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Application of dynamic mechanical analysis (DMA) to determine the mechanical properties of pellets

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Abstract

Pellets of a wide range of mechanical properties were produced by the process of extrusion and spheronisation using various formulation factors. A range of mechanical properties from a simple fracture load to detailed load/displacement curves obtained when pellets were subjected to diametral compression test and a bed of pellets was compacted, were used to provide measure of tensile strength, deformability, linear strain, elastic modulus, yield and shear strength. Such conventional techniques resulted in irreversible damage to the structure of the pellets and were unable to establish the viscoelastic properties of the pellets. The application of the dynamic mechanical analysis (DMA), however, allowed the determination of (1) an accurate Young's modulus of elasticity, which was found to be between 8.4 and 24-fold higher than that determined from the diametral compression test, (2) the presence of a reversible elastic deformation even after the yield point in terms of storage modulus and (3) a change in the values of the phase angle, which illustrates the increase in viscoelasticity of the pellets formed with ethanol, glyceryl monostearate (GMS) or glycerol, while a decrease in viscoelasticity with the incorporation of lactose into the microcrystalline cellulose (MCC) pellets. This work further demonstrated that the only feasible technique for determining the elastic and plastic deformability of the pellets is the one which subjects the specimen to stress/relaxation cycles and can determine the dissipated energy in terms of loss modulus or phase angle, and that is DMA.

Keywords: Dynamic mechanical analysis (DMA); Extrusion and spheronisation; Mechanical properties; Pellets

1. Introduction

Conventionally pellets are filled into hard gelatin capsules. The lower production cost, higher production rate, and less sensitivity to tampering (e.g. Tyleno® and Sudafed-12) (Çelik, 1994), less risk of adherence to oesophagus during swallowing (Marvola et al., 1983), better patient compliance (Bodmeier, 1997) have made the design and development of pellets in the form of compressed tablets increasingly desirable. Tabletting pellets as opposed to powders will also result in reduction of dust (Conine and Hadley, 1970). It may also provide an opportunity to understand the compaction process by examining the change in size, shape and density of the pellets after their compaction and retrieval of individual pellets from disintegration tubes (Aulton et al., 1994) or from the highly lubricated compacts, which provides a reduction in the coherence of the pellets (Johansson and Alderborn, 1996).

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Tablets formed from compacted pellets need to have an optimum strength to withstand the mechanical impacts encountered during their production, packaging, shipping and dispensing. Thus, a comprehensive knowledge of how the pellets behave during tabletting, as well as how the material and/or process related parameters affect the performance of that formulation as a drug delivery system is essential. Despite the significant amount of work that has been performed in the field of tabletting of agglomerates, the actual process of compression of pharmaceutical agglomerates is still not fully understood (Çelik, 1994). Not only a conceptually oriented view of the compaction process but an in-depth understanding of the mechanical properties of the individual agglomerates is needed in order to predict more accurately the tabletting behaviour and its optimisation.

A range of properties from a simple fracture load to detailed load/displacement curves have been used to characterise the mechanical properties of agglomerates in terms of tensile strength (Shipway and Hutchings, 1993), resistance to deformability (Shotton and Edwards, 1974; Wikberg and Alderborn, 1992), shrinkage or linear strain (Kuno and Okada, 1982; Dyer et al., 1994), and elastic modulus (Dyer et al., 1994). Moreover, from compaction of a bed of agglomerates, the yield strength can be determined from the inverse of the Heckel Plot (Heckel, 1961a, b). A shear strength can also be determined from a relation between natural logarithm of compaction pressure and natural logarithm of the strain of the agglomerate-bed as suggested by Adams et al. (1994). All these techniques result in irreversible damage to the structure of the agglomerates and their compacts. Consequently, limited information can be learned about the viscoelastic properties of the specimen.

Rippie and Danielson (1981) and Danielson et al. (1983) demonstrated the presence of viscoelasticity in some pharmaceutical powders by measuring the stress-relaxation phenomena during the unloading and post-compression periods in the die of a rotary tablet press. These authors postulated viscoelastic parameters that can provide insight into kinetically controlled changes in structure. A powerful tool available for the study of the viscoelastic properties of materials is dynamic mechanical analysis (DMA). In a dynamic mechanical test, the sample stiffness and energy loss are measured. The sample stiffness will depend on its modulus of elasticity, and the modulus measured itself will depend upon the choice of geometry and mode of strain, i.e., Young's modulus applies to tension and compression, shear modulus to torsion. For materials that exhibit time-independent deformation, for example, ceramics at room temperature, any measurement of strain will lead to a constant value of the modulus. However, for materials that exhibit time dependent deformation, such as polymers, the quoted modulus must include a time to be valid. DMA testing offers here a powerful advantage by measuring the time dependent loss or storage of energy simultaneously.

The aim of this work was to determine the mechanical properties of pellets, which had been designed to change their properties by using different formulations, by the application of conventional techniques as well as a DMA and to examine the advantages of the DMA by comparing it with the different commonly employed techniques.

2. Materials and methods

2.1. Materials

The microcrystalline cellulose (MCC) used was Avicel PH-101, batch no. CA01148 (FMC International, Little Island, Cork, Ireland) and had a mean volume particle diameter of $54.80 \pm 0.54\,\mu m$ as measured by Malvern master sizer (Malvern, Worcester, UK). It was used as received and incorporated in all the formulations studied as pelletization enhancer. The lactose used was SorboLac® 400 having a mean volume particle diameter of $16.80 \pm 0.32\,\mu m$, batch no. 022-000405 (Meggle GmbH, Wasserburg, Germany). The glyceryl monostearate (GMS) used was IMWITOR® 900 Powder, batch no. 608-233 (CONDIA Chemie GmbH, Witten, Germany). The GMS was sieved and a particle size smaller than $125\,\mu m$ was used. The model drug was paracetamol fine crystals (90–125 μm BS sieve fraction), batch no. AFPJ043 (Knoll AG, Ludwigshafen, Germany). Three binding liquids were used, freshly purified water prepared by reverse osmosis (USF-Elga, Elga Ltd., High Wycombe, UK), ethanol (BDH GPR, Merck Ltd., Poole, UK), and glycerol, a laboratory grade with batch no. K281 19660 035 (BDH, Merck Ltd., Poole, UK).

