ELSEVIER

International Journal of Pharmaceutics 120 (1995) 13–20

international journal of pharmaceutics

The effect of moisture content on the energies involved in the compaction of ibuprofen

A. Nokhodchi [a], M.H. Rubinstein [a,*], H. Larhrib [b], J.C. Guyot [b]

[a] *School Of Pharmacy, Liverpool John Moores University, Liverpool L3 3AF, UK*
[b] *Faculte de Pharmacie, Lille, France*

Received 26 November 1993; revised 8 July 1994; accepted 9 August 1994

Abstract

The influence of moisture content and compression speed on the ejection force, plastic and elastic energies of ibuprofen was measured. It was found that moisture can significantly reduce the force required to initiate ejection by the breaking of tablet/die-wall adhesions. At all compression speeds, an increase in moisture content resulted in a marked reduction in the ejection force of ibuprofen compacts. The plastic energy was found to increase with moisture content up to 2.5% w/w, ascribed to an increase in particle-particle interactions. Subsequent decrease in plastic energy at higher moisture contents was probably due to a decrease in particle interaction due to the moisture separation of the particles of ibuprofen. The elastic energy was found to decrease with increasing moisture content up to about 2.5% w/w. This is believed to be due to the strong bonding of particles, brought about by moisture facilitating the formation of interparticle hydrogen bonding and so reducing the interparticle separation. Subsequent increase of elastic energy with increasing amount of moisture beyond 2.5% w/w was thought to be due to the formation of multilayers of water at the surfaces of the particles. This excess moisture increased the elastic energy, by decreasing particle-particle interaction.

Keywords: Ibuprofen; Plastic energy; Elastic energy; Moisture content; Ejection force; Compression speed

1. Introduction

The presence of moisture in pharmaceutical powders can play a significant role in influencing the consolidation properties and often produces changes in flow properties particularly after storage. Occasionally moisture is added deliberately in order to produce a more cohesive mass suitable for further processing. Interest has been expressed in the moisture uptake and the liquid-solid interactions of starches and cellulose by Zografi et al. (1984) and these workers have suggested that water sorbed to such materials most likely exists in at least three states; tightly bound to anhydroglucose units, less tightly bound, and bulk water. These researchers have also discussed some implications of such behaviour for pharmaceutical systems (Zografi and Kontny, 1986).

Garr and Rubinstein (1992a) found that the incorporation of up to 6% w/w moisture at a

* Corresponding author.

0378-5173/95/$09.50
SSDI 0378-5173(94)00372-6

compression speed of 24 mm/s improved the tablet strength of paracetamol compacts. An increase in tensile strength with increasing moisture content has been explained by two possible mechanisms. Firstly, adsorbed water could function as a surface restructuring medium leading to an increased amount of solids bridges (Ahlneck and Alderborn, 1989). An increase in mechanical strength with increasing moisture content for sodium chloride has been suggested to be a result of a restructuring of surfaces in the tablet (Lordi and Shiromani, 1983). Another possible explanation for an increase in tensile strength is that immobile water layers sorbed at particle surfaces can enhance the particle-particle interaction. An adsorbed water vapour layer can according to this theory contribute in two ways to the strength of the interaction: (a) tightly bound water vapour layers can be regarded as a part of the particles which reduces the interparticular surface distances and thus results in increased intermolecular attraction forces (Coelho and Harnby, 1978); (b) adsorbed layers can touch or penetrate each other which will increase the attraction forces between neighbouring particles (Turner and Balasubramanian, 1974). A decrease in tensile strength has been explained as a result of the formation of multilayers of water at the particle surfaces. Such layers may then disturb or reduce intermolecular attraction forces and thereby reduce the tablet strength (Kristensen et al., 1985; Ahlneck and Alderborn, 1989).

For the compaction of materials and formation of strong compacts, energy is needed and it seems logical to correlate the properties of the compact with the energy input rather than the compression pressure. The energy used during compaction can be calculated from punch force and displacement. For a system where both punches are mobile, the punch separation may be plotted against upper punch force or mean punch force.

