the final tablet density. The latter reaches a maximum that is independent on compaction pressure but depends on compaction speed.

Tablet properties such as strength and drug release, are often affected by the porosity (ϵ) of the tablet (e.g. 14,15). It is directly related to the density of the tablet by:

$$\epsilon = 1 - \frac{\rho_{\mathrm{compact}}}{\rho_t} \qquad (7)$$

with ρ_{compact} the density of the compact, and ρ_t the true density of the material. Fig. 4b gives the minimum attainable porosity measured under various circumstances. The figure clearly shows that the minimum attainable porosity increases rapidly when the compaction temperature approaches the glass transition temperature. Compaction at temperatures higher than the glass transition temperature of the material yields capped tablets. When the compaction temperature is more than 30 K under the glass transition temperature of the material, minimum attainable porosity increases slightly.

Compact Porosity as a Result of Particle Deformation

The fact that the final porosity of the tablets is much larger than the calculated porosity under pressure shows that relaxation phenomena predominantly determine tablet porosity (Figure 4a). Previous papers stated that the amount of stored energy

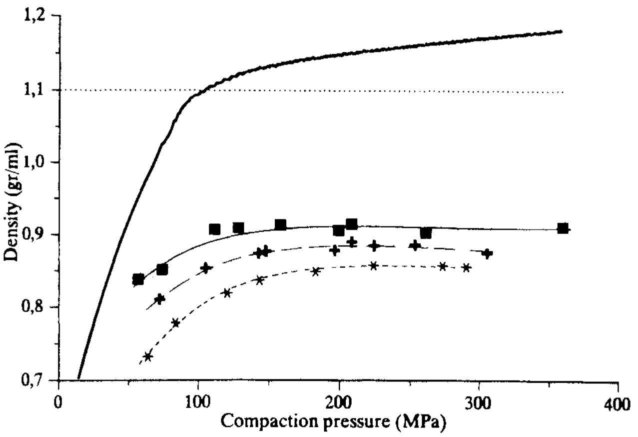

Fig. 4a. Compact density under pressure of the copolymer powder with an LMA fraction of 0.36 (solid line) and the true density (dotted line) measured by pycnometry. The symbols give the densities of tablets after relaxation compressed at speeds of 3 (■), 30 (+) and 300 (*) mm·s^{-1}.

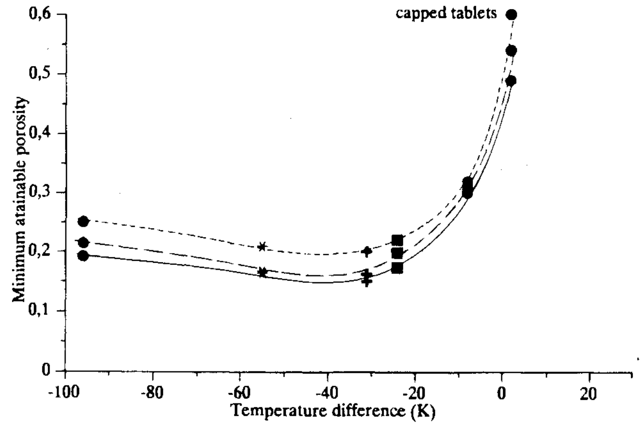

Fig. 4b. Minimum attainable porosity of the copolymers as a function of temperature difference. Symbols as in Figure 1.

can very well be regarded as the driving force for relaxation, whereas the increase in porosity is regarded as an expression of relaxation (4,10). It should hence be possible to relate the minimum attainable porosity (which is numerically equal to the increase in porosity) with stored energy. Figure 5 shows the relation between the minimum attainable porosity (expressed as void ratio) and stored energy for the materials with different glass transition temperatures. The figure clearly gives an almost unique relation between minimum attainable void ratio and stored energy. This shows that the final tablet porosity is determined by relaxation phenomena that can be quantified with the amount of stored energy.