Table 1
The proportion by weight of each constituents in the wet mass of the five pellet formulations

Formula	Constituents in the wet mass						
	MCC	Paracetamol	Lactose	GMS	Water	Ethanol	Glycerol
MCC	9	1	0	0	9	0	0
Lactose	9	2	9	0	10	0	0
GMS	9	2	0	9	10	0	0
Ethanol	9	1	0	0	4	4	0
Glycerol	18	2	0	0	9	0	9

2.2. Methods

2.2.1. Production of pellets

Based on the formulations given (Table 1), first the powders were weighed on a laboratory balance (SAUTER RC 1631, August Sauter GmbH, Ebingen, Switzerland) and blended in a planetary mixer (Model A200, Hobart Ltd., London, UK) for 10 min. The speed of the impeller was at the lowest rate to reduce its effect on the surface properties of the powders. The liquid binders were mixed together previously (if more than one liquid was included in a formulation) and were added into the mixed powder using a syringe. The rate of addition of liquid was approximately 50 ml/min. The mixing process was continued for further 15 min. The sides of the bowl and the stirrer were scraped every 5 min to detach the material adhering and to ensure a homogenous mixture. The wet mass was placed in a sealed container until it was extruded.

The wet mass was extruded using a ram extruder mounted in a mechanical press (Lloyd Instruments, MX50, Warsash, Southampton, UK), which was fitted with a 50 kN load cell. About 100 g of the wet mass was manually packed into the stainless steel barrel of 2.54 cm internal diameter and approximately 20 cm long fitted with a centrally mounted die of 1.0 mm diameter and 5.0 mm length, by inserting a stainless steel piston. The cross-head positioned above the piston-barrel-die assembly was driven down at a constant speed, 200 mm/min, to extrude the wet mass. The extrudate was collected in a plastic bag before it was spheronized. The force acting on the material during extrusion was recorded as a function of time, and a force–time profile was produced by an attached computer. The average of about 250 points in the steady state flow stage (Harrison, 1982) of the force–time curve was calculated and recorded as an average extrusion force of the run. The mean of at least 10 runs was used to describe the mean steady state extrusion force of a formulation. About 250 g of extrudate, at a time, was spheronized on a 22.5 cm diameter spheronizer (G. B. Caleva, Sturminster Newton, Dorset, UK), fitted with a parallel grooved plate, for about 15 min at a speed of 1000 rpm. All pellets were dried in a laboratory fluid bed drier (Laboratory fluid bed dryer Model No. FBD/L70, PRL Engineering, Mostyn, Flintshire, UK). About 200 g of the pellets were dried at 60 °C with the exception of 40 °C for those GMS containing formulations. This technique was efficient to dry the pellets in 30 min and the moisture content was found to be less than 5% (w/w) as determined by thermogravimetric analysis (TGA) (HI-RES TGA 2950, TA Instruments, Leatherhead, Surrey, UK). Glycerol was the only liquid binder retained in the pellets after drying as it has a higher boiling point than the drying temperature.

2.2.2. Size and shape of pellets

Pellets of 1.0–1.18 mm size fraction were separated using a set of sieves, BS sieves (Endecotts Ltd., London). In determining the two-dimensional shape factor, e_R (Podczeck and Newton, 1994) of the pellets, one hundred pellets of each batch were placed on black slides and analysed with a Seescan image analyzer (Sonata 512, Seescan, Cambridge, UK) connected to a black and a white camera (CCD-4 miniature video camera module, Rengo, Toyohashi, Japan) and zoom lens (18-108/2.5 Olympus, Hamburg, Germany). A top cold light source (Type FLQ 85E; Olympus Co. Europe) was used to reduce the influence of shadow on the image processing, as has been described by Podczeck and Newton (1995). The two-dimensional shape factor, $e_{R,}$ was calculated in

accordance with the method described by Podczeck and Newton (1994). The illumination technique, position of the light source, minimum pixel resolution, and number of pellets measured (Podczeck et al., 1999) were optimised for the size range of pellets used in this experiment. For comparison, the results of aspect ratio, circularity, and projection sphericity were also measured.

2.2.3. Density and porosity of pellets

The apparent pellet density (Ph. Eur. 2.9.23, BP. Appendix XVII K) was determined by using a helium pycnometer (Multi-Pycnometer, Quantachrome Corporation, UK). The technique employs Archimedes principle of fluid displacement to determine the volume. The displaced fluid was helium gas, which could penetrate the finest pores, one Angstrom (10^{-10} m), to ensure maximum accuracy. The apparent density was determined by measuring the pressure difference when a known quantity of helium under pressure was allowed to flow from a precisely known reference volume into a sample cell containing the pellets. This was performed after the system was purged with helium to remove the adsorbed gases from the pellets. By applying the gas-law and standard calibration using steel balls, the reference volume (V_R) and the total volume of the system (V_c) were determined. The apparent pellet density was then determined as a ratio of the mass of the pellets to the apparent volume of the pellets determined from the following equation.

$$V_p = V_c - V_R \left[\left(\frac{P_1}{P_2} \right) - 1 \right]$$

where V_p is the apparent volume of the pellets, V_c is the total volume of the system; P_1 and P_2 are pressures of the definite amount of gas in a reference volume and in sample cell, respectively. Three experiments were undertaken for each batch of pellets, and their average value was recorded as the apparent density of the pellets. In such experiment, the open pores are excluded form the apparent volume of the pellets as they are accessible to the helium gas. Thus, the porosity calculated is that of closed pores. The same technique was used to determine the density of pellets coated with 5% weight gain of ethyl cellulose as described by Bashaiwoldu (2002). The film closed the open pores and provided the opportunity to study the internal structure of the pellets by comparing the porosity values obtained before and after coating. The difference of these porosities is the volume of the open pores, which was accessible by helium gas before coating.

2.2.4. Mechanical properties of pellets

The mechanical strength of 30 pellets from each batch was determined as the crushing load needed to break the pellets using a CT-5 (Engineering Systems, Nottingham, UK). The speed of the upper mobile platen fitted with a 5 kN load cell was set at 1 mm/min. For brittle pellets, the platen returned back automatically when a significant drop in the load was observed. For ductile pellets, however, it was necessary to identify the reduction in the load observed on the force/time graph obtained with a chart recorder (Servogor-120, J. M. Instruments, Kent, UK) attached to the CT-5. Compression was then stopped and the first peak was recorded as a breaking load. The surface tensile strength was derived from the crushing force and pellet diameter using the equation suggested by Shipway and Hutchings (1993). The Weibull-modulus, m, which is a measure of the variability of the failure properties of a pellet batch and the Weibull-constant, X_0, a characteristic strength value of the pellets were analysed by using the numerical methodology described by Erck (1994) and used by Salako et al. (1998). The shear strength of the pellets was also determined according to the procedure provided by Adams et al. (1994). This involves the compaction of a bed of pellets (750 mg and 140 mm in height) at a rate of 0.5 cm/min using the Universal Testing Instrument (Instron Ltd. Model TT, High Wycombe, UK) equipped with flat-faced punches having a die of 12.0 mm diameter. From the linear portion of the curve produced by the natural logarithm of pressure as a function of natural logarithm of strain, between 5 and 10 points, which would make the R^2 value of the linear regression about 0.99 were chosen and used to determine the shear strength using the equation of Adams et al. (1994). The average of five values has been considered as a mean shear strength of the pellets. Finally, a bed of 750 mg pellets was compressed at a rate of 0.5 cm/min using the Universal Testing Instrument (Instron Ltd. Model TT, High Wycombe, UK) equipped with flat-faced punches having a die of 12.0 mm diameter, from which the yield strength was determined as an

inverse of the slope of the linear portion of the Heckel plot.