De Blaey and Polderman (1970, 1971) used energy to characterise the various stages of compaction. Processes which consume energy during tablet compression include: closer packing of loose powder particles, interparticle friction, particle-die wall friction, elastic deformation, plastic deformation, fragmentation and the formation of bonds. The work needed for particle rearrangement and to overcome interparticle friction has been considered negligible (De Blaey and Polderman, 1971). It was further assumed that the work for plastic deformation, i.e., the total net work or a certain fraction of it, was used for bond formation, which would explain the good correlation between net work and tablet crushing strength (De Blaey and Polderman, 1971).

The method of calculating the net work has been discussed (Ragnarsson and Sjogren, 1983) and the basic assumptions have been widely accepted. Ragnarsson and Sjogren (1985) investigated the influence of particle interaction, i.e., friction and bonding, on the net work during compaction and on Heckel plots. This was done by investigating the effect of particle size, lubrication or the moisture content, on the net work and it was found that the net work was significantly affected by particle interaction.

Little work has been carried out to examine the effect of moisture on the energies of compaction. The aim of the present investigation therefore was to assess the effect of moisture content of ibuprofen on the plastic and elastic energies and ejection force.

2. Materials and methods

2.1. Materials

Ibuprofen B.P powder grade was obtained from Boots Co. Ltd Nottingham, UK, and apyrogen water was from Pharma Halmelen (GmbH, Germany). Particle size fractions 45–125 μm sieve fractions of ibuprofen powder were obtained by sieving the materials through test sieves on a mechanical vibrator (Pascal Engineering, UK). The sieved fractions were dried in an oven to constant weight at 50°C. Due to the melting point of ibuprofen a low drying temperature had to be used.

2.2. Moisture content determination

Four samples of ibuprofen powder were poured into individual evaporating basins and accurately weighed. A vacuum oven was set to 50°C and allowed to equilibrate. Due to the low melting point of ibuprofen (78°C) a lower drying temperature had to be used and 50°C was found to be satisfactory. The basins were placed in the oven, the samples were removed at regular intervals and reweighed. When consistent weights were maintained the weight loss was calculated and the moisture content of the ibuprofen calculated.

2.3. Moisture sorption by the ibuprofen and addition of moisture

Dried samples were placed in tared 5 cm diameter petri dishes and exposed to different relative humidities ranging from 5 to 98% in a desiccator prepared with saturated salt solutions. The petri dishes containing the ibuprofen were periodically taken out of the desiccator at regular intervals and accurately weighed, to determine any changes in weight of the ibuprofen. It was found that no moisture increase occurred at relative humidities below 90%. Furthermore, the increase in moisture content after storage for 2 weeks at 98% R.H. was less than 0.5%.

Moisture content of the oven-dried samples was increased to 1, 2.5, 3.5, 5, 7.5 and 10% w/w by spraying calculated weights of apyrogenic water from a microsprayer. The ibuprofen was then blended by stirring in a glass bottle attached to an electric motor rotating at 40 rpm for 10 min. The containers were then shaken manually three-dimensionally with simultaneous rotation about the axis and were subsequently sealed in air-tight bags, placed in a dry chamber and compression was then completed with a minimum of delay.

2.4. Compression

Compressions were carried out using the Liverpool School of Pharmacy Modified High Speed Compaction Simulator (ESH Testing Ltd, Brierley Hill, West Midlands, UK), fitted with 12.5 mm flat-faced punches. The simulator consists of a load frame, hydraulic power pack and electronic control unit. A sawtooth time-displacement profile was used to control both upper and lower punches. The data points of the profile are output at a predetermined rate via a digital/analogue converter to a servo controller in the main control unit and onto the control valves situated on the load frame. The signal supplied to the valves determines the flow of hydraulic fluid from the power pack through the valves to the actuators. It is this flow of fluid which causes movement of the actuators according to the intended profile. The output rate of the profile may be set to produce compaction rates up to 3000 mm/s and to a maximum compaction force of 50 kN. Four tablets were produced at compression speeds from 15 to 240 mm/s. 400 mg constant weight was maintained for all the samples and each tablet was compressed to a maximum compaction force of 10 kN for assessment of the ejection force and energy analysis. The die wall was cleaned with acetone and prelubricated with 4% w/w magnesium stearate in acetone before each compression.

