Variations in Compaction Behaviour for Tablets of Different Size and Shape, Revealed by Small-Angle X-Ray Scattering

PETER R. LAITY, LIANGHAO HAN, JAMES ELLIOTT, RUTH E. CAMERON

Department of Materials Science and Metallurgy, Pfizer Institute for Pharmaceutical Materials Science, University of Cambridge, New Museums Site, Pembroke St. Cambridge CB2 3QZ, UK

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ABSTRACT: Local variations in compaction behaviour were investigated, for specimens of different shapes and thickness, comparing predictions from finite element (FE) modelling and results from a recently developed method using small-angle X-ray scattering (SAXS). Good agreement was generally obtained between these methods, in terms of the variations of density, compaction strain and principal strain direction within the specimens examined. The combination of SAXS and FE methods appeared particularly suitable for studying pharmaceutical tablets, revealing effects (such as nano-strain of intragranular morphology and strain direction) that are not easily observed by other methods, and which may have significant effects on tablet integrity or swelling and drug delivery characteristics.

INTRODUCTION

It is well known that friction against tooling during powder compaction generally results in significant density variations within the tablet. This has been demonstrated in numerous investigations using various techniques: Briscoe and Rough employed the ‘coloured layer method’ to infer local variations within compacted alumina powder; Macleod and Marshall used the natural radioactivity of uranium dioxide to image density variation; Kandeil and de Malherbe revealed patterns of hardness variations within compacted aluminium powder; similar effects were also observed for compacted synthetic polymers by Crawford et al.; Sinka et al. used microindentation to measure hardness variations, magnetic resonance imaging (MRI) after infiltration with a nonswelling liquid to observe porosity variations and X-ray microtomography (XµT) to measure density variations within compacted microcrystalline cellulose (MCC); XµT was also used by Busignies et al. to study MCC tablets. In addition to these and other experimental works, density variations have also been demonstrated in computer-based simulations of compaction behaviour, using finite element methods.

The variations in compaction behaviour revealed by these studies can have a considerable effect on the strength and mechanical integrity of the compacted product. This is of particular concern in the pharmaceutical industry, which is heavily dependent on compacted tablets. Chipping, capping or other forms of tablet fracture can adversely affect delivery of the drug—either because part of the dose is lost with the fragments or through changes in the swelling and disintegration rates of the damaged tablets.

We recently reported on a new application of small-angle X-ray scattering (SAXS) to investigate powder compaction. Work with pregelatinised starch and spheronised microcrystalline cellulose (s-MCC) demonstrated that their two-dimensional (2D-SAXS) patterns became elongated in the compaction direction, to an extent that depended on the applied compaction pressure. Moreover, in addition to indicating local density variations, SAXS offers two advantages over other methods. Firstly, it reveals the resultant direction of compaction, which can be significantly affected by wall friction and the geometry of compaction tooling. Secondly, since the scattering originates from the nanometre-scale structures within powder granules, the changes in SAXS can be used to measure the deformation experienced by this morphology during compaction (herein referred to as ‘nano-strain’).

This is distinct from the ‘macro-strain’ experienced by the powder bed as a whole, which may also include significant contributions from
granule rearrangements and fragmentation, decreasing intergranular porosity.

SAXS is widely used and well-established for studying the nanometre-scale morphology of materials. Excellent descriptions of the underlying principles, experimental procedures and data analysis are given by Roe,\textsuperscript{20} Higgins and Stein\textsuperscript{21} and others.\textsuperscript{22–24} Moreover, the practical details\textsuperscript{16,17} and underlying theory\textsuperscript{18,19} for SAXS studies of powder compaction are discussed in detail elsewhere, so will only be summarised here.

The present work used a combination of 2D-SAXS analysis and finite element (FE) simulations to investigate the effects of thickness and shape on compaction behaviour, for a series of cylindrical s-MCC tablets with flat or domed faces. Further work comparing results from SAXS analyses with predictions from FE modelling, for specimens of more complex shapes will also be reported separately.\textsuperscript{25}

**MATERIALS AND METHODS**

Full experimental details are given elsewhere;\textsuperscript{10,16,17} only the most important aspects are summarised here.