During the diametral compression of the pellets, an attached plotter (Servogor-120, J.M. Instruments., Kent, UK) recorded the load/time profile (kg/min). By determining the proportion of the horizontal distance of the plotter to that of the platen displacement, and converting the load (kg) to force (N), a force/displacement profile was produced. Three different measurements were made from this curve, namely: (i) The inverse of the slope of the force/displacement curve, from the initial point where the platen started to exert pressure on the pellet up to the maximum load at which the pellets failed in tension, was determined. The average of 30 samples from each batch was taken as the resistance to deformability (deformability) of the pellets. (ii) From the unidirectional decrease in the dimension of the pellet along the direction of the compressing force, linear strain or "shrinkage" was also determined as a ratio of a decrease in height of the pellets before they broke to their original height. (iii) The 'elastic modulus' was determined as a ratio of the pressure to the linear strain as described by Dyer et al. (1994).

2.2.5. Dynamic mechanical analysis

Dynamic mechanical testers apply a small sinusoidal stress or strain to a sample and measure the resulting strain or stress response. Due to the time-dependent properties of viscoelastic materials the resultant response is out-of-phase with the applied stimulus. The observed complex modulus, G^{**}, is defined as the instantaneous ratio of stress/strain (σ_0/γ_0).

$$G^{**} = \left(\frac{\sigma_0}{\gamma_0}\right)\cos\delta + \mathrm{i}\left(\frac{\sigma_0}{\gamma_0}\right)\sin\delta$$

To understand the deformation mechanics occurring in the material this is resolved into an in-phase or elastic response, being recoverable stored energy ($G' = (\sigma_0/\gamma_0)\cos\delta$) and out-of-phase or imaginary or viscous response, this being proportional to the irrecoverable or dissipated energy ($G'' = (\sigma_0/\gamma_0)\sin\delta$). The angle, δ, is the measured phase lag between the applied stimulus and the response. $\tan\delta$ is given by the ratio of loss (G'') to storage (G') modulus and is proportional to the ratio of energy dissipated/energy stored ($\tan\delta = G''/G'$). This is called the loss tangent or damping factor. Radebaugh and Simonelli (1983) and Jones (1999) have presented the mathematical description of the dynamic experiment under strains within a sample's range of linear viscoelasticity.

DMA was carried out using a DMA7 (Perking Elmer Corp., High Wycombe, UK) with a parallel plate geometry in conjunction with a personal computer (DELL, Optiplex Gx1). The DMA7 was attached to the computer via TAC7/DX thermal analysis instrument controller, which was controlled by Pyris software for windows. TAC7/DX thermal analysis controlled the analyser and digitised the analog output from the detector before sending it to the computer.

A single pellet was placed in the centre of the sample platform. A parallel plate measuring system with a plate diameter of 3 mm was employed, which comprises a central core and probe. The central core rod was suspended in a magnetic field, which ran the length of the analyser. It was driven by a linear force motor, which in turn was controlled by a computer. The probe was attached to the lower end of the core rod lowered down to hold the sample in place for testing. The environmental system included a purge gas helium-cooling device, and the furnace, which was raised and locked into place. The prescribed force generated by the force motor was applied to the sample through the core rod. Helium gas was used as purge in the furnace and an electrical intra-cooler (fridge) provided an isothermal environment. The purge gas was supplied through the top of the measuring system and provided uniform atmosphere for the sample. Stresses induced in the sample were transmitted through the upper test fixture to a detector where deflections were converted to electrical signals and relayed to a TAC7/DX thermal analysis instrument controller. The thermal analysis instrument controller then resolved the signals into elastic and viscous components of the complex modulus and the phase angle as their function. A point contact between pellet and plates was assumed for this calculation.

The samples were equilibrated at $20 \pm 0.1\,^{\circ}\mathrm{C}$ and purged with helium (20 ml/min) during testing. The results were the mean and standard deviation of 20 pellets. Static scans to obtain a value for the elastic modulus of the pellets were performed between 0 and 2600 mN at a loading rate of 200 mN/min. Dynamic scans to evaluate the viscoelastic properties of the pellets were undertaken from 0.00 to 600 mN at a rate of 25.0 mN/min employing a static force of 2000 mN,

static tension control of 120% and a frequency of 1 Hz. From the dynamic scans, a wide variety of measurements can be obtained. Here, the storage modulus and phase angle as a function of dynamic force were recorded. Podczeck and Almeida (2002) found that the storage modulus as a function of dynamic force applied changes initially rapidly in a non-linear fashion. However, at higher dynamic forces this function becomes linear. The authors observed that the slope of the linear portion of the storage modulus-dynamic force curve increased with an increase in pellet porosity, and hence, in this work the slope was determined using the Pyris software, which determines the linear portion of a function by differentiation.

2.2.6. Statistical analysis

Each set of related results was analysed by one-way analysis of variance using the formula as influence factor. Multiple paired comparisons ("post hoc tests") were performed using the Scheffé test. All calculations were performed with SPSS 10.0 (SPSS Inc., Woking, UK).

3. Results and discussion

The basic formulation in this work was a mixture of MCC:parcetamol:water (9:1:9). Fifty percent of the MCC was replaced by lactose or glyceryl monostearate (GMS) in the second and third formulations, while ethanol or glycerol was incorporated in the liquid binder in the last two formulations (Table 1). The force needed to extrude the wet mass varied based on the viscosity of the wet mass of the different formulations as well as the ability of the liquid binders to lubricate the die wall. It varied from the wet mass containing ethanol (3.8 kN), only MCC (4.0 kN), lactose (4.2 kN), GMS (4.5 kN), to glycerol (5.8 kN). The variation in extrusion force did not affect the spheronisation time and was not related to the mechanical properties of the pellets. The pellets produced were spherical in shape with approximately the same shape factor (Podczeck and Newton, 1994) and other commonly used sphericity measuring techniques (Table 2). This validates the assumption of sphericity of agglomerates in determining their mechanical properties using the conventional techniques. The pellets from the different formulations, however, had different porosity and porosity distribution between the internal and external structure of the pellets (Table 2). The rapid evaporation of ethanol produced pellets of the highest total porosity (28%) and lowest closed porosity, presumably by reducing the shrinkage of the pellet and rendering access to the internal pores. All pellets from the other formulations had less than 11% total porosity. Especially for pellets containing glycerol, the porosity was less than 5%, as the liquid filled the space between the particles in the structure of the pellets. Eighty-six percent of the total porosity of the MCC pellets was closed in the form of sealed pores, while 89% of the total porosity of the pellets containing lactose was open, hence accessible to the helium gas.