During compression, upper punch load and punch separation were monitored to an accuracy of ± 0.05 kN and ± 12 μm, respectively (Bateman, 1988; Bateman et al., 1989).

2.5. Manipulation of compression data

The force and displacement data from the upper and lower load cells and the linear variable differential transducers (LVDTs) were captured using a microlink transient recorder and plotted in the form of separate load/time and displacement/time curves using a computer programme. The data were subsequently converted for examination as well as storage on to floppy disk and again transferred to a mainframe computer, using a fortran programme to sort the data. The area under the compression curve (mean punch force vs punch separation) was evaluated.

2.6. Measurement of plastic energy and elastic energy

For a system where both punches are mobile, the punch separation may be plotted against upper punch force. The area under this curve will be the work done or energy. The plastic and elastic energy of compaction of ibuprofen tablets at various speeds were measured using energy analysis on the force-punch separation plot. A computer programme was employed to calculate gross, plastic and elastic energies from the transient recorder data.

Fig. 1 illustrates schematically the force-punch separation plot, where A is punch separation at the first measurable force. B is the force at minimum punch separation, D represents the minimum punch separation and C is the decompression force (less than or equal to zero). The area under the curve [AUC] ABD gives the gross energy, whilst that under curve [AUC] CBD corresponds to the decompression energy or elastic energy.

The net compaction energy or plastic energy (E_c) was determined as

$$E_c = ([\text{AUC}]ABD) - ([\text{AUC}]CBD)$$

3. Results and discussion

The relationship between moisture content and reduction of ejection force of ibuprofen compacts at different speeds of compression to 10 kN is illustrated in Fig. 2. At all compression speeds,

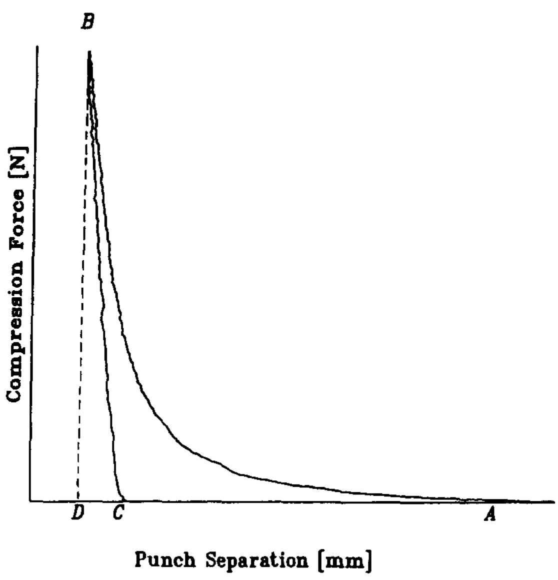

Fig. 1. Schematic diagram of force-displacement plot in the energy analysis.

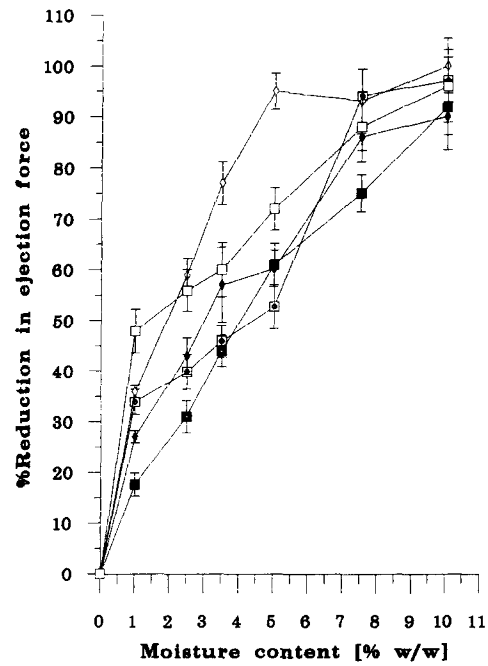

Fig. 2. Effect of moisture content on percent reduction of ejection force at varying speeds (maximum force, 10 kN): (⊡) 15 mm/s, (■) 25 mm/s, (◇) 66 mm/s, (◆) 140 mm/s, (□) 240 mm/s. Maximum standard deviation, ±7.89.