In conclusion, the data show that there is a direct relation between the minimum attainable porosity of tablets and the mechanical properties of the material. However, a porosity is generally not the main goal to strive for, but in many cases porosity largely affects properties of compacts with pharmaceutical relevance (14,15). So, the final tablet porosity is an important parameter here. As reported earlier (9), minimisation of porosity is essentially the same aim as maximisation of tablet strength because the porosity of tablets of these materials completely determines its strength (results not shown). Moreover, according to Figure 5, minimisation of tablet porosity is essentially minimisation of stored energy. In order to minimise stored energy it is necessary to choose the material with high elastic modulus and low yield strength (Eq. 4). These two aims (one material with both high elastic modulus and low yield strength) are conflicting, however. A material has a high elastic modulus when the temperature of measurement is much lower than the glass transition temperature of the material (Figure 1) but a low yield strength when the temperature of measurement is higher than the glass transition temperature of that material (Figure 2). It is therefore necessary to choose circumstances where elastic modulus is not too low, yield strength not too high, and, consequently, stored energy has a minimum. According to Figure 3, stored energy has a minimum when the temperature of measurement is 20 K lower than the glass transition temperature of the material. The material is than a glass with relatively high elastic modulus and the yield strength is relatively low. At higher temperature differences, there is a sharp decrease in elastic modulus causing large values of stored energy. At lower temperature differences, yield strength increases too much, also causing larger values of stored energy. The observation that the material must be a glass, but with a glass transition temperature not much higher than the tabletting temperature is in accordance with previous observations where amorphous potato starch was plasticised with water (4).

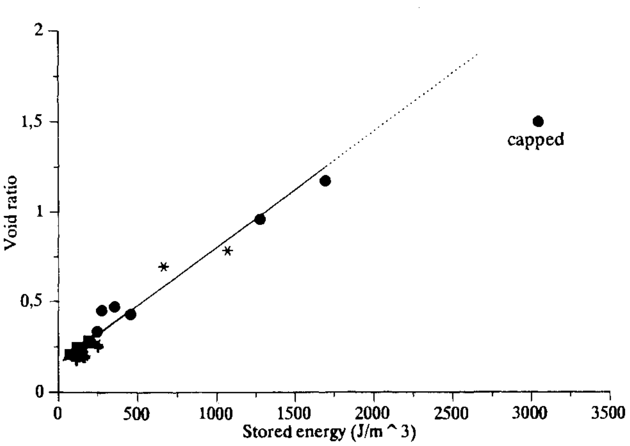

Fig. 5. Minimum void ratio as a function of stored energy. Symbols as in Figure 1.

An increase in compaction speed causes a small increase in elastic modulus (Figure 3) and a relatively large increase in yield strength (Figure 4) causing an increase in stored energy with a factor of about 2 when the compaction speed increases two decades (Figure 5). As the stored energy is unequivocally related to tablet porosity, it is shown that the decrease in tablet porosity is, again, purely an effect of increased relaxation of the material.

ACKNOWLEDGMENTS

The authors would like to thank Mrs. J. Beekhuis for accurately preparing the manuscript

REFERENCES

1. R. J. Roberts and R. C. Rowe. *J. Pharm. Pharmacol.* **37**:377–384 (1985).
2. C. E. Bos, G. K. Bolhuis, H. Van Doorne, and C. F. Lerk. *Pharm Weekblad Sci. Ed.* **9**:274–282 (1987).
3. J. E. Rees and K. D. Tsardaka. *Eur. J. Pharm. Biopharm.* **40**:193–197 (1994).
4. K. Van der Voort Maarschalk, K. H. Vromans, W. Groenendijk, G. K. Bolhuis, and C. F. Lerk. *Eur. J. Pharm Biopharm.* Submitted (1996).
5. R. C. Rowe and R. J. Roberts. In G. Alderborn and C. Nyström (eds.) *Pharmaceutical powder compaction technology,* Dekker, New York, 1996, pp. 283–322.
6. J. M. G. Cowie. *Polymers; Chemistry and Physics of Modern Materials,* Blackie, London, 1991.
7. D. W. Van Krevelen, *Properties of polymers,* Elsevier, Amsterdam, 1990.
8. R. J. Crawford. *Plastics Engineering,* Pergamon, Oxford, 1987.
9. K. Van der Voort Maarschalk, K. Zuurman, H. Vromans, G. K. Bolhuis, and C. F. Lerk. *Int. J. Pharm.* **140**:185–193 (1996).
10. K. Van der Voort Maarschalk, H. Vromans, G. K. Bolhuis, and C. F. Lerk. *Eur. J. Pharm. Biopharm.* **42**:49–55 (1996).
11. R. W. Heckel. *Trans. Met. AIME.* **221**:671–675 (1961).
12. R. W. Heckel. *Trans. Met. Soc. AIME.* **221**:1001–1008 (1961).
13. H. F. Mark, *Encyclopaedia of Polymer Science and Engineering,* Wiley, New York, 1987.
14. W. Duckworth. *J. Am. Ceram. Soc.* **36**:68 (1953).
15. R. Steendam and C. F. Lerk. *J. Contr. Release.* Submitted.