**Preparation of Specimens**

Specimens were prepared in-house,\textsuperscript{16,17} by single-sided compaction of s-MCC (Celphere SCP100, Asahi-Kasei, Japan) in an unlubricated, stainless-steel die (10 mm internal diameter, Specac Ltd, Smiths Industries, Kent, UK), to a maximum compaction force of 20 kN (corresponding to an average upper punch pressure of 255 MPa), using a mechanical testing rig (Instron Ltd, High Wycombe, Buckinghamshire, UK), operated at 3 mm min$^{-1}$ for both loading and unloading stages. The upper punch was driven, while the lower punch was static. Force-displacement data were recorded during each preparation, to permit further analyses; immediately after unloading, specimens were ejected and their dimensions (height and diameter) measured using callipers with a vernier scale (to $\pm 0.02$ mm); finally, the specimens were weighed using a top-pan balance (to $\pm 0.003$ g), in order to calculate the densities.

Flat-faced cylindrical specimens of different thickness were obtained using different powder charges compacted to the same average upper punch pressure. Specimens with domed faces were prepared in a similar manner, using concave punches (radius of dome curvature 7.5 mm).

**Measurement of SAXS**

‘Peri-diametral’ sections, roughly 2 mm thick, across the diameter of the specimen, were prepared by hand, using a sharp scalpel. Sections were mounted individually on the programmable sample stage of a Nanostar camera (Bruker AXS, Inc., Madison, WI), which was set up and operated as described previously.\textsuperscript{16,17} The Bragg angle ($2\theta$) was calibrated using the 2D-SAXS pattern from silver behenate and the modulus of the scattering vector was calculated by:

$$q = \frac{4\pi}{\lambda X} \sin \theta \quad (1)$$

where the wavelength ($\lambda X$, for Cu K$_\alpha$) was 0.154 nm. By programming the co-ordinates of the sample stage, the X-ray spot was automatically rastered over the specimen and scattering patterns were collected over 900 s at each location.

**SAXS Analysis and Extraction of Results**

An example of the SAXS data is shown in Figure 1. Analysis was performed manually, using SAXS for Windows\textsuperscript{11} NT software (Bruker AXS, Inc.). Elongation of the 2D-SAXS pattern in the meridional direction (i.e. vertical, parallel to the compaction),
compared with the equatorial direction (i.e. perpendicular to the compaction) is clearly evident in Figure 1a. The differences between meridional and equatorial intensity can also be observed in 1D-scans through the data, as shown in Figure 1b. In all cases, the intensity decreased smoothly from the edge of the beam-stop shadow (at around \( q = 0.1 \text{ nm}^{-1} \)) until it eventually merged into the background. Further analysis of the data suggested that the intensities roughly followed power-law behaviour:
\[
I(q) = I_0 q^{-\alpha}
\]
where \( I_0 \) is a constant that describes the overall intensity of the scattering and \( \alpha \) is a constant related to the nanometre-scale intragranular morphology (with \( \alpha \approx 2.5 \) for s-MCC).

Azimuthal variations in 2D-SAXS (i.e. measured around the direction of the incident X-ray beam) were quantified using the Hermans orientation parameter,\(^{20}\) which was evaluated from azimuthal intensity scans, \( I(\phi) \), using:
\[
H = \frac{3\langle \cos^2 \phi \rangle - 1}{2}
\]
where:
\[
\langle \cos^2 \phi \rangle = \frac{\int_0^{360} I(\phi) \cos^2 \phi |\sin \phi| d\phi}{\int_0^{360} I(\phi) |\sin \phi| d\phi}
\]

Use of \( |\sin \phi| \) avoided the change of sign at 180°, allowing the integration to be performed between 0 and 360° and giving better accuracy. Hence, it was generally possible to determine \( H \) to \( \pm 0.003 \).