an increase in moisture content resulted in a marked reduction in the ejection force of ibuprofen compacts (Fig. 2). This indicates that the absorbed water film decreases the particle surface energy and decreases the adhesion of the tablet to the die wall. This would appear to be a simple water lubrication effect In addition, the expressed water film on the die wall during compaction functioned as a low viscosity lubricant. The increase in lubrication was indicated by a decrease in the ejection forces.

The effect of moisture content and compression speed on the plastic energy is illustrated in Fig. 3. Increasing moisture content up to 1–2.5% w/w, generally increased plastic energy, whilst beyond this point plastic energy significantly decreased. The initial increase in plastic energy of ibuprofen tablets with increasing moisture content is believed to be due to an increase in particle-particle interactions. One-way analysis of variance at varying moisture content showed that the moisture has significant effect ($p < 0.05$) on the increase of plastic energy when the moisture content increased from 0 to 2.5% w/w. This statistical test also showed that moisture has a significant effect ($p < 0.01$) on the decrease of plastic energy at higher moisture contents (3.5 up to 10% w/w).

Ragnarsson and Sjogren (1985) showed that a decrease in net work appears to be due solely to a reduction in particle interaction, i.e., friction and bonding. The decrease in plastic energy as moisture content increases beyond 1–2.5% w/w could therefore be due to the water beginning to form multilayer adsorption on the surface of the particles thereby acting as a lubricant and thus reducing the frictional forces responsible for attraction between particles.

The plastic energy was found to increase with compression speed (Fig. 3). With increasing speed of compaction, more compaction energy appeared to be required for elastic deformation, fragmentation of particles and formation of bonds (Garr and Rubinstein, 1990, 1992b). There was a good correlation between the natural logarithm of net energy (compaction energy) and natural logarithm of compression speed (Fig. 4 and Table 1). There was also a good correlation between the natural logarithm of compression speed and the natural logarithm of gross energy (Fig. 5 and Table 1). They can be described by the equations:

$$\ln E_c = A_1 + K_1 \ln S \quad (1)$$

$$\ln E_g = A_2 + K_2 \ln S \quad (2)$$

where E_c and E_g denote the compaction energy (J) and gross energy (J) respectively, S is the compression speed (mm/s), A_1 and A_2 represent the intercept and K_1 and K_2 are the slope of the lines. There is a possibility that part of the

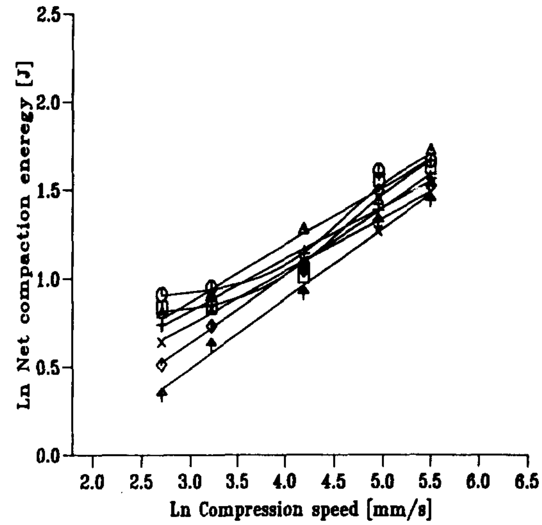

Fig. 4. Relationship between net compaction energy and compression speed of ibuprofen at varying moisture contents (compression force, 10 kN): (□) 0%, (○) 1%, (△) 2.5%, (+) 3.5%, (×) 5%, (◇) 7.5%, (♁) 10% w/w. C.V. values were less than 8.7% for all the samples.

