# On the role of API in determining porosity, pore structure and bulk modulus of the skeletal material in pharmaceutical tablets formed with MCC excipient

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## Abstract

The physical properties and mechanical integrity of pharmaceutical tablets are of major importance when loading with active pharmaceutical ingredient(s) (API) in order to ensure ease of processing, control of dosage and stability during transportation and handling prior to patient consumption. The interaction between API and excipient, acting as functional extender and binder, however, is little understood in this context. The API indomethacin is combined in this study with microcrystalline cellulose (MCC) at increasing loading levels. Tablets from the defined API/MCC ratios are made under conditions of controlled porosity and tablet thickness, resulting from different compression conditions, and thus compaction levels. Mercury intrusion porosimetry is used to establish the accessible pore volume, pore size distribution and, adopting the observed region of elastic intrusion-extrusion at high pressure, an elastic bulk modulus of the skeletal material is recorded. Porosity values are compared to previously published values derived from terahertz (THz) refractive index data obtained from exactly the same tablet sample sets. It is shown that the elastic bulk modulus is dependent on API wt% loading under constant tablet preparation conditions delivering equal dimensions and porosity. The findings are considered of novel value in respect to establishing consistency of tablet production and optimisation of physical properties.

## 1. Introduction

Pharmaceutical tableting is well-known as being amongst the most convenient ways of delivering active pharmaceutical ingredients (APIs) to the recipient. The development of APIs is the main focus of industrial and academic research in terms of medicinal efficacy. The tableting and delivery functionality of a formulation, however, is dominated by two main components, the excipient, which is present in by far the greater quantity, and the API, which is designed to have the specific in-vivo activity.

Excipients range broadly in type and functionality. Many excipients are considered to be an inert extender during drug delivery but are crucial in tableting, generally in respect to material

flow, compressibility and compaction, uniformity and control of API dose distribution within the tablet etc. An example of such an excipient is standard ground or precipitated calcium carbonate, which, in fine or granulated particulate form, aids the packing and uniformity of compression in the tableting process, and dissolves typically in the acidic gastric environment, releasing the drug dose as desired (Ridgway *et al.*, 2004). Increasingly, however, the design of targeted drug release requires specialist development of functional excipients, for example, to provide rapid oral dispersibility, to encapsulate an API (Kathpalia *et al.*, 2014), to provide protective access into the small and large intestine or to enhance aqueous solubility of APIs that are essentially hydrophobic in the bulk (Huwyler *et al.*, 2014; Stirnimann *et al.*, 2013). One such excipient is microcrystalline cellulose (MCC). Its proven flowability and compressibility in granulated form, together with its binding properties, (Thoorens *et al.*, 2014), are highly advantageous enabling manufacturing of tablets by direct compression. Furthermore, being cellulose, and thus of plant origin, its inert properties in-vivo make it an ideal material support. In MCC water can be absorbed into the inter-particle pore structure or diffuse into the cellulose inter-polymer space. The relative influence of these different physical liquid transport regimes can be adjusted by particle design, and this, together with the excellent surface wetting properties of MCC by water, opens a wide range of potential applications ranging from orally dispersible tablets to time controlled delivery when using MCC as an encapsulant (Bangudu and Pilpel, 1985; Baumgartnera *et al.*, 2000; Malamataris *et al.*, 1984; Thoorens *et al.*, 2014).

Since the tablet microstructure strongly impacts on the disintegration and dissolution performance, control thereof is a major quality control target in the pharmaceutical industry. In this study we track changes in pore structure of an MCC-based formulation with increasing tableting compression, and consider the role of API particles in the compaction process. We achieve this using two distinct analytical techniques, each taken to a level of analysis not normally applied in routine pore structure measurements. Due to the very different mechanical properties of MCC and a typical API, indomethacin, it is possible to differentiate between the materials in respect to their bulk material modulus. Using the technique of mercury intrusion porosimetry and, thereby, isolating the elastic compression under extremely high pressure of

the skeletal material defining the pore network structure. This structural response analysis, along with the pore size distribution determination offered by intrusion porosimetry, enables us to consider the comparative response in the terahertz (THz) region of the electromagnetic spectrum under irradiation of the formulated tablets. Using time of flight in transmission we can determine the frequency-dependent effective refractive index and the absorption coefficient. By utilising the effective refractive index obtained from terahertz time-domain measurements, the porosity can be calculated.

By combining the various analyses, porosity values can be compared derived from accessible pore mercury intrusion and by using a homogeneous model for the statistical effective refractive index average of the material components and air as well as a direct relative density determination. Thus, it is possible to evaluate the level of pore accessibility versus isolated non-accessible pores, and so ultimately be in a position to consider properties of liquid absorption volume and rate, vital for the design of oral dispersibility, for example.

The effective refractive index of the MCC pharmaceutical compacts used in this study has been interpreted with *a priori* known properties, including height, diameter, weight and porosity, as determined by varying the conditions of tablet formation and compression based on previous findings using multiple samples of such tablet constructs (Bawuah *et al.*, 2014). Porosity dependent elastic properties, such as the Young's modulus of elasticity, are related to the pore structure, and so, in principle, can be correlated for structurally similar tablets, i.e. when forming an homologous series to provide pore network scaling, and are, therefore, analysable using the effective refractive index of the porous tablets (Peiponen *et al.*, 2015). In the latter case it has thus been suggested that mechanical properties of porous media in general can, under the defined conditions above, be predicted by terahertz sensing (Peiponen *et al.*, 2015). Hence, this sensing method provides a non-destructive technique to gain information on the elasticity of porous media.