Table 3 presents the values of the mechanical properties of the pellets as determined from the force–displacement curve obtained during diametral compression test using a CT-5. This work addresses the effect of the four formulation factors (lactose,

Table 2
The structural properties of the drug pellets in the1.0–1.18 mm size fraction, produced from a wet mass of different composition

Structural properties of the pellets	Formula				
	MCC	Lactose	Ethanol	GMS	Glycerol
Shape factor (e_R)	0.56 (0.02)	0.49 (0.01)	0.53 (0.02)	0.55 (0.03)	0.49 (0.01)
Aspect ratio	1.09 (0.1)	1.11 (0.2)	1.11 (0.2)	1.08 (0.1)	1.11 (0.1)
Circularity	0.83 (0.04)	0.77 (0.03)	0.86 (0.04)	0.78 (0.04)	0.74 (0.03)
Projected sphericity	0.87 (0.04)	0.85 (0.04)	0.86 (0.04)	0.87 (0.04)	0.84 (0.04)
Apparent pellet density (g/cm^3)	1.35 (0.05)	1.48 (0.06)	1.50 (0.07)	1.21 (0.05)	1.33 (0.04)
Porosity (closed) (%)	9.32 (0.50)	1.18 (0.01)	0.64 (0.01)	0.59 (0.01)	2.91 (0.01)
Porosity (open and closed) (%)	10.8 (0.2)	10.5 (0.2)	28.1 (0.3)	8.4 (0.1)	4.8 (0.2)

The results are the mean (standard deviation) of one hundred replicates for the shape and five for the density and porosity values.

Table 3
Mechanical properties of the pellets of 1.0–1.18 mm size fraction

Some mechanical properties of pellets	Formula				
	MCC	Lactose	Ethanol	GMS	Glycerol
Tensile strength (MPa)	5.46 (0.61)	3.85 (0.78)	2.41 (0.39)	0.91 (0.25)	0.66 (0.11)
Deformability (mm/kN)	10.78 (0.90)	8.64 (0.84)	16.99 (2.89)	23.28 (5.41)	95.48 (16.74)
Linear strain (%)	12.55 (1.27)	7.08 (1.38)	8.61 (1.26)	4.38 (0.92)	13.22 (1.24)
Elastic modulus (MPa)	109.05 (8.75)	136.50 (13.62)	70.47 (10.69)	52.53 (11.21)	12.63 (2.34)
Weibull-constant	5.79	4.246	2.616	0.997	0.724
Weibull-modulus	8.207	4.73	5.946	4.82	5.69
Yield strength (1/*k*, MPa)	43.1 (2.1)	49.5 (2.4)	65.4 (3.2)	24.7 (1.2)	18.4 (0.9)
Shear strength (MPa)	1.67 (0.06)	1.68 (0.03)	0.47 (0.02)	0.43 (0.02)	0.011 (0.01)
Tensile/shear strength ratio	3.27	2.29	5.15	2.14	60

The results for shear strength and yield strength are the mean (standard deviation) of five replicates, while the results for other measurement are the mean and (standard deviation) of 30 replicates.

GMS, ethanol, and glycerol) in changing the mechanical properties of the pellets by presenting a comparative change in the properties in respect to the values of the starting formula. There was a statistically significant difference in the tensile strength between the pellets of the five formulations ($P < 0.01$). The rank of their mean tensile strength in descending order was MCC, lactose, ethanol, GMS, and glycerol. The shear strength of the pellets also followed a similar rank order. However, the values were lower than the corresponding values of the tensile strength of the pellets (Table 3). The differences in the values of MCC and lactose containing pellets as well as pellets containing GMS and those produced with ethanol were only marginal, hence were not statistically significant at ($P < 0.05$).

The Weibull-modulus (Table 3) of the pellets indicates that all the pellets could be considered as brittle for the values were less than 10. The variation between the formulations, however, indicated a greater relative brittleness of pellets containing lactose or GMS. This was supported by the lower tensile to shear strength ratio of these two formulations. The lower melting point of GMS could be the reason for the formation of a hard and brittle crust on the pellets during drying, while the relative brittleness of lactose containing MCC compacts is a well-documented observation (e.g. Newton et al., 1993).

The deformability of the pellets increased from lactose, MCC, ethanol, GMS, to glycerol containing pellets. This was in reverse order to the increase in tensile strength, shear strength and Weibull-constant values of the pellets. All the differences were statistically significant ($P < 0.01$). The order of the linear strain of the pellets increased from GMS, lactose, ethanol, MCC to glycerol (Table 3) with statistically significant difference at ($P < 0.01$). These results were in agreement with the values of yield strength (Table 3). The more deformable the pellets, the lower was the yield strength above which the pellets deformed plastically. For pellets formed with ethanol, however, the yield strength was the highest. This could be due to the effects of higher porosity, fragmentation as well as the different pressure range (where the Heckel plot was linear) selected to measure the yield strength.

The ‘elastic modulus’ of the pellets, was observed to increase from glycerol, GMS, ethanol, MCC to lactose containing pellets (Table 3). The ‘elastic modulus’ of the pellets had a similar order to that of the shear and tensile strength of the pellets, with the exception of MCC pellets, which had the greatest tensile strength. The relatively higher linear strain could have reduced the ‘elastic modulus’ of the MCC pellets compared to those containing lactose, as the ‘elastic modulus’ was calculated as a ratio of the compressing pressure to the linear strain as suggested by (Dyer et al., 1994). Bashaiwoldu (2002) has presented a detailed study on the effects of each of these formulation factors on mechanical properties of the pellets as a function of their proportions and various storage times.

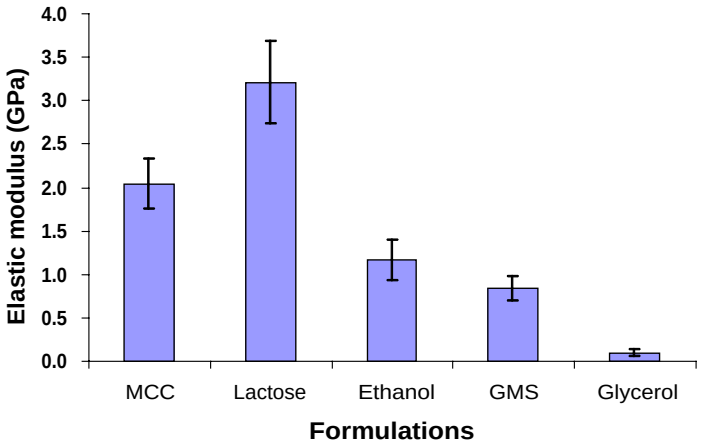

Fig. 1. The elastic modulus of the drug pellets of 1.0–1.18 mm size fraction, determined by DMA.