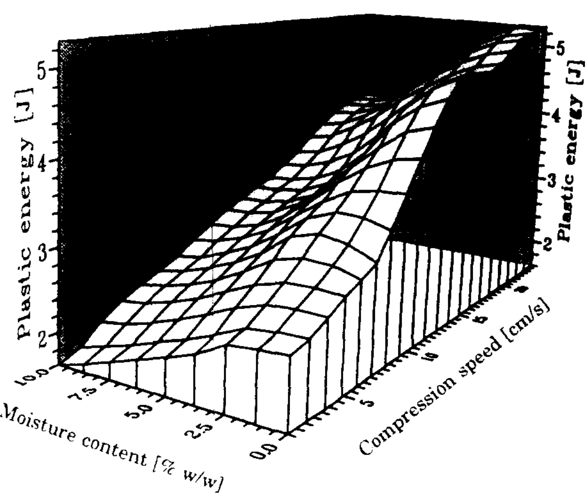

Fig. 3. Relationship between moisture content, compression speed and plastic energy for ibuprofen (compression force, 10 kN).

Table 1
Correlation coefficient between the natural logarithm of compression speed and (a) natural logarithm of gross energy (GE), (b) natural logarithm of net compaction energy (NCE) of ibuprofen at various moisture content (compaction force, 10 kN)

Moisture content (%)	Correlation coefficient	
	(a) GE	(b) NCE
0.0	0.999	0.956
1.0	0.990	0.950
2.5	0.996	0.993
3.5	0.999	0.999
5.0	0.994	0.994
7.5	0.990	0.998
10.0	0.959	0.994

net energy might be utilised in particle rearrangement, die-wall friction and increased inter-particulate friction that may occur at high compression speeds. Eq. 1 and 2 hold for ibuprofen and it would be interesting to determine their applicability to other powders that deform primarily by a plastic deformation mechanism.

The effect of moisture content and compression speed on the elastic energy is shown in Fig. 6. With increasing moisture content up to 2.5% w/w, elastic energy generally decreased, whereas at higher moisture contents elastic energy increased. The initial decreased in elastic energy of ibuprofen compacts with increasing moisture content is believed to be due to the formation of moisture film around the particles. This tightly bound water can be regarded as part of the surface molecular structure of the particles, which facilitate the formation of interparticle hydrogen bonding and therefore increases the Van der Waals' forces, smoothing out the surface microirregularities and reducing the interparticle separation. Therefore this moisture film reduced elastic energy, by minimising tablet expansion in the die. The presence of an excessive amount of moisture increased the elastic energy, by increasing the distance between particles so reducing particle-particle interactions.

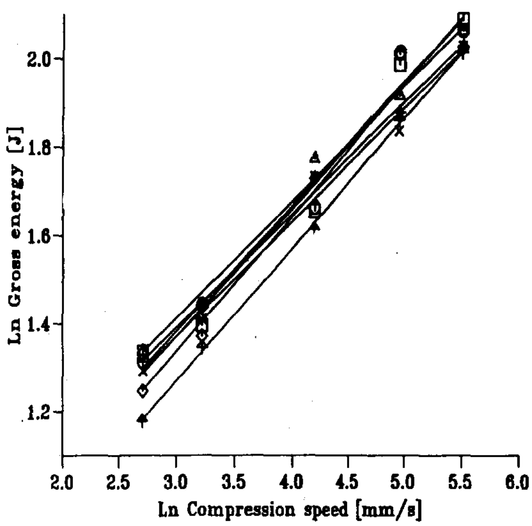

Fig. 5. Relationship between gross energy and compression speed of ibuprofen at varying moisture contents (compression force, 10 kN): (□) 0%, (○) 1%, (△) 2.5%, (+) 3.5%, (×) 5%, (◇) 7.5%, (⟡) 10% w/w. C.V. values were less than 8.7% for all the samples.