This paper studies the bulk modulus elastic compressibility of the skeletal material constituting the pore wall structure of the tablets using mercury porosimetry, adopting the elastic

compression correction methodology established by Gane *et al.* (Gane *et al.*, 1996). To this end, the pore volume and the specific pore volume, pore size analysis, together with the skeletal material bulk modulus, are studied as a function of API content and porosity. Individual tablets from previously analysed sets (Bawuah *et al.*, 2016a; Bawuah *et al.*, 2014; Peiponen *et al.*, 2015), plus tablets from two further sets, are newly characterised in this way. Terahertz effective refractive index values are presented, which in turn are used to calculate the porosity of the powder compacts. These links can in turn provide a means to monitor the tablet properties directly from THz measurement.

## 2. Materials and methods

Four flat-faced pharmaceutical tablet sets have been further studied following previous original analyses (Bawuah *et al.*, 2016a; Bawuah *et al.*, 2016b; Chakraborty *et al.*, 2016). Indomethacin (Hangzhou Dayangchem Co. Ltd., Hangzhou, China), in its crystalline gamma polymorph, was used as the API in the tablet sets. Indomethacin has a density of 1.3701 $gcm^{-3}$. The volume median particle size of indomethacin is typically 13 μm for the primary particles, though they can range to as fine as 2 μm, with a small number of agglomerates ~20 μm. Though not in this case, the material can be nano-milled in practice to provide improved efficacy (Thinky, USA, 2017 web link).

The tablets were compressed incorporating MCC as excipient (Avicell PH101, FMC BioPolymer, Philadelphia, USA). MCC has a true density of 1.5573 $gcm^{-3}$ and volume median particle size of 50 μm, according to the supplier's specification.

Given the ratio of particle size between the coarser MCC and the finer indomethacin, it can be envisaged that the packing void volume can be more easily decreased under compaction when mixed, although the absolute volume at a given total tablet density may be greater with indomethacin present per unit tablet weight due to the reduced density of the indomethacin compared with MCC.

The tablets were compacted with a compaction simulator (PuuMan, Kuopio, Finland) with controlled processing parameters, as described previously (Ervasti *et al.*, 2012), to produce sets of tablets with known compaction parameters. The tablets are labelled following the convention *n.m.x*,

where *n* = set number (1 - 4)

*m* = formulation of production condition (1 - 8)

*x* = tablet repeat production number ($\bar{x}$ indicating averaged data derived from *x* running from 1 to 5)

The bulk density ($\rho_b$) of each pharmaceutical tablet was calculated from its dimensions, i.e. height, *H*, diameter, *d*, and weight, *W*, as

$$\rho_b = \frac{W}{\pi\left(d/2\right)^2 H}. \quad (1)$$

The tablet dimensions were measured with a micrometer (Digitrix, NSK, Japan), and weighed using an analytical balance (Mettler Toledo AG245, Schwerzenbach, Switzerland). The porosity, *f*, of the tablets was first estimated from the bulk density and the weighted average of the true density of each constituent within the formulation (i.e. the true density of the tablet, $\rho_t$) as follows,

$$f = 1 - \frac{\rho_b}{\rho_t}. \quad (2)$$

The porosity was derived using data obtained from stable samples, after any time-dependent mechanical relaxation has occurred following tableting compression. Bulk volume, bulk density and specific pore volume are then derived from the tablet dimensions and the calculated porosity.

The specific API weight percentage, tablet dimensions, calculated porosity and bulk properties are given in Table 1. Sets $n$ = 1 and 2 are compressed with a constant API mass fraction of 10 wt%. Set $n$ = 1 is made with a decreasing porosity but maintaining the tablet sample height, achieved by increasing the sample weight and, hence, resulting sample density. The change in the porosity is from 0.46 down to 0.36, Table 1. Set $n$ = 2 tablets all have similar porosity values, 0.36, whereas the height (thickness) of the tablets is increased as the bulk volume increases proportionally to the tablet weight. The height of the tablets increases from 0.27 cm to 0.39 cm. In the case of set $n$ = 3, the nominal porosity of the tablets is held the same, namely 0.36, and the weight percentage portion (wt%) of API is changing from 0 to 15 wt%. Set $n$ = 4 also contains increasing amounts of API in respect to MCC excipient, the range, however, is smaller and lies in the middle region of that of set $n$ = 3. In the case of set $n$ = 4, both porosity, 0.28 - 0.50, and API concentration are variables.

**Table 1** Tablet physical properties [the specific samples listed are those additionally analysed using mercury porosimetry]. For each tablet set, errors in the calculations made for the nominal porosities are diameter ± 0.008 mm, height ± 0.005 mm (standard deviation of the sample mean), weight ± 0.01 mg (readability of the scale) and porosity ± 0.2 % (calculated using the error propagation law).

| Tablet identification | API $\varphi$ (x100) / wt% | Diameter $d$ / cm | Height $H$ / cm | Weight $W$ / g | Porosity *via density calculation* $f$ | Bulk volume $V_{