3.1. Dynamic mechanical analysis of drug pellets

The Young's modulus of elasticity of the pellets was calculated from the slope of the linear portion of the stress-strain curve obtained from the static scan using a DMA. Fig. 1 depicts the values of the elastic modulus of the pellets.

The value of Young's modulus of the starting formula was increased by incorporation of lactose, reduced by GMS, glycerol and inclusion of ethanol in the preparation of the pellets. All the factors had a statistically significant effect (Table 4).The results are a reflection of the rigidity of the individual ingredient in the pellets. Substitution of 50% (w/w) of the MCC by lactose, increased the elastic modulus of the pellets. Lactose, which has a Young's modulus of 24.1 GPa (Roberts et al., 1991), is more rigid than MCC, whose value is 10.3 GPa (Mashadi and Newton, 1987). GMS is a soft solid, while glycerol is a viscous liquid, and their presence reduced the stiffness of the pellets.

Table 4
ANOVA of the elastic modulus of pellets of 1.0–1.18 mm size fraction determined by DMA

No.	Formula	Elastic modulus (GPa)		Mean square	*F*	*P*
		Mean	S.D.			
1	MCC	2.044	0.29	–	–	–
2	Lactose	3.208	0.47	1353.5	87.33	<0.001
3	Ethanol	1.173	0.23	759.2	108.93	<0.001
4	GMS	0.835	0.14	1462.3	280.88	<0.001
5	Glycerol	0.106	0.04	3779.1	878.31	<0.001

The results are the mean and standard deviation of 20 replicates.

In the prediction of the elastic properties of composite materials, a generalised modulus equation known as the 'rule of mixtures' has been proposed by Radebaugh et al. (1989). A composite, which is also referred to as a filled system, is defined as materials with a continuous matrix phase and a discontinuous filler phase. The filler phase can be solid, liquid or gas. This relation is denoted by the following equation (Radebaugh et al., 1989):

$$E = E_1\phi_1 + E_2\phi_2$$

where, E is the elastic modulus of the filled system, E_1 is the elastic modulus of the pure matrix phase, E_2 is the elastic modulus of the filler phase, while N_1 and N_2 are the volume fractions of the matrix phase and the filler phase, respectively. For compacted polymeric materials where the filler is gaseous void space, N_2 is equal to the porosity and E_2N_2 is equal to zero, since E of air is zero. Hence, the elastic modulus of the composite decreases with increase in porosity. Radebaugh et al. (1989) observed a six-fold increase in elastic modulus of MCC from 0.55 to 0.88 solid fraction as a result of reduction in porosity. Similarity, the values obtained in this work illustrated the reduction of the elastic modulus by 43% for the porous MCC pellets produced with ethanol in the liquid binder, which increased the porosity by 18%.

Dyer et al. (1994) determined the 'elastic modulus' of pellets from the ratio of pressure to the linear strain

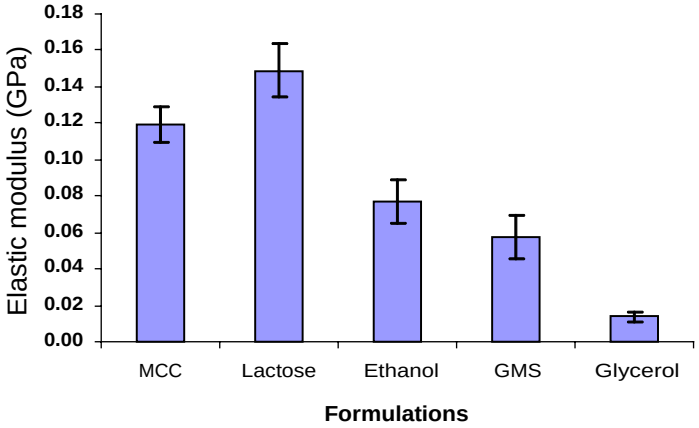

Fig. 2. The elastic modulus of pellets of 1.0–1.18 mm size fraction, determined from the force/displacement curve obtained during diametral compression of the pellets.

obtained during the diametral compression of the pellets. A similar procedure was used for pellets of all the formulations made in this work. The results obtained are presented in Fig. 2. The two Young's modulus determining techniques provided a similar rank order and comparable proportion in deviation of the factor's effect on elastic modulus. However, the absolute value of the elastic modulus determined by DMA was between 8.4–24-fold higher than that from the CT-5. The results from the static scan using a DMA is accurate, for the slope is determined from the real elastic region, less than 5% of strain in most cases, and from a nearly linear portion of the curve, in a range of about 0.5–1% of the linear strain. In the diametral compression test using CT-5, however, the slope was determined from the whole range of the strain, up to 15% in some cases, and the whole region was assumed as linear, hence the range of the strain was more than 10% in most cases. At the higher region of compression, plastic deformation of the pellets might have occurred to strain the pellets to a greater extent without significant increase in pressure, as a result the elastic modulus would have been underestimated.

From the dynamic scan, the storage modulus was initially observed to change as a function of dynamic force applied, i.e., at low dynamic force values the storage modulus reduced rapidly in a non-linear fashion. At higher dynamic forces, this function became linear. The onset of the linear portion, i.e., the dynamic force for this to occur was determined. In addition, the storage modulus at the maximum dynamic force (600 mN) and the slope of the linear portion of the function were obtained. Moreover, the phase angle as function of the dynamic force employed increased steadily with increasing dynamic force (Fig. 3). The phase angle at the onset of the linear portion of the storage modulus-dynamic force curve was read after smoothing of the phase angle curve using standard algorithms and a window size of 300 points. Furthermore, the phase angle at the maximum dynamic force (600 mN) was determined in the same way, the difference between the two measured phase angles was also calculated (Figs. 4–9).

The effect of the factors on the storage modulus measured at the fixed dynamic force (Fig. 4) was proportional to that of elastic modulus determined by the static scan. This shows that in both cases the measured parameter was the reversible elastic deformation. The values of elastic modulus were, however, about 50-fold higher than those of storage modulus, indicating the variation in the force range at which these values were determined. Moreover, the storage modulus indicated the presence of a reversible force, although small, even after the pellets had deformed plastically. The storage modulus-dynamic force curve, started to be linear at different dynamic forces for pellets of different formulations. The difference from that of the starting formula was only significant ($P < 0.01$) in the pellets containing glycerol or those produced with ethanol (Table 5).