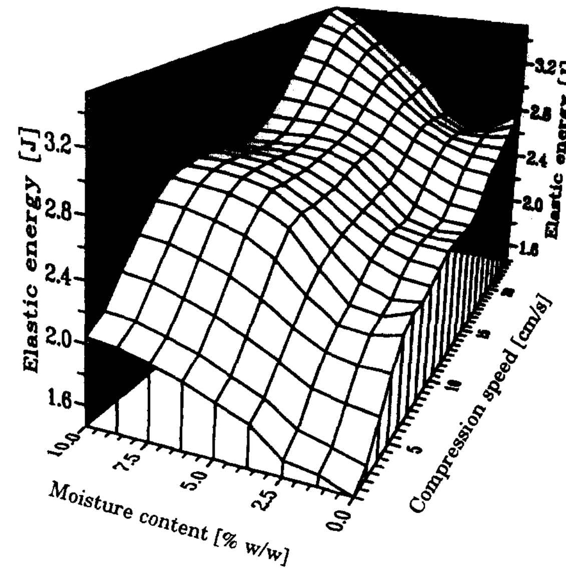

Fig. 6. Relationship between moisture content, compression speed and elastic energy for ibuprofen (compression force, 10 kN).

Increase in elastic energy can thus be explained as a result of the formation of multilayers of water at the particle surfaces (Fig. 6). One-way analysis of variance at varying moisture content showed that the moisture has significant effect ($p < 0.05$) on the decrease of elastic energy when the moisture content increased from 0 to 2.5% w/w. This statistical test also showed that moisture has significant effect ($p < 0.01$) on the increase of elastic energy at higher moisture contents (3.5 up to 10% w/w).

Increasing compression speed, increased elastic energy (Fig. 6), due to the reduction of time available for particle bonding. As the dwell time became shorter the stress relaxation will be correspondingly reduced and less particle-particle bonds will be formed.

A direct correlation between plastic energy and tablet crushing strength is shown in Fig. 7 at varying compression speeds.

A correspondingly reverse correlation between elastic energy and crushing strength of ibuprofen tablet at varying compression speeds is shown in Fig. 8. This shows that with an increase of elastic

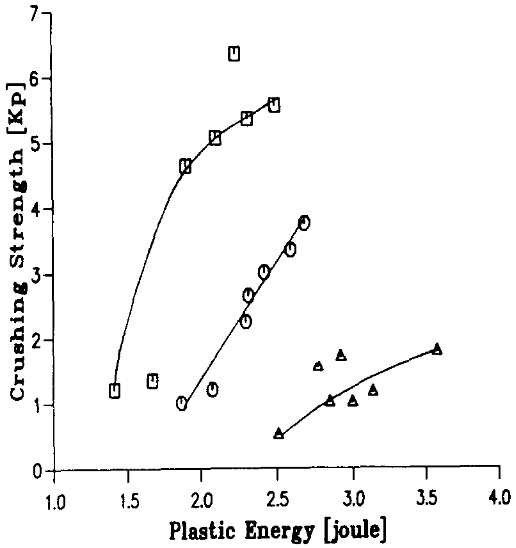

Fig. 7. Correlation between compact crushing strength and plastic energy at varying compression speeds (maximum force, 10 kN) of ibuprofen tablets: (□) 15 mm/s, (○) 25 mm/s, (△) 66 mm/s. C.V. values were less than 14.6 and 8.4% for crushing strength and plastic energy, respectively.

energy, crushing strength of ibuprofen compacts correspondingly decrease. Elastic energy is not used for bonding, but is stored as deformation

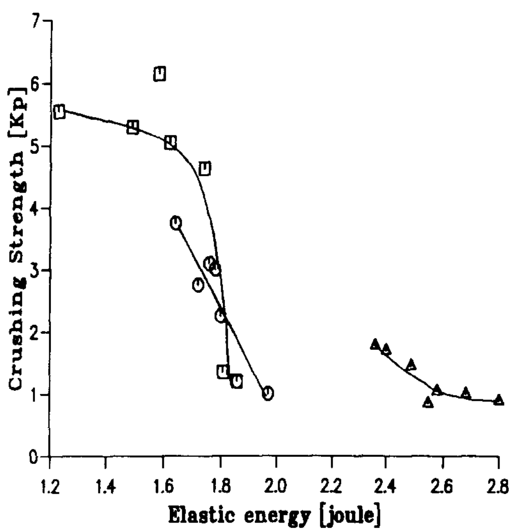

Fig. 8. Correlation between compact crushing strength and elastic energy at varying compression speeds (maximum force, 10 kN) of ibuprofen tablets: (□) 15 mm/s, (○) 25 mm/s, (△) 66 mm/s. C.V. values were less than 14.6 and 5.6% for crushing strength and plastic energy, respectively.