In some cases, the principle axis (i.e. the longer axis, indicating the local compaction direction) deviated from vertical (i.e. the applied compaction direction in the laboratory frame of reference). In these cases, the principal axis of each 2D-SAXS pattern was evaluated by substituting:
\[
\phi = \phi_L + \kappa
\]
where \( \phi_L \) is the azimuthal angle, measured from the vertical in the ‘laboratory frame’ and searching for the value of \( \kappa \) that maximised \( H \), using the ‘Solver’ subroutine in Microsoft Excel.\(^{16}\)

Relative Density, Macro- and Nano-Strain Estimates from 2D-SAXS

The effects of compaction pressure on relative density and changes in 2D-SAXS patterns were reported previously.\(^{15,16}\) A relationship was obtained between the Hermans orientation parameter and relative density; for compacted s-MCC, this is described by:
\[
\rho_{rel} = \frac{\rho_{bulk}}{\rho_{true}} = 0.433 + 0.411H + 0.449 \left[ 1 - \exp \left( -\frac{H}{0.008} \right) \right]
\]
where the true density (\( \rho_{true} \)), measured by helium pycnometry, was 1580 kg m\(^{-3} \). Although clearly related to the compaction behaviour of MCC, this relationship was essentially empirical, depending on the balance between deformation within the sub-granular nanometre-scale morphology and the overall compaction of the powder bed.

Uncertainty in the values of relative density from Eq. (4) arose in two ways: at low densities, it was mainly attributable to the errors in measuring \( H \) (\( \pm 0.003 \)); this improved at higher densities, but was limited by the variability in the relative densities (\( \pm 0.02 \)) of the calibration samples used to obtain the relationship. Hence, the uncertainty was estimated to be \( \pm 0.05 \) at \( \rho_{rel} = 0.77 \), decreasing to \( \pm 0.02 \) for \( \rho_{rel} = 0.85 \) and less than \( \pm 0.01 \) for \( \rho_{rel} \geq 0.90 \).

Macro-strain refers to the overall deformation of the compacted powder bed, from the initial filling density of the powder in the die (\( \rho_{fill} = 0.433 \), for Celphere SCP100), to the final local density within the ejected compact. This was calculated using:
\[
\varepsilon_{macro} = \ln \left( \frac{\rho_{rel}}{\rho_{fill}} \right)
\]
where a positive value indicates compaction. It should be noted that the contributions to macro-strain may include granule rearrangement and fracture, as well as deformation of the granules themselves. The uncertainty in estimating relative density from \( H \) (i.e. using Eqs. 3a, 3b and 4) also produced uncertainty in the macro-strain obtained using Eq. (5). This corresponded to \( \pm 0.065 \) at \( \rho_{rel} = 0.77 \) and \( \varepsilon_{macro} = 0.576 \), but improved with increasing relative density, to \( \pm 0.01 \) for \( \rho_{rel} \geq 0.90 \).

A model was developed previously,\(^{19} \) which linked the changes in 2D-SAXS to compression of the nanoscale intragranular morphology due to granule deformation within the compacted powder bed. Although the deformation may be varied and irregular within individual granules, the aggregated effect over a large number of granules appeared to be equivalent to initial spherical elements of volume being compressed by a scaling factor \( (b) \) along the direction of applied stress, into ellipsoids. Assuming strictly affine deformation of the morphology during compaction (i.e. with volume reduction, due to the partial collapse of intragranular voids), this model predicted that:
\[
I_{comp}(q, \phi) = I_{eq}(q) \left( \frac{b^2 \sin^2 \phi + \cos^2 \phi}{b^2} \right)^{\alpha/2}
\]
where $\phi$ is the azimuthal angle and $I_{eq}(q)$ is the intensity measured in the equatorial (i.e., perpendicular to the primary strain or compaction) direction. Since $b \leq 1$, Eq. (6) predicts that scattering in other directions will be greater than $I_{eq}(q)$, by an amount that depends on the extent of deformation. Hence, the value of $b$ can be obtained by fitting the model to data. An example of this is shown in Figure 1c; the good agreement between the model and experimental data suggests that the underlying theory provides a reasonable description for the behaviour of the compacted s-MCC granules used in this work.

Deformation of the subgranular morphology can also be described in terms of a nano-strain ($\varepsilon_{nano}$), which is related to the scaling factor:

$$\varepsilon_{nano} = -\ln b$$  \hspace{1cm} (7a)

From the theory developed previously,\textsuperscript{19} a relationship was also established between $\varepsilon_{nano}$ and $H$; for s-MCC (Celphere SCP100), this was described by:

$$\varepsilon_{nano} = 2.9006H - 1.1104H^2$$  \hspace{1cm} (7b)

Since the relationship of Eq. (7b) is almost linear, the uncertainty in $H$ produced an almost constant uncertainty in estimates of nano-strain, which decreased only slightly for more compacted specimens. Thus, the uncertainty in $\varepsilon_{nano}$ was $\pm 0.009$ at $H = 0.01$ (corresponding to $\rho_{rel} = 0.770 \pm 0.065$), decreasing to $\pm 0.008$ at $H = 0.1$ (corresponding to $\rho_{rel} = 0.934 \pm 0.005$).

**Finite Element Model**

FE simulations of the entire compaction process, including ejection, were performed using a modified density-dependent Drucker-Prager Cap (DPC) plasticity model, in ABAQUS version 6.7 (Dassault Systèmes, Vélizy Villacoublay, France) finite element software, as described elsewhere.\textsuperscript{9,10} Changes in the mechanical properties of the powder bed during compaction were accommodated using tabulated values and a user-defined subroutine. Experimental validation of this model for MCC (Avicel PH101) powder was reported previously by Han et al.,\textsuperscript{10} whereas Celphere SCP100 was used for the experiments; however, comparison between the compaction behaviour of the two materials, as shown in Figure 2, suggested that this parameterisation also provided a reasonable basis for modelling Celphere SCP100.

Axisymmetric models were employed, consistent with the geometry and constraints expected in the experimental compactions. Each model was constructed to represent a particular experimental setup, consisting of a deformable powder bed, which was contained between two (flat or curved) rigid punches and a rigid die wall, each of radius 5.00 mm. The simulated powder charge matched the weight of the experimental specimen; the initial filling height ($h_0$) was calculated for a filling density of 300 kg m$^{-3}$ (equivalent to $\rho_{rel} = 0.189$), which was observed for loosely poured, uncompacted Avicel PH101.

The rigid punch and die were modelled as analytical rigid bodies; the powder bed was modelled using axisymmetric continuum elements and elements of the CAX4R type, comprised of a network of 4-node quadrilaterals, each with a single integration point and ‘hourglass control’. Large strains were involved in the compaction process and some elements became too severely distorted. In order to remedy this, a ‘mesh-to-mesh solution mapping’ remeshing technique provided in ABAQUS/Standard was used; this replaced the deformed mesh with a mesh of better quality, before continuing the simulation. The contact between the powder and the rigid tooling was modelled by defining contact pairs of surfaces. The tooling surface was associated with a rigid body by its specified reference node, on which the loads or displacement of a rigid body were applied. The Coulomb friction law was used to describe frictional contact between contact surfaces. A wall friction coefficient ($\mu = 0.2$) was used in FE simulations of MCC against non-lubricated surfaces, based on previous measurements using an instrumented die.\textsuperscript{10}

The simulation was carried out through three steps, representing compression, decompression and ejection, respectively. In the first step, the upper punch head was moved toward the powder by applying a displacement to its reference point, to simulate the compression process, while the die and the lower punch remained motionless. In the second step, the upper punch was moved out of the die by applying a displacement to its reference point to simulate the decompression process. For the sake of
simplicity, the third step was simulated by releasing all the contact forces between powders and the die set, in the following way: first, all the displacements of a compact within the die were frozen to their current state (i.e., after unloading) by applying a displacement boundary condition; then, all the contacts were removed by disabling the mechanical interaction between contact surfaces; finally, the displacement boundary defined in the previous step was removed, to allow free recovery of the simulated compact.

RESULTS

In order to check the validity of the model parameterisation (based on Avicel PH101) for modelling Celphere SCP100 (used in the experiments), the compaction behaviour of these materials is compared in Figure 2. Although both materials have the same true density (1580 kg m\(^{-3}\)), the Avicel compaction started from a lower relative density (\(\rho_{\text{rel}} = 0.26\)) than the Celphere (\(\rho_{\text{rel}} = 0.43\)). This may be attributed to the more irregular granular shapes of the former, which resisted densification due to the powder settling during die filling and the weight of the upper punch. The effects due to the shapes of individual particles were not included in the FE model, however, which treated the powder as a continuum, with a phenomenological model to describe its stress-strain response.

The Avicel curves lay to the left of the Celphere curves (indicating higher average punch pressure for the former), over the low density range, but gradually converged by about \(\rho_{\text{rel}} = 0.84\) at 100 MPa. Subsequently, at higher pressures, the compaction behaviour for the two materials appeared essentially indistinguishable, which included most of the relative density range observed for the compacted specimens used in this study. Since the stress-strain relationships of two types of MCC were similar, particularly at higher density, it appeared that parameterisation of the FE model based on Avicel data provided a reasonable basis for simulating the present experimental compactions using Celphere.

Relative density variations for a series of flat-faced cylindrical tablets of different thickness from 2D-SAXS analysis are compared with predictions from FE simulations, in the form of colour-coded maps, in Figure 3. Since the results were expected to be axisymmetric (with cylindrical symmetry), only radial sections are shown for each. This allowed SAXS measurements to be made across both sides of the diametral section, then averaged to give the results shown.

Due to the finite size of the X-ray spot (approx. 1 mm diam.), strong reflections ‘contaminated’ the SAXS data from within 0.5 mm of an edge, so that reliable measurements were not possible. Lines are drawn around each map indicating the edges of each specimen. Although the FE simulation did not incur the same limitations, it was decided to omit the outermost results, in order to facilitate comparisons with the SAXS data. Also, although the FE method was capable of predictions at a much higher spatial resolution, the results were locally averaged to match the spatial resolution (0.5 mm) of the SAXS results.

Good agreement was observed between the SAXS results and the FE simulation, in terms of both the numerical ranges and distribution patterns of the relative densities. The patterns of variations revealed
within each cross-section were in keeping with expectations based on previous reports.\(^1\)\(^{–}\)\(^{17}\) The highest density was in the upper corner (i.e. the tablet rim, close to the die wall and just below the driven punch), while the lowest was in the bottom corner. Intermediate densities were indicated closer to the tablet centres, with a moderately high density region located centrally, just above the lower (static) face and a lower density region just below the middle of the upper (driven) face.

Although the FE simulations predicted slightly higher relative densities overall, compared with SAXS, the differences were generally consistent with experimental uncertainties in measuring the average relative density of each specimen (±0.02, which affected the FE simulation) and the Hermans parameter (±0.003, which affected the SAXS results). The largest discrepancies were observed in the bottom corners of the thickest specimens, where the relative densities estimated from SAXS were consistently about 0.12 below the values predicted by FE simulation. Although these were only slightly greater than the expected experimental uncertainties and decreased for the thinner specimens, this may suggest a systematic error between SAXS and FE modelling, possibly due to the friction against the tooling being slightly higher in the experiments than allowed for in the model.

The arrows in Figure 3, superimposed over the coloured maps of relative density, indicate the principal compaction direction corresponding to each location. Again, this showed good agreement between the SAXS results and the FE simulation. Over the majority of each cross-section, the local compaction direction appeared to be effectively vertical (i.e. parallel to the externally applied compaction force). Pronounced deviations from vertical were observed close to the side of the diametral sections, however, with the principal axes appearing to ‘lean inwards’ towards the centre of the specimen. This was consistent with previous observations.\(^{16}\)\(^{,}\)\(^{17}\) and may be attributed to the effect of wall friction; the effect was absent from FE simulations without wall friction (not shown). The changes in principal stress direction appeared to be essentially symmetrical between either side of the diametral section and largely independent of tablet thickness, but deviations from vertical appeared to increase towards the bottom corner of each specimen.

Both SAXS experimental results and FE simulations indicated that increasing tablet thickness produced more pronounced variations: the minimum density fell significantly, while the maximum density remained essentially constant, as shown in Figure 4. This was consistent with expectations: the maximum density was governed by the maximum applied punch pressure, which was held constant in the present work; by contrast, wall friction caused a reduction in the local stress available to compact the bottom corners of the tablet. Hence, as the frictional losses increased with tablet height, the density differences between top and bottom corners also increased.

Denser compacts are generally stronger.\(^{1}\)\(^{,}\)\(^{11}\)\(^{,}\)\(^{26}\) Consequently, the more extreme density variations observed with increasing thickness may be expected to compromise the tablet integrity. For example, based on the relationship between porosity and critical stress intensity factor used by Inman et al.,\(^{26}\) it may be expected that the bottom corners of the thicker tablets (where \(r_{\text{rel}} = 0.75\)) would be only about 30% as strong as the rest of the tablet (with \(r_{\text{rel}}\) in the range 0.90–0.92). Moreover, recent work\(^{27}\) has also suggested a link between tablet density and the speed of water ingress, which could affect swelling and disintegration behaviour.

Maps of macro- and nano-strain estimates from SAXS data are compared in Figure 5. Both sets of results showed the same qualitative patterns, in line with the density variations in Figure 3 (from which the macro-strain was calculated). There were important numerical differences between the results, however, due to the different underlying mechanisms. The macro-strain referred to the overall increase in density—irrespective of the compaction mechanism. Hence, this included granule movement, re-orientation, fracture and deformation, as the overall volume of the powder bed was reduced. By contrast, nano-strain referred only to deformation of the nano-scale intragranular morphology, which occurred as the granules deformed in response to compaction.\(^{19}\) Hence, the macro-strain was consistently larger than the nano-strain.

Moreover, the relationship between the nano-strain and macro-strain estimates from SAXS was highly non-linear, of the form shown in Figure 6.
(which was obtained using Eqs. 4, 5 and 7b). Hence, there appeared to be negligible nano-strain within the regions of lowest relative density or macro-strain, in the bottom corners of the thicker specimens. Conversely, the regions of highest relative density experienced significantly greater (typically more than double) amounts of nano-strain than other parts of the tablet. This effect was explained previously in terms of individual granules undergoing plastic deformation (or yielding) when the local stresses became sufficiently high. Moreover, it may be expected that, after the particles have rearranged and the original intergranular voids have been largely filled with material, the only thing left to deform is the particles themselves—producing more nano-strain within the most highly compacted regions.

Macro-strain includes mechanisms that operate at the level of the macroscopic powder bed. Consequently, it can also depend on factors such as granule shape and size distribution, which affect the filling density. By contrast, nano-strain refers only to deformation of the intragranular morphology, which appears to be more intimately associated with the mechanical properties of the excipient itself.

Relative density and strain direction variations from SAXS analysis and FE simulations for a bi-convex tablet are compared in Figure 7. Again, results from the two methods were in reasonable agreement, although FE simulation predicted slightly higher density overall and larger angular variations. The biggest discrepancy concerned the low density region just below the upper face; SAXS indicated this to be slightly more extensive and of lower \( \rho_{\text{rel}} \) compared with the FE simulation.

The effects of wall friction on strain direction appeared to be augmented by punch geometry,
causing deviations from the vertical over a larger fraction of the cross-section. This change in shape also produced a significant difference in density distribution, compared with the flat-faced specimens, with regions of almost constant high density extending down the sides, while the centre was of lower density.

The changes in the patterns of relative density variations between the flat-faced and bi-convex tablets suggested differences in their abilities to resist chipping. Whereas the bottom corners of the flat-faced cylindrical tablets were of low density, the bi-convex tablets appeared to present well compacted regions over most of their surfaces. Hence, the latter may be expected to withstand chipping and abrasion losses better. Since, these changes in density distribution are related to the local porosity fractions, this may also be expected to cause significant differences in the water ingress, swelling and disintegration behaviour, between flat-faced and bi-convex tablets. Given the potential importance to the strength and drug delivery characteristics of the tablet, these potential effects merit further investigation in subsequent work.

Nano-strain distributions are compared for flat-faced, cylindrical and bi-convex specimens in Figure 8. Whereas the change from the highest to lowest strain occurred down the sides of the former, this occurred radially, from the circumference to the centre of the bi-convex specimen. The possible implications of this are discussed below.

### DISCUSSION

The effect of friction against the tooling, producing density variations within compacted tablets is well known. Also, important connections between tablet density, strength\(^1\),\(^11\),\(^26\) and water penetration\(^27\) have already been noted. Consequently, reliable methods for investigating density variations are very important for understanding the characteristics and behaviour of tablets. Although other methods based on microindentation,\(^5\) MRI to observe the distribution of a non-swelling liquid\(^6\) and X\(_\mu\)T\(^7\),\(^8\) are available, the results presented here, in other recent publications\(^16\),\(^17\) and work to be reported elsewhere\(^25\) suggest that density measurements from SAXS can provide a very useful contribution to the subject.

Moreover, the good agreement obtained between SAXS measurements and FE simulations in the present work gives credence to both methods and...
suggests that the combination is especially powerful for studying powder compaction. In particular, SAXS results could be used as a ‘reality check’ for FE simulations, while the latter can be used to investigate behaviour during intermediate stages (i.e. loading, unloading and ejection, but before the tablet has completely emerged from the die) that are not easily amenable to experimental studies.

In addition to density measurements, from which the macro-strain during compression can be obtained, it appears that SAXS measurements can also provide information concerning the nano-strain that occurred at the sub-granular level during compaction. While the macro-strain includes processes operating at the bulk powder scale, such as granule re-arrangement and fragmentation, nano-strain refers only to deformation of the intragranular morphology. Hence, nano-strain measurements from SAXS may be more closely linked to the ‘materials’ properties of the excipients and more informative, with respect to some aspects of tablet behaviour. Some possibilities are discussed below.

Some nano-strain may involve plastic deformation of the intragranular morphology, as suggested by the irregular contact-force measurements obtained using atomic force microscopy. This could represent an important mechanism for energy dissipation and the mechanical heating that has been observed during compaction. This phenomenon is widely known in the pharmaceutical industry, although it has received relatively little research attention. Moreover, since it could affect many aspects of the tabletting process, including compaction behaviour, strength, lubrication, friction, ejection forces and the crystal form or chemical stability of the drug, this merits further investigation.

In addition, some elastic nano-strain could occur. While the changes in SAXS patterns cannot distinguish between plastic and elastic strain, the latter may change with time, given suitable relaxation conditions. Also, while the changes in SAXS are related to strain, rather than stress, the presence of elastic nano-strain infers a possible link to stored compaction stresses.

Elastic nano-strain could affect other tablet behaviour, such as tablet expansion and a propensity towards ‘capping’, which appear to be linked to the release of stored compaction stress. Capping is an important failure mode that can be observed when certain materials, such as lactose, are compacted; internal cracks form during unloading and ejection, which result in a large fragment or ‘cap’ separating from the tablet. Hence, it may be interesting to explore to what extent ‘capping’ is driven by the relaxation of elastic stress stored in regions of highly compacted material causing cracking in adjacent regions of lower compaction and strength. This could help to explain the changes in shapes of the fragments lost by ‘capping’ between flat-faced cylindrical and bi-convex tablets of different dome depth. Due to its industrial importance, this merits further investigation.

Although MCC tablets are not generally prone to failure by ‘capping’, the patterns of nano-strain revealed in this material may indicate the potential stress accumulation in other more elastic materials, where the problem can occur. Moreover, the SAXS method can also be applied to other materials; previous work has demonstrated similar effects in pre-gelatinised starch and hydroxypropyl-methylcellulose, while attempts to study lactose failed due to the weakness of the tablets, which prevented the preparation of suitable ‘peri-diametral’ section for SAXS measurements. Given the range of materials used in tabletting, within the pharmaceutical industries, or subjected to compaction processing in other industries, further investigations into the changes in SAXS following compaction are desirable.

The relaxation of elastic nano-strain may also explain the predominantly axial expansion often observed during swelling. Recent work using XpT to follow the movements of embedded glass microsphere tracers revealed that expansion was generally faster in the axial than radial direction, with some formulations showing dramatic differences. Moreover, while the process appeared to be triggered by moisture, comparison with observations of water ingress by MRI suggested that this expansion could occur ahead of significant water ingress and was distinct from swelling due to the hydration of polymer chains. Indeed, this led to a novel suggestion that the expansion could actually provide a mechanism for ‘sucking’ water into the tablet, as part of the swelling process. Further investigation of this will be reported elsewhere.

CONCLUSIONS

This work has demonstrated the use of the recently developed 2D-SAXS analysis and FE methods for investigating powder compaction. The results from the two methods were generally in close agreement, revealing effects (such as nano-strain of intragranular morphology and changes in principal strain direction) that are not easily observed by other methods. The combination of SAXS and FE appears to be particularly powerful for investigating the compaction behaviour of pharmaceutical dosage forms, which may affect mechanical integrity, as well as swelling and disintegration behaviour.

The occurrence of nano-strain during compaction, as revealed by SAXS, may affect various aspects of tablet behaviour, which merit further investigation.
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