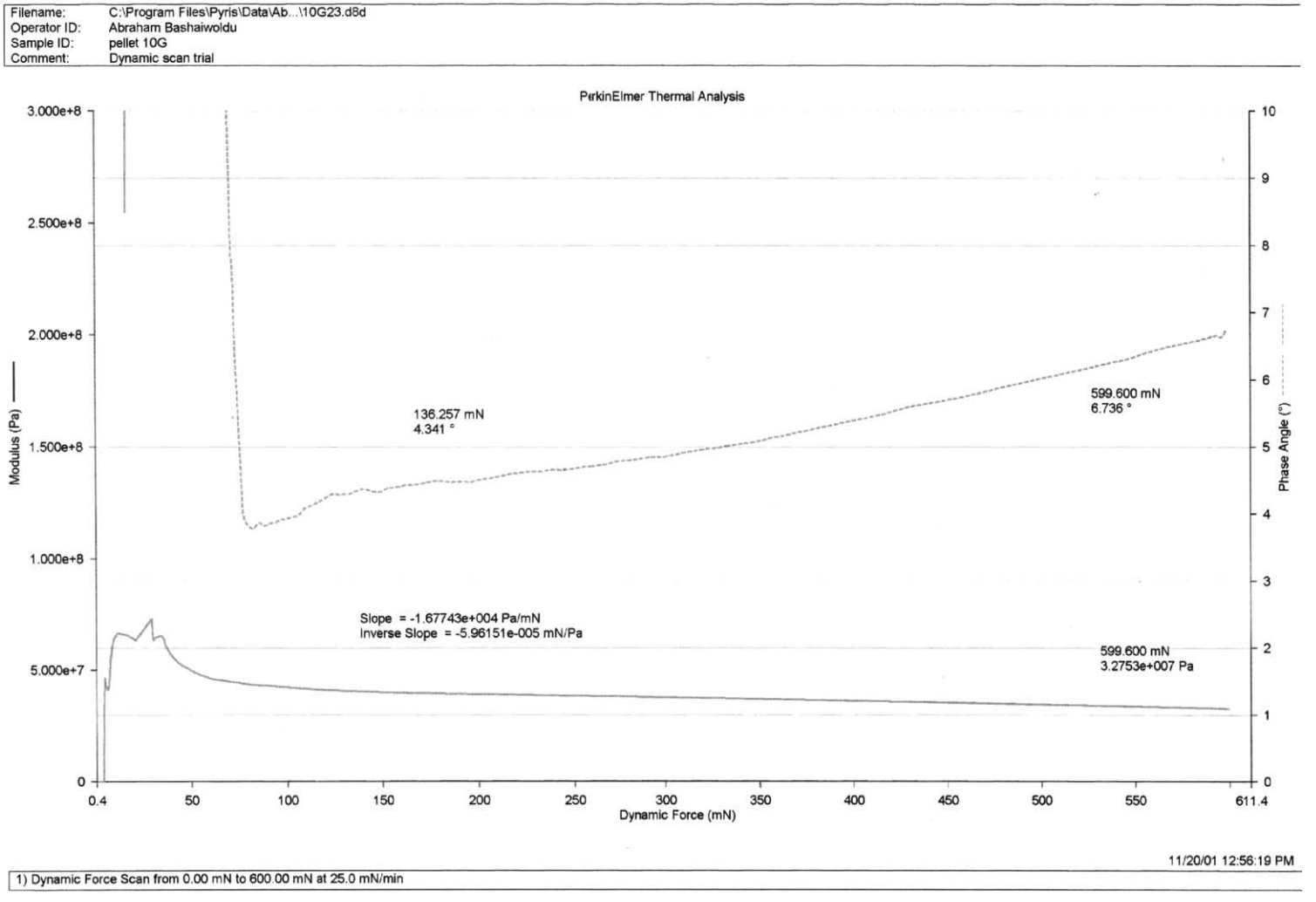

Fig. 3. A typical dynamic scan of a pellet containing microcrystalline cellulose:glyceryl monostreate:paracetamol (9:9:2).

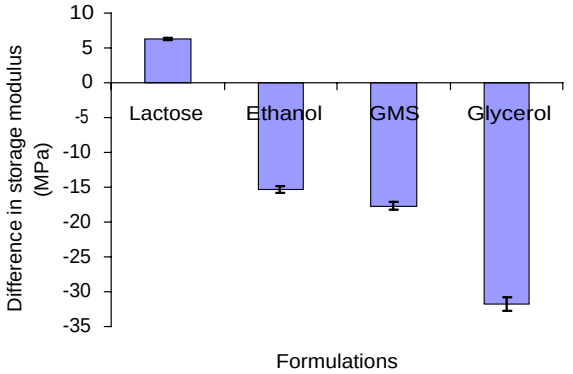

Fig. 4. The effect of each formulation factor on changing the storage modulus of the MCC pellets of 1.0–1.18 mm size fraction determined at dynamic force of 600 mN.

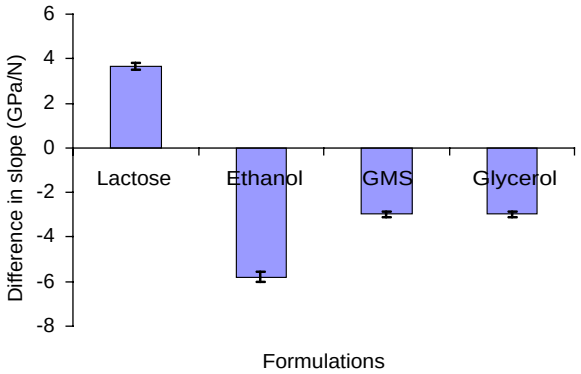

Fig. 6. The effect of each formulation factor on changing the slope of the linear portion of the storage modulus-dynamic force curve of MCC pellet of 1.0–1.18 mm size fraction.

Lactose pellets needed a relatively higher dynamic force, while all the other pellets needed a lower dynamic force to produce a linear storage modulus-dynamic force curve, when compared to that of MCC pellets (Fig. 5). This seems to be related to the yield strength of the pellets, as determined from the inverse of the slope of Heckel plot (Table 3). This, in conjunction with Young's modulus and storage modulus illustrates the stiffness of lactose containing pellets. The storage modulus of all the pellets increased in a linear manner with the increase of the dynamic force, but to a different extent. The slope of the curve for lactose containing pellets was higher than that of MCC pellets indicating a rapid decrease in the reversible energy, while the other pellets had a lower slope than that for MCC pellets (Fig. 6) illustrating viscous nature of the materials even at lower dynamic force. Nevertheless, the effect of lactose was statistically insignificant, while that of GMS and glycerol was significant at ($P < 0.05$) and pellets produced with ethanol at ($P < 0.01$).