energy under stress. The release of this stored energy at the end of compression cycle allows the distorted particles to return to their original shape and so rupture weak particle-particle bonds (Yu et al., 1988), so decreasing crushing strength. In conclusion, the results suggested that the energies involved during compaction and particle interaction are significantly affected by moisture content and compression speed. It was found that the moisture can reduce the force required to eject tablets.

References

Ahlneck, C. and Alderborn, G., Moisture adsorption and tabletting: I. Effect on volume reduction properties and tablet strength for some crystalline materials. *Int. J. Pharm.*, 54 (1989) 131–141.

Bateman, S., The effect of compression speed on the properties of compacts. Ph.D Thesis, School of Pharmacy, Liverpool John Moores University (1988) pp. 28–120.

Bateman, S., Rubinstein, M.H., Rowe, R.C., Roberts, R.J., Drew, P. and Ho, A.Y.K., A comparative investigation of compression simulators. *Int. J. Pharm.*, 49 (1989) 209–212.

Coelho, M.C. and Harnby, N., Moisture bonding in powders. *Powder Technol.*, 20 (1978) 201–205.

De Blaey, C.J. and Polderman, J., Compression of pharmaceutical: I. The quantitative interpretation of force displacement curves. *Pharm. Weekbl.*, 105 (1970) 241–250.

De Blaey, C.J. and Polderman, J., II. Registration and determination of force-displacement curves, using a small digital computer. *Pharm. Weekbl.*, 106 (1971) 57–65.

Garr, J.S.M. and Rubinstein, M.H., Consolidation and compaction characteristics of a three-component particulate system. *Int. J. Pharm.*, 82 (1992b) 71–77.

Garr, J.S.M. and Rubinstein, M.H., Direct compression characteristics of xylitol. *Int. J. Pharm.*, 64 (1990) 223–226.

Garr, J.S.M. and Rubinstein, M.H., The influence of moisture on consolidation and compaction properties of paracetamol. *Int. J. Pharm.*, 81 (1992a) 187–192.

Kristensen, H.G., Holm, P. and Schaefer, T., Mechanical properties of most agglomerates in relation to granulation mechanisms. Part I. Deformability of moist densified agglomerates. *Powder Technol.*, 44 (1985) 227–237.

Lordi, N. and Shiromani, P., Use of sorption isotherms to study the effect of moisture on hardness of aged compacts. *Drug Dev. Ind. Pharm.*, 9 (1983) 1399–1416.

Ragnarsson, G. and Sjogren, J., Force displacement measurement in tableting. *J. Pharm. Pharmacol.*, 37 (1985) 145–150.

Ragnarsson, G. and Sjogren, J., Work of friction and net work during compaction. J. Pharm. Pharmacol., 35 (1983) 201–204.

Turner, G.A. and Balasubramanian, M., Investigations of the contributions to the tensile strength of weak particulate masses. *Powder Technol.*, 10 (1974) 121–127.

Yu, H.C.M., Rubinstein, M.H., Jackson, I.M. and Elsabbagh, H.M., Multiple compression and plasto-elastic behaviour of paracetamol and microcrystalline cellulose mixtures. *J. Pharm. Pharmacol.*, 40 (1988) 669–673.

Zografi, G. and Kontny, M.J., The interactions of water with cellulose- and starch-derived pharmaceutical excipients, *Pharm. Res.*, 3 (1986) 187–194.

Zografi, G., Kontny, M.J., Yang, A.Y.S. and Brenner, G.S., Surface area and water vapor sorption of microcrystalline cellulose. *Int. J. Pharm.*, 18 (1984) 99–116.