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Application of Dynamic Mechanical Analysis (DMA) to the determination of the mechanical properties of coated pellets

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Abstract

Pellets containing a model drug, paracetamol, and microcrystalline cellulose (MCC) were designed to vary their mechanical properties by the incorporation of lactose, glyceryl monostearate (GMS), ethanol, or glycerol, and were produced by the process of extrusion and spheronization. The pellets were coated with an aqueous dispersion of ethyl cellulose (Surelease®) to different levels of weight gain (5, 10, and 20%). The tensile strength, deformability, linear strain, elastic modulus, and shear strength of the coated and uncoated pellets were determined by conventional techniques, which are obtained from diametral compression test of individual pellets and compaction of a bed of pellets. Dynamic Mechanical Analysis (DMA) was performed on single pellets to determine the storage modulus and phase angle of the coated pellets. This work demonstrated that the coating film affected the mechanical properties of the pellets differently depending on the properties of the core pellets. Analysis of variance established a significant increase in the strength of the soft GMS- or glycerol-containing pellets with coating, while the effect of the coating material was not significant with respect to the elastic modulus, storage modulus, and phase angle of such pellets. The effects of the coating material on the elastic modulus, deformability, storage modulus, and phase angle of the rigid lactose-containing pellets were significant. The sinusoidal stress–relaxation cycle of the DMA illustrated the increase in the viscoelasticity of all the pellets after coating. Finally, the work demonstrate the advantages of DMA in determining the reversible or dissipated energy by means of storage modulus or phase angle when compared with the irreversible structural destruction of the pellets by conventional techniques.

Keywords: Coating; Dynamic Mechanical Analysis (DMA); Extrusion and spheronization; Mechanical properties; Pellets

1. Introduction

There are numerous reasons for which film coatings are applied to pellets: controlled release, taste masking, improved stability, elegance, and mechanical integrity can be mentioned as examples. Polymers used in the film coating fall into two broad groups based on either cellulosic or acrylic polymers (McGinity, 1989; Cole et al., 1995), which are commonly formulated into aqueous colloidal dispersions and organic solutions, respectively. The high cost of solvents, higher price of solvent recovery system, strict air quality controls, and potential toxicity and explosiveness are the

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main disadvantages of the organic solvent-based coating processes (Chang et al., 1987). This was resolved with the advent of aqueous polymer latexes and pseudolatexes in 1970s, which improved the lengthy processing time, higher viscosities and lower polymer content (Fukumori, 1994).

The individual polymeric particles in the dispersion have to be fused to form a continuous film for an efficient application to controlled release pharmaceutical dosage forms. The theories that describe the mechanism of film formation from such aqueous polymeric dispersions have been reviewed by Lahmann and Steuernag (1989). Moreover, the polymeric particles have to be mechanically deformable to form films under specified conditions. This is achieved at a softening temperature (Yang and Ghebre-Sellassie, 1990), which corresponds to a sharp increase in polymer chain mobility (Okhamafe and York, 1988), hence viscous flow, which eliminates the boundaries between adjacent polymer particles to complete coalescence (Porter, 1989). In addition to the possible incomplete fusion of the colloidal particles during the coating process (Chang and Rudnic, 1991), the residual internal stresses within the film coating created by shrinkage of the film upon solvent evaporation and the differences in the thermal expansions of the coating and the substrate, can produce flaws and cracks in the film coating (Rowe, 1981). Moreover, the drastic shape and density change as well as the friction and impact of the die and punch surfaces during tableting of coated pellets could compromise the integrity of the coat, hence the controlled drug release property. Thus, the mechanical properties of the polymeric film and its response to stresses of different types must be studied to determine its ability to remain intact during the lifetime of the product.

The mechanical properties of ethyl cellulose film casts were studied in terms of tensile strength (Arwidsson and Johansson, 1991; Narisawa et al., 1994), brittleness, puncture strength, and elongation (Bodmeier and Paeratakul, 1994). Recently, Lafferty et al. (2002a,b,c) have demonstrated the benefits of studying free films by the application of Dynamic Mechanical Analysis (DMA), especially where mixtures of films are involved. Moreover, Narisawa et al. (1994) performed in vitro dissolution tests of ethyl cellulose film coated theophylline beads with abrasives (polystyrene beads) that could generate mechanical destruction or induce erosion of the film by frictional force. They were able to determine the ability of the film to withstand the mechanical stresses by quantifying the rate of drug release. If pellets are to be compacted, it is important to know something of the mechanical properties of the pellets with respect to how they respond to the application of the forces during compaction.