The phase angle results from the time necessary for the molecular rearrangements and is associated with relaxation phenomena. It indicates the dissipation of energy as a result of permanent plastic deformation of the material Radebaugh and Simonelli (1983) and Jones (1999). In this work, the phase angle was determined at the start of the linear portion of the storage

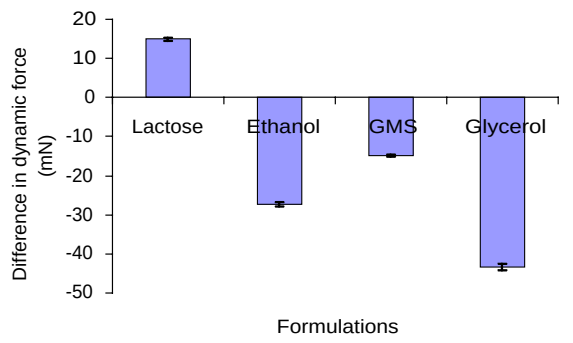

Fig. 5. The effect of each formulation factor on changing the dynamic forces of the MCC pellets of 1.0–1.18 mm size fraction determined at the beginning of the linear portion of the storage modulus-dynamic force curve.

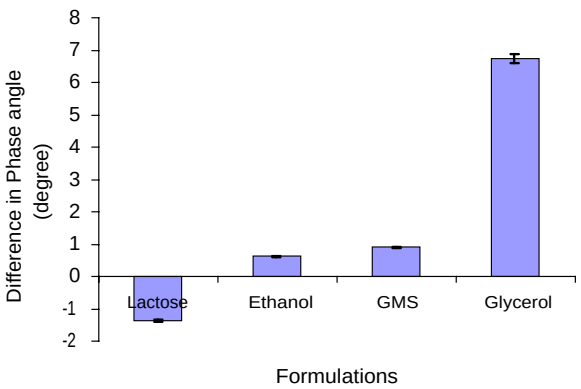

Fig. 7. The effect of each formulation factor on changing the phase angle, at the beginning of the linear portion of the storage modulus-dynamic force curve, of MCC pellets of 1.0–1.18 mm size fraction.

Table 5
ANOVA of the dynamic force at the beginning of a linear storage modulus-dynamic force curve for pellet, 1.0–1.18 mm size fraction from various formulations

Formula	Dynamic force (mN)		Degree of freedom	Mean square	*F*	*P*
	Mean	S.D.				
MCC	157.49	27.75	1	–	–	–
Lactose	172.37	23.97	1	2216	3.3	0.077
Ethanol	130.28	19.45	1	7406	12.9	0.001
GMS	142.55	18.31	1	2233	4.45	0.042
Glycerol	114.06	22.13	1	18857	29.93	<0.001

The results are the mean and standard deviations of 20 replicates.

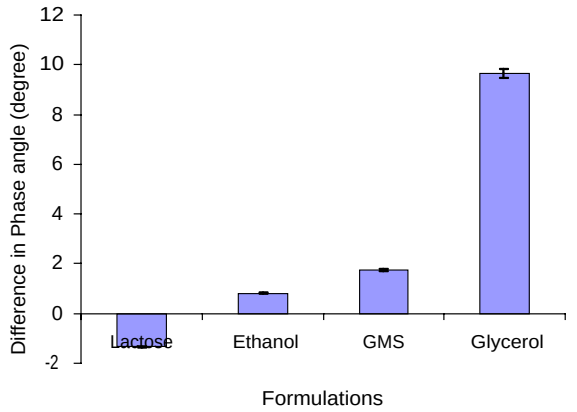

Fig. 8. The effect of each formulation factor on changing the phase angle, at dynamic force of 600 mN, of MCC pellets of 1.0–1.18 mm size fraction.

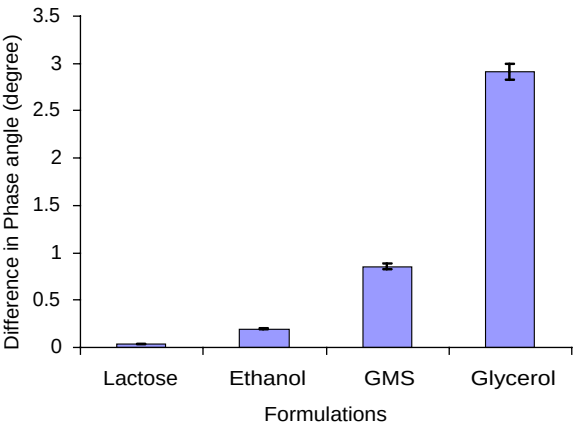

Fig. 9. The effect of each formulation factor on the increase in Phase angle at 600 mN of dynamic force from the force at the beginning of the linear portion of the storage modulus-dynamic force curve of MCC pellets of 1.0–1.18 mm size fraction.

modulus-dynamic force curve and at a fixed dynamic force (600 mN). Inclusion of lactose reduced the value of the phase angle, while the other additives increased the value when compared to MCC pellets at both measured phase angles (Figs. 7 and 8). The effect of each factor was significant in both cases. This illustrates the increase in viscous nature of the pellets with the incorporation of GMS, glycerol or increase in porosity, while decrease in viscous nature was noted in the presence of lactose. This was in agreement with the rank order of deformability of pellets determined from diametral compression (Table 3). In all cases the phase angle increased with the increase of the dynamic force, but in non-linear manner. The difference of the two phase angles taken (at 600 mN of dynamic force and at the start of the linear curve of the storage modulus-dynamic force) varied for the different formulation factors, however, it was higher in all factors than that of MCC pellets (Fig. 9). Nevertheless, the difference was insignificant with the lactose containing pellets and pellets produced with ethanol, while it was significant with those of GMS or glycerol containing pellets ($P < 0.01$). Generally, it was possible to identify the relatively greater plastic deformability of pellets containing glycerol or GMS by determining the phase angle at the same constant dynamic force or at the point where the storage modulus-dynamic force function started to relate linearly.

4. Conclusion

This work has shown that the determination of Young's modulus of elasticity of the pellets from the diametral compression tests using conventional diametral strength testing equipment was not capable

of providing accurate evaluation of the elastic portion of the deformation. This resulted in underestimated values of the actual elastic modulus when the values were compared to those determined by DMA. These two techniques provided values, which had the same rank order and comparable proportion in deviation of the factor's effect on elastic modulus. The absolute value of the elastic modulus determined by DMA was, however, about 16.6-fold higher than that from the diametral compression. The results from the static scan using a DMA is accurate, as the slope is determined from the real elastic region (<5% strain) and the stress–strain curve formed was nearly linear. In the diametral compression test using CT-5, however, the slope was determined from the whole range of the stress/stain curve. At the higher region of compression, plastic deformation of the pellets occurs to strain the pellets to a greater extent without a significant increase in pressure, as a result the elastic modulus is underestimated. The effect of the factors on the storage modulus measured at the fixed dynamic force during dynamic scan was proportional to that of elastic modulus determined by the static scan. The values of elastic modulus were, however, about 50-fold higher than that of storage modulus, indicating the variation in the force range at which these values were determined. From the dynamic scan, increase in the values of storage modulus and the decrease in the values of phase angle were obtained with the same rank order starting for pellets containing lactose, only MCC, those produced with ethanol, containing GMS to those containing glycerol. This indicates an increase in the viscoelasticity of the pellets in this order. Lactose containing pellets needed a high dynamic force to produce a linear relation between the storage modulus and dynamic force. The same pellets also had the greatest change in storage modulus per unit dynamic force. These observations may be related to the greatest yield strength and highest rigidity of the pellets produced with lactose. From these results it is possible to conclude that the plastic deformation of the pellets could only be determined from the dynamic scan using the dynamic mechanical analyser. The 'deformability' values calculated from the force/displacement curve obtained during diametral compression of the pellets do not reflect the plastic property of the pellets for they do not identify the possible structural recovery. The only feasible technique is the one, which subjects the specimen to stress/relaxation cycles and could determine the dissipated energy in terms of loss modulus or phase angle, that is DMA. For a screening purpose of materials of a considerable variation in viscoelastic property, however, the 'deformability' value from the diametral compression test could be used as brittle materials would snap after a very limited strain.

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References

Adams, M.J., Mullier, M.A., Seville, J.P.K., 1994. Agglomerate strength measurement using a uniaxial confined compression test. Powder Technol. 78, 5–13.

Aulton, M.E., Dyer, A.M., Khan, K.A., 1994. The strength and compaction of millispheres: the design of a controlled-release drug delivery system for ibuprofen in the form a tablet comprising compacted polymer-coated millispheres. Drug Dev. Ind. Pharm. 20, 3069–3104.

Bashaiwoldu, A.B., 2002. Studies on the Influence of Composition and Processing on the Mechanical Properties of Pellets and Compacted Pellets, Ph.D. Thesis, University of London, UK.

Bodmeier, R., 1997. Tableting of coated pellets. Eur. J. Pharm. Biopharm. 43, 1–8.

Çelik, M., 1994. Compaction of multiparticulate oral dosage forms. In: Multiparticulate Oral Drug Delivery. 1st. ed. Ghebre-Sellassie, Marcel Dekker, New York, pp. 181–215.

Conine, J.W., Hadley, H.R., 1970. Preparation of solid pharmaceutical spheres. Drug Cosmetic Ind. 106, 38–41.

Danielson, D.W., Morehead, W.T., Rippie, E.G., 1983. Unloading and post compression viscoelastic stress versus strain behaviour of pharmaceutical solids. J. Pharm. Sci. 72, 342–345.

Dyer, A.M., Khan, K.A., Aulton, M.E., 1994. Effects of the drying method on mechanical and release properties of pellets prepared by extrusion-spheronisation. Drug Dev. Ind. Pharm. 20, 3045–3068.

Erck, R.A., 1994. Pin-pull adhesion measurements of copper film on ion-bombarded alumina. Thin Solid Films 253, 362–366.

Harrison, P. J., 1982. Extrusions of Wet Powder Masses. Ph.D. Thesis, University of London.

Heckel, W., 1961a. An analysis of powder compaction phenomena. Trans. Metal. Soc. A.I.M.E. 221, 671–675.

Heckel, W., 1961b. Density–pressure relationships in powder compaction. Trans. Metal. Soc. AIME. 221, 1001–1008.

Johansson, B., Alderborn, G., 1996. Degree of pellet deformation during compaction and its relationship to the tensile strength of tablets formed of microcrystalline cellulose pellets. Int. J. Pharm. 132, 207–220.

Jones, D.S., 1999. Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance. Int. J. Pharm. 179, 167–178.

Kuno, H., Okada, J., 1982. The compaction process and deformability of granules. Powder Technol. 33, 73–79.

Marvola, M., Rajamiemi, M., Marttila, E., Vahervuo, K., Sothmann, A., 1983. Effect of dosage form and formulation factors on the adherence of drugs to the oesophagus. J. Pharm. Sci. 72, 1034–1037.

Mashadi, A.B., Newton, J.M., 1987. Characterizing of mechanical properties of microcrystalline cellulose: a fracture mechanics approach. J. Pharm. Pharmacol. 39, 961–965.

Newton, J.M., Alderborn, G., Nystrom, C., 1993. A method of evaluating the mechanical characteristics of powders from the determination of the strength of compacts. Powder Technol. 72, 97–99.

Podczeck, F., Almeida, S.M., 2002. Determination of mechanical properties of pellets and film coated pellets using dynamic mechanical analysis (DMA). Eur. J. Pharm. Sci. 16, 209–214.

Podczeck, F., Newton, J.M., 1994. Shape factor to characterize the quality of spheroids. J. Pharm. Pharmacol. 46, 82–85.

Podczeck, F., Newton, J.M., 1995. The evaluation of a three-dimensional shape factor for the quantitative assessment of the sphericity and surface roughness of pellets. Int. J. Pharm. 124, 253–259.

Podczeck, F., Rahman, S.R., Newton, J.M., 1999. Evaluation of a standardised procedure to assess the shape of pellets using image analysis. Int. J. Pharm. 192, 123–138.

Radebaugh, G.W., Simonelli, A.P., 1983. Phenomenological viscoelasticity of heterogeneous pharmaceutical semisolids. J. Pharm. Sci. 72, 415–422.

Radebaugh, G.W., Babu, S.R., Bondi, J.N., 1989. Characterization of the viscoelastic properties of compacted pharmaceutical powders by a novel nondestructive technique. Int. J. Pharm. 57, 95–105.

Rippie, E.G., Danielson, D.W., 1981. Viscoelastic stress/strain behaviour in pharmaceutical tablets: analysis during unloading and post compression periods. J. Pharm. Sci. 70, 476–482.

Roberts, R.J., Rowe, R.C., York, P., 1991. The relationship between Young's modulus of elasticity of organic solids and their molecular structure. Powder Technol. 65, 139–146.

Salako, M., Podczeck, F., Newton, J.M., 1998. Investigations into the deformability and tensile strength of pellets. Int. J. Pharm. 168, 49–57.

Shipway, P.H., Hutchings, I.M., 1993. Attrition of brittle spheres by fracture under compression and impact loading. Powder Technol. 76, 23–30.

Shotton, E., Edwards, N.J., 1974. The effects of binding agents on granule and tablet strength. J. Pharm. Pharmacol. Suppl. 26, 107P.

Wikberg, M., Alderborn, G., 1992. Compression characteristics of granulated materials. V. Mechanical properties of individual granules, assessed by diametral compression, in granulation of different volume reduction behaviour. STP Pharm. Sci. 2, 313–319.