Most studies on compaction of pellets coated with ethyl cellulose revealed damage to the coating film with a loss of the sustained release properties (e.g. Chang and Rudnic, 1991; Bansal et al., 1993; Sarisuta and Punpreuk, 1994; Maganti and Celik, 1994). Addition of different plasticizers was not enough for the film to deform and resist rupturing (Sarisuta and Punpreuk, 1994). According to Bodmeier and Paeratakul (1994), this was attributed to the very brittle and weak nature of the film, with low puncture strength and elongation (i.e. $<5\%$). Coat damage was also related to the variation in mechanical properties between the coat and the core pellets (Aulton et al., 1994) as well as the size of the pellets (Ragnarsson et al., 1987; Ragnarsson and Johansson, 1988; Bechard and Leroux, 1992). The correlation of the mechanical properties of the pellets to that of polymeric coat determined from the free film is, however, difficult. For this reason, Ghaly and Ruiz (1996) and Wang et al. (1996, 1997) incorporated the polymeric dispersion in the binding liquid and tried to study the change in the mechanical properties of their compacts. Nevertheless, it was again impossible to extrapolate the property of a film-coated pellet from the employment of the polymer dispersion as a liquid binder. Therefore, a detailed study of the mechanical properties of the core pellets versus the properties of the coated pellets seems to be an alternative approach to provide an insight into how the final coating system behaves.

The objective of this work was to determine the mechanical properties of aqueous dispersion of ethyl cellulose, Surelease®-coated pellets, produced from different formulations using conventional techniques as well as DMA. The changes induced in the mechanical properties of pellets, which have been previously reported by Bashaiwoldu et al. (2004) will now be considered when these pellets are coated to different thicknesses and to compare and contrast the various measuring techniques employed.

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 Instruments, Malvern, UK). It was used as received and incorporated in all the formulations studied as pelletization enhancer. The lactose used was SorbaLac 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 Pulver, 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 of EP quality, 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, England, UK), ethanol (BDH GPR, Merck Ltd., Poole, UK), and glycerol, a laboratory grade with batch no. K281 19660 035 (BDH, Merck Ltd.). The coating material, Surelease®, is an aqueous dispersion of ethyl cellulose-containing dibutylsebacate (plasticizer), oleic acid (stabilizer/co-plasticizer), and ammonium hydroxide solution (aqueous base). The Surelease® (Colorcon, Dartford, UK) used was taken from batch no. IN 502749.

2.2. Production and structural characterization of pellets

Based on the formulations given (Table 1) spherical pellets with more than 0.5 shape factor, e_R (Podczeck and Newton, 1994), were produced by the process of extrusion and spheronization as described by Bashaiwoldu (2002). Pellets of 1.0–1.18 mm size fraction were separated using a set of sieves, BS sieves (Endecotts Ltd., London, UK). 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) as described by Bashaiwoldu et al. (2004). 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 from 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 et al. (2004). 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 were accessible by helium gas before coating.

Pellets were coated in a fluid bed coater (Aeromatic AG Strea-1, ACM Machinery, Tadley, UK) that had an 8.5 cm diameter perforated bottom plate with a bottom spray pneumatic nozzle. Preliminary studies established that the optimum conditions, i.e. even coating without pellet agglomeration, was possible with 40 g of pellets per batch, inlet air temperature of 60 °C, outlet air temperature of 40 °C, atomized air pressure of 0.2 bar, and coating feed rate of 0.6 ml/min. The coating suspension was heated to 60 °C and was applied for 45 min for each 5% weight gain. Each batch of the pellets was coated at three levels (i.e. 5, 10, and 20% (w/w)). To assess friability, some uncoated pellets were fluidized in the coater without the spray of

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

Formula name	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

the coating material for 60 min and the loss in weight was found to be negligible. Coated pellets were cured in a hot air oven at 60 °C for 2 h.

2.3. 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 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 (Model TT, Instron Ltd., 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, the shear strength was determined according the procedure discussed by Bashaiwoldu et al. (2004) using the equation of Adams et al. (1994). The average of five values has been considered as mean shear strength of the pellets.

During the diametral compression of the pellets, an attached plotter (Servogor-120, J.M. Instruments) 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 was determined from the initial point, where the platen started to exert pressure on the pellets, up to the maximum load at which the pellets failed in tension. 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 pellets 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).

2.4. Dynamic Mechanical Analysis

Dynamic mechanical testers apply a small sinusoidal stress or strain to a sample and measure the resulting strain or stress response (Jones, 1999). Due to the time-dependent properties of viscoelastic materials the resultant response is out-of-phase with the applied stimulus (Radebaugh and Simonelli, 1983). Bashaiwoldu et al. (2004) have discussed the observed complex modulus and its resolution into the recoverable stored energy (storage modulus) and dissipated energy in the form of loss modulus or phase lag. In this work, DMA was carried out using DMA7 (Perking Elmer Corp., High Wycombe, UK) with parallel plate geometry in conjunction with a personal computer (DELL, Optiplex Gx1). The DMA7 was attached to the computer via a TAC7/DX thermal analysis instrument controller, which was controlled by the Pyris software for windows. The TAC7/DX thermal analysis controlled the analyzer and digitized the analogue output from the detector before sending it to the computer.

A single pellet was placed in the center 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 analyzer. 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 and lowered down to hold the sample in place for testing. The furnace 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 gas (20 ml/min) in the furnace and an electrical intra-cooler (fridge) provided an isothermal environment inside the furnace. 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 lower 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. 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 loading 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. Also, the slopes of the linear portion of the storage modulus–dynamic force curves were determined as described by Podczeck and Almeida (2002).

3. Results and discussion

The basic formulation in this work was a mixture of MCC:paracetamol:water (9:1:9). Fifty percent of the MCC was replaced by lactose or 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 pellets produced were spherical in shape with approximately the same (about 0.5) shape factor (Podczeck and Newton, 1994), which 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 (Bashaiwoldu et al., 2004). The pellets were coated with aqueous dispersion of ethyl cellulose, Surelease®, to weight gain of 5, 10, and 20%.

The mechanical properties of the pellets were determined from the force–displacement curve obtained during diametral compression test using a CT-5. Coating the pellets with a different weight-by-weight percentage of ethyl cellulose film affected the surface

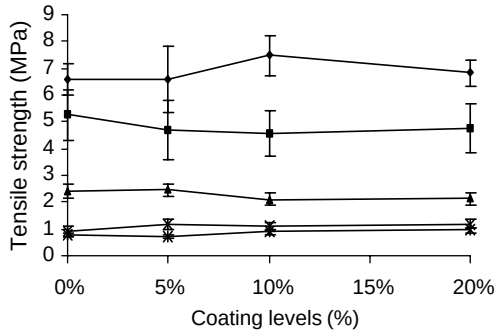

Fig. 1. The influence of coat thickness (%, w/w) on the surface tensile strength of coated pellets of 1.0–1.18 mm size fraction. The results are the mean (standard deviation) of 30 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

tensile strength of the pellets, but to different extent based on the formulations of the pellets (Fig. 1). From the linear regression of the results, it was found that the values of the surface tensile strength of GMS- or glycerol-containing pellets increased by 20.4 and 29.5%, respectively, while those of lactose-containing pellets or those of pellets produced with ethanol reduced by 7.4 and 13.5%, respectively, when they were coated to 20% weight gain. The slight increase in the value of the surface tensile strength of coated MCC pellets was not statistically significant. In the soft pellets (GMS- or glycerol-containing pellets) the coating film formed a rigid crust, which resisted the compression force, while in the porous pellets produced with ethanol, the gap between the film and the core pellet could be the reason for the reduction in the support of the film which failed at a smaller compression pressure.

The shear strength of the pellets was reduced with the increase in the coating material in all formulations except for glycerol-containing pellets (Fig. 2). The latter pellets had the lowest values of shear strength before coating. Coating them with the polymer produced a layer, which increased the resistance to shearing by 0.19 MPa when coated to 20% weight gain. The decrease in the values of shear strength of pellets produced with ethanol was statistically significant between 5 and 20% (w/w) coating levels ($P < 0.01$), however, a similar shear strength at 0% (w/w) coating was found when comparing with pellets containing only MCC or lactose. The pellets with the greatest shear strength, MCC- and lactose-containing pellet

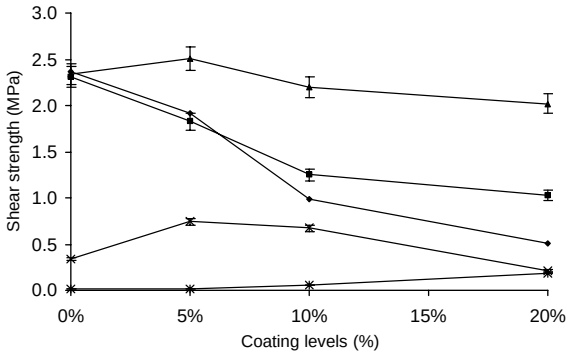

Fig. 2. The influence of coat thickness (%, w/w) on the shear strength of coated pellets of 1.0–1.18 mm size fraction. The results are the mean (standard deviation) of five replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

had the highest reduction in shear strength values after coating at 20% (w/w) level, i.e. 1.91 and 1.27 MPa, respectively. This could be caused by peeling off the film as a result of the tangential compression force during compaction. The overall result in this work illustrates that the coating film affects the surface tensile and shear strength of the pellets differently depending on the properties of the core pellets.

The deformability of the coated pellets increased only slightly with the increase in the coating material, but to different extent with the different types of pellets (Fig. 3). Lactose-containing pellets had the greatest change in this property, and at 20% (w/w) coating the deformability was increased by 72.6%. Pellets produced with ethanol, GMS or only MCC showed a smaller increase (8–24%) in this property, while the effects of the composition of the uncoated pellets were previously found to be significant (Bashaiwoldu et al., 2004). Pellets produced with glycerol did not show an increase in deformability with coating, presumably due to the similarity in deformability of these semisolid-like pellets and the coating material. The linear strain of all the coated pellets increased with the exception of pellets produced with ethanol (Fig. 4). These pellets showed a reduction of 5% in linear strain, while pellets containing glycerol, GMS or lactose showed an increase in 31, 52, and 58%, respectively, when coated with 20% (w/w) ethyl cellulose. Increase in the strength with coating may have caused glycerol- or GMS-containing pellets to be strained to a greater extent. For lactose-containing pellets, the slope of the force–displacement curve was markedly reduced, mainly due to the uptake of some of the compression force by the deformable coating material as well as the local spreading of the coated pellets at the surface of the platens. This was observed to increase the deformability of the pellets, likewise their ability to reduce in unilateral dimension with compression (linear strain). In pellets produced with ethanol, the coating material may have filled some of the open pores, hence reduced linear strain presumably due to the limited space left for the primary particles to rearrange themselves with compression. The "elastic modulus", determined from the stress–strain curves,

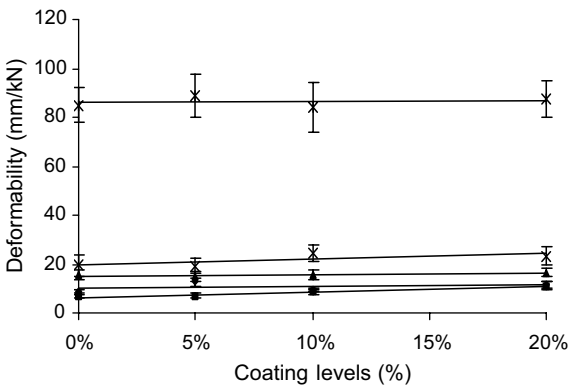

Fig. 3. The influence of coat thickness (%, w/w) on the deformability of coated pellets of 1.0–1.18 mm size fraction. The results are the mean (standard deviation) of 30 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

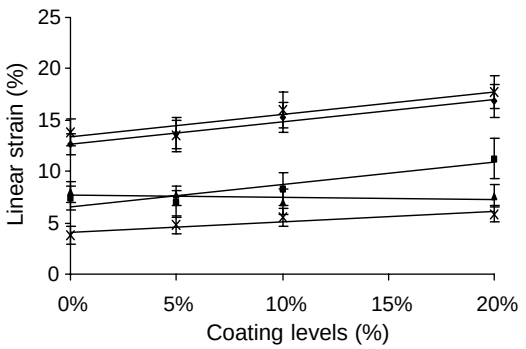

Fig. 4. The influence of coat thickness (%, w/w) on the linear strain of coated drug pellets of 1.0–1.18 mm size fraction. The results are the mean (standard deviation) of 30 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

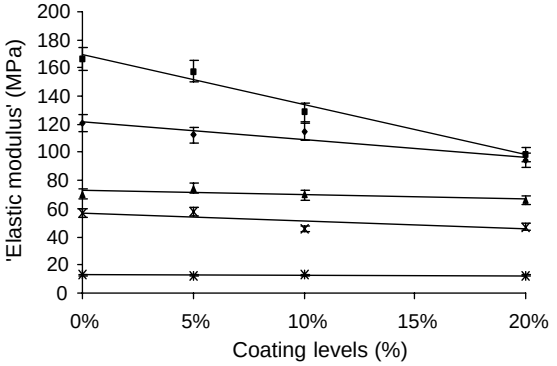

Fig. 5. The influence of coat thickness (%, w/w) on the "elastic modulus" of coated drug pellets of 1.0–1.18 mm size fraction. The results are the mean (standard deviation) of 30 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

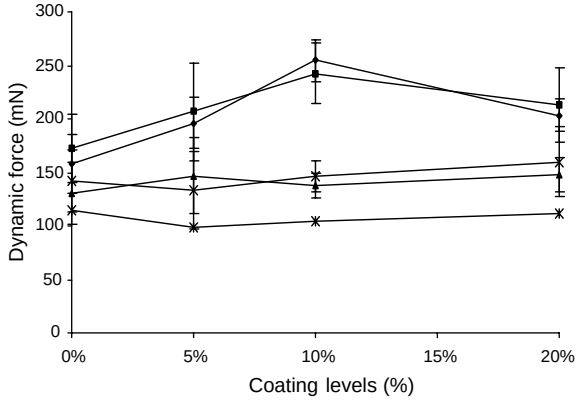

Fig. 6. The dynamic forces, determined at the onset of the linear portion of the storage modulus−dynamic force slope, of the pellets (1.0–1.18 mm size fraction) from different formulations and coated at different coating levels (i.e. 0, 5, 10, and 20% (w/w)). The results are the mean (standard deviation) of 20 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

of all the pellets from different formulations was reduced with the increase in coating material (Fig. 5). Lactose-containing pellets, which had the highest initial value of "elastic modulus" had the greatest reduction in the value of this property after coating. The order of reduction at a 20% weight gain of coating was: lactose (42.7%), MCC (20.9%), GMS (20.8%), ethanol (8.4%), and glycerol pellets (1.5%). These results demonstrated the change in the elasticity of the pellets, although to different extent caused by coating. The most rigid pellets (lactose-containing) were affected to the greatest extent, while the softest pellets (glycerol-containing), were hardly affected showing the dependency of the effects of the coating material on the mechanical properties of the core pellets.

3.1. Dynamic Mechanical Analysis of coated drug pellets

The dynamic force at which the storage modulus–dynamic force curve started to be linear was smaller for pellets produced with glycerol, GMS, and ethanol than pellets with MCC only for all coating levels, while it was greater for lactose-containing pellets (Fig. 6). These values represent the "stiffness" of the core pellets. At all coating thicknesses, the rank order for the dynamic force at the start of the linear curve was the same. However, the change induced by coating lactose pellets was statistically insignificant, while for the rest of the formulations this effect was significant ($P < 0.01$). With the increase in the coating thickness, there was a general trend to increase the dynamic force at the start of the linear curve; however, it was statistically insignificant for all pellets produced with ethanol, glycerol, or GMS. Nevertheless, increasing the coating thickness significantly increased ($P < 0.05$) the dynamic force at which linearity occurred for MCC- and lactose-containing pellets. Coating lactose- or only MCC-containing pellets by 20% (w/w) ethyl cellulose increased the dynamic force by 19.9 and 24.7%, respectively, while for those pellets produced with ethanol or glycerol, there was only an increase of 9.6 and 1.8% respectively. For the two former formulations, however, the highest increase was at only 10% (w/w) coating level, after which the values reduced significantly for no apparent reason.

The storage modulus or elasticity of the pellets at 600 mN dynamic force had the same rank order for all pellets from the different formulations regardless of the coating thickness (Fig. 7). The change of formulations reduced the storage modulus of MCC pellets at corresponding coating thicknesses with the exception of lactose. This finding was statistically significant ($P < 0.05$) except for lactose-containing pellets coated with 5% (w/w). Here again, the effect of the core material still influenced the elastic properties of the coated pellets. The relative effect of the coating material was, however, different and dependent on the elasticity of the core pellets. The more

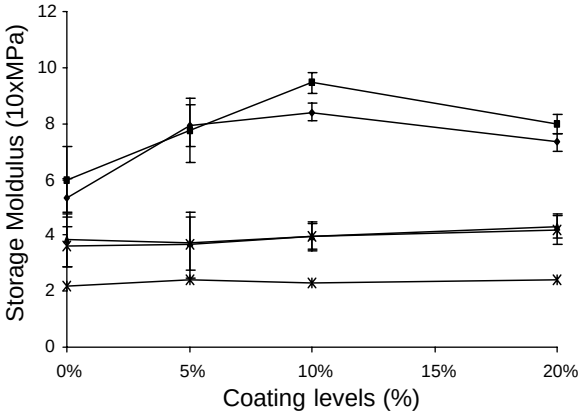

Fig. 7. The storage modulus, determined at dynamic force of 600 mN, of the pellets (1.0−1.18 mm size fraction) from different formulations and coated at different coating levels (i.e. 0, 5, 10, and 20% (w/w)). The results are the mean (standard deviation) of 20 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

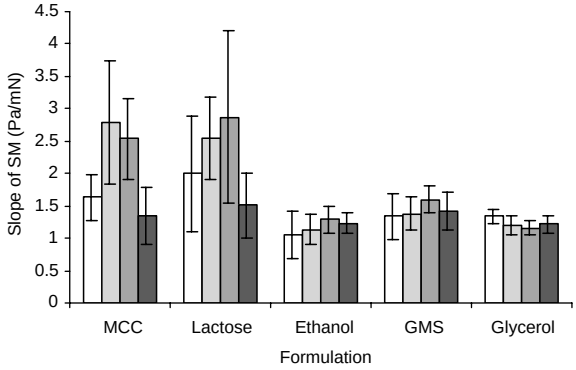

Fig. 8. The slope (10,000×) of the linear portion of the storage modulus–dynamic force curve of pellet (1.0–1.18 mm size fraction) from the different formulations and coated at different coating levels (i.e. 0, 5, 10, and 20% (w/w)). The results are the mean (standard deviation) of 20 replicates. No coating (□); 5% coating (▒); 10% coating (▒); 20% coating (■).

rigid the pellets were, the more was the increase in their storage modulus after coating. At 20% (w/w) coating level, the increase in storage modulus in descending order was lactose (36.6%), MCC (22.6%), GMS (18.1%), ethanol (15.4%), and glycerol (6.3%).

The rank of the mean slope of the linear portion of the storage modulus–dynamic force curve in descending order was: lactose, MCC, GMS, glycerol to pellets produced with ethanol. There were considerable variations within each batch, as is indicated by the standard deviation on the graph (Fig. 8). This indicates the approximately similar change in response of the latter three formulations to the sinusoidal stimuli of various magnitudes, and also the similarity of the former two formulations in terms of response. The effect of the coating material seems to be minimal. Pellets formed with lactose, ethanol, and GMS showed an increase in values up to their 10% (w/w) coating levels. All formulations coated with 20% (w/w) had a lower slope than those with 10% (w/w) indicating the presence of a threshold. The pellets from all the formulations had approximately the same slope when coated with 20% (w/w) ethyl cellulose. This indicates that the property studied was mainly that of the surface of the pellets, hence only the coating material in the latter case. Uncoated glycerol-containing pellets, however, had the greater slope compared to those of coated ones.

Generally, it is possible to conclude that comparison of the formulations in terms of their storage modulus has a similar rank order to that of Young's modulus of elasticity determined by static scans of the pellets (Bashaiwoldu et al., 2004). Moreover, the coating material (ethyl cellulose) seems to have dominated the results found, as the storage modulus was observed to increase with increase in coating levels. The slopes of the curves, however, showed marginal differences with considerable variability; hence it was not possible to draw a conclusion as to the effect of the formulations on the storage modulus for pellets formed with ethanol, GMS, or glycerol. For lactose- or only MCC-containing pellets, however, a difference was observable, but due to even higher variability the results were statistically insignificant (Fig. 8). From the comparison of the results of the formulations coated at different levels, it is possible to observe that the difference in the values for the storage modulus, dynamic force, and slope of the storage modulus–dynamic force curve was the lowest for pellets coated with 20% (w/w). Especially, the values of the slope of the curves were approximately the same irrespective of the properties of the core material. This illustrates that at higher coating level, it is the property of the coating material, which is being measured.

The phase angle of the formulations measured at both positions (at 600 mN of dynamic force and at the start of the linear position of the storage

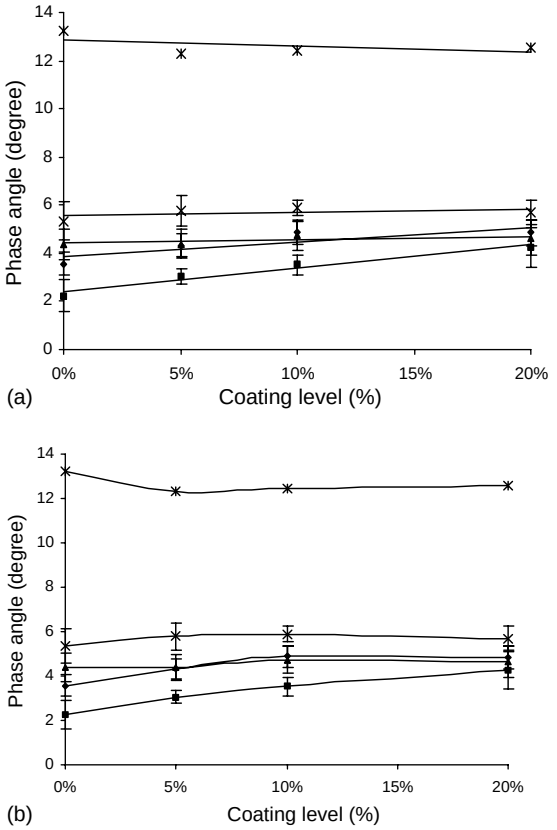

Fig. 9. The phase angle, determined (a) at the beginning of the linear portion of the storage modulus–dynamic force curve (b) at dynamic force of 600 mN, of the pellets (1.0–1.18 mm size fraction) from the different formulations and coated at different coating levels (i.e. 0, 5, 10, and 20% (w/w)). The results are the mean (standard deviation) of 20 replicates. (◆) MCC; (■) lactose; (▲) ethanol; (×) GMS; (✱) glycerol.

modulus–dynamic force curve) had the same rank order, which increased from pellets produced with lactose (79.1%), MCC (31.0%), ethanol (6.8%), GMS (5.3%) to glycerol (−3.7%) (Fig. 9a and b). This was in the reverse order of the storage modulus and Young's modulus of the pellets. In both cases there was an increase in phase angle value with the increase in the coating levels. This again indicates the plasticity of the polymer (ethyl cellulose). The effect of the coating material was, however, significant ($P < 0.05$) only in pellets containing lactose or only MCC. For GMS- and glycerol-containing pellets, the effect of the coating material was small, presumably due to the comparable plasticity of the core pellets and the coating material. Moreover, the effect of coating material on the phase angle of pellets produced with ethanol was marginal.

In all formulations, the phase angle increased with the increase of the dynamic force, although to different extents. For pellets produced with ethanol, lactose, or only MCC, the increase in phase angle at 600 mN dynamic force was approximately the same (1.25°), while for pellets containing GMS or glycerol, an increase by 2 and 4.5°, respectively, was observed. The effect of the coating material was not appreciable in these cases; in fact, in pellets produced with ethanol and those containing GMS there was a slight reduction in the rate of increase of phase angle with increase in coating levels. This indicates the dominance of the effects of the composition of the core pellets, which resulted in different proportions of dissipated energy.

3.2. Comparison of the techniques

Bashaiwoldu et al. (2004) have shown the superiority of the DMA in determining the Young's modulus of elasticity of uncoated pellets when compared to the diametral compression test using conventional tablet crushing equipment. For coated pellets, however, it was not possible to obtain a linear stress–strain curve from static scan using a DMA mainly due to the highly viscous nature of the coating polymer. The increase in the percentage of the storage modulus values, when the pellets were coated with 20% (w/w) ethyl cellulose, was only half of the increase in the percentage of the "elastic modulus" of the coated pellets determined from the diametral compression test. This shows the variation in the pressure upon which these values were obtained, as well as the variation in sensitivity of the techniques employed. The effect of the coating material in both techniques was of the same rank order, but the difference between pellets produced with ethanol or GMS was marginal for the storage modulus values obtained from the dynamic scan of the DMA. The values of the storage modulus of the coated pellets at 600 mN dynamic force had the same rank order to those of uncoated pellets. With the increase of the coating material up to 10% (w/w), the storage modulus of the pellets from the different formulations increased. At 20% (w/w) coating thickness, however, all pellet batches had the same values for the storage modulus, suggesting that at this high level of coating, the slope of storage modulus–dynamic force

graphs represented that of the coating material itself. In the case of the values of "elastic modulus" of the coated pellets determined by the diametral compression test, this dominant elastic property of the film was not demonstrated.

At all coating thicknesses the rank order for the dynamic force at the start of the linear storage modulus–dynamic force curve was the same. It was also the same as the rank order of the uncoated pellets illustrating the dominance of the properties of the core pellets. These ranks were in a descending order from lactose, MCC, ethanol, GMS to pellets produced with glycerol. This was in the same order to the yield strength of the pellet as determined by Bashaiwoldu et al. (2004). With the increase in the coating thickness, however, there was a general trend to increase the dynamic force at the start of the linear curve between the storage modulus and dynamic force.

From the diametral compression test (Fig. 3), the highest increase (72.6%) in the deformability of lactose-containing pellets with coating, as well as the lowest increase (0.01%) in the same property of the pellets containing glycerol with coating was noted. From the dynamic scan of the DMA a similar result was obtained. Coating increased the phase angle of lactose-containing pellets to the greatest extent, i.e. by 79% with 20% (w/w) coating, while for glycerol-containing pellets coating with 20% (w/w) reduced the phase angle by 3.6%. There seems to be a reasonable agreement between the relative values of the two techniques. However, in the diametral compression test the pellets suffered permanent structural failure and the possible reversible part of the deformation could not be identified.

4. Conclusion

From this work it was possible to conclude that the mechanical properties of the pellets were affected by coating. Increase in strength of the pellets with a soft core and increase in elasticity and deformability of the pellets with a rigid core were suggested by the conventional technique, which employs the diametral compression test. It was also 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 from DMA measurements. Moreover, the lowest level of plastic deformability of lactose-containing pellets was illustrated by this technique. Increase in coating material, ethyl cellulose, was observed to increase the apparent plasticity of mainly lactose or MCC pellets. However, its effect on pellets of the other formulations was not appreciable. This could be due to the variation of the properties of the core pellets, i.e. GMS- or glycerol-containing pellets had a comparable plasticity to that of coating material as illustrated by the minimal change in the phase angle with increase in coating levels. Finally, this work has established that the elastic and plastic deformation of the pellets could only be determined from the dynamic scan using the DMA. The "deformability" values calculated from the force–displacement curve obtained during diametral compression of the pellets does not reflect the plastic behavior of the pellets for it does not identify the possible structural recovery. Using DMA, however, the sinusoidal stress–relaxation cycles enabled the determination of the dissipated energy in terms of loss modulus or phase angle.

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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.

Arwidsson, H., Johansson, B., 1991. Application of intrinsic viscosity and interaction constant as a formulation tool for film coating. Part 3. Mechanical study on free ethyl cellulose films, cast from organic solvents. Int. J. Pharm. 76, 91–97.

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 of a tablet comprising compacted polymer-coated millispheres. Drug Dev. Ind. Pharm. 20, 3069–3104.

Bansal, P., Vasireddy, S., Plakogiannis, F., Parikh, D., 1993. Effect of compression on the release properties of polymer coated niacin granules. J. Control. Release 27, 157–163.

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

Bashaiwoldu, A.B., Podczeck, F., Newton, J.M., 2004. Application of Dynamic Mechanical Analysis (DMA) to determine the mechanical properties of pellets. Int. J. Pharm. 269, 329–342.

Bechard, S.R., Leroux, J.C., 1992. Coated pelletized dosage forms: effect of compaction on drug release. Drug Dev. Ind. Pharm. 18, 1927–1944.

Bodmeier, R., Paeratakul, O., 1994. Mechanical properties of dry and wet cellulosic and acrylic polymer films prepared from aqueous colloidal polymer dispersions. Pharm. Res. 11, 882–888.

Chang, R.K., Rudnic, E.M., 1991. The effect of various polymeric coating systems on the dissolution and tableting properties of potassium chloride microcapsules. Int. J. Pharm. 70, 261–270.

Chang, R.K., Hisiao, C.H., Robinson, J.R., 1987. Review of aqueous coating techniques and preliminary data on release from a theophylline product. Pharm. Technol. 11, 56–68.

Cole, G., Hogan, J., Aulton, M.E., 1995. Pharmaceutical Coating Technology. Taylor and Francis, London.

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–spheronization. Drug Dev. Ind. Pharm. 20, 3045–3068.

Fukumori, Y., 1994. Coating of multiparticulate using polymeric dispersions: formulation and processing considerations. In: Ghebre-Sellassie, I. (Ed.), Multiparticulate Oral Drug Delivery. Marcel Dekker, New York, pp. 79–113.

Ghaly, E.S., Ruiz, N.R., 1996. Compressibility characteristic of matrices prepared with ethyl cellulose aqueous dispersion. Drug Dev. Ind. Pharm. 22, 91–95.

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

Lafferty, S.V., Newton, J.M., Podczeck, F., 2002a. Dynamic Mechanical Thermal Analysis of polymer films prepared from aqueous dispersion. Int. J. Pharm. 235, 107–111.

Lafferty, S.V., Newton, J.M., Podczeck, F., 2002b. Characterisation of the mechanical properties of polymer films formed from aqueous polymer dispersions by creep testing. Int J. Pharm. 239, 143–148.

Lafferty, S.V., Newton, J.M., Podczeck, F., 2002c. Kinetic examination of the mechanical transition of polymethyl methacrylate films prepared from aqueous dispersions. Int. J. Pharm. 239, 179–183.

Lahmann, K., Steuernag, S., 1989. Chemistry and application properties of poly-methacrylate coating systems. In: McGinity, J.W. (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. Marcel Dekker, New York, pp. 153–245.

Maganti, L., Celik, M., 1994. Compaction studies on pellets. Part 2. Coated pellets. Int. J. Pharm. 103, 55–67.

McGinity, J.W., 1989. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. Marcel Dekker, New York.

Narisawa, S., Yoshino, H., Harakawa, Y., Noda, K., 1994. Porosity-controlled ethyl cellulose film coating. IV. Evaluation of mechanical strength of the porous ethyl cellulose film. Chem. Pharm. Bull. 42, 1491–1495.

Okhamafe, A.O., York, P., 1988. Studies of interaction phenomena in aqueous-based film coatings containing soluble additives using thermal analysis technology. J. Pharm. Sci. 77, 438–443.

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.

Porter, S.C., 1989. Controlled-release film coatings based on ethyl cellulose. Drug Dev. Ind. Pharm. 15, 1495–1521.

Radebaugh, G.W., Simonelli, A.P., 1983. Phenomenological visco-elasticity of heterogenous pharmaceutical semisolids. J. Pharm. Sci. 72, 415–422.

Ragnarsson, G., Johansson, M.O., 1988. Coated drug cores in multiple unit preparations influenced of particle size. Drug Dev. Ind. Pharm. 14, 2285–2297.

Ragnarsson, G., Sandberg, A., Johansson, U.E., Sjogren, J., 1987. Development of a new controlled release metoprolol product. Drug Dev. Ind. Pharm. 13, 1495–1509.

Rowe, R.C., 1981. The crack of film coatings on film-coated tablets: a theoretical approach with practical implications. J. Pharm. Pharmacol. 33, 423–427.

Sarisuta, N., Punpreuk, K., 1994. In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets. J. Control. Release 31, 215–222.

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

Wang, C., Zhang, G., Shah, N.H., Infeld, M.H., Malick, A.W., McGinity, J.W., 1996. Mechanical properties of pellets containing acrylic polymers. Pharm. Dev. Technol. 1, 213–222.

Wang, C., Zhang, G., Shah, N.H., Infeld, M.H., Malick, A.W., McGinity, J.W., 1997. Influence of plasticizers on the mechanical properties of pellets containing Eudragit RS 30 D. Int. J. Pharm. 152, 153–163.

Yang, S.T., Ghebre-Sellassie, I., 1990. Effect of product bed temperature on the microstructures of Aquacoat-based controlled release coating. Int J. Pharm. 60, 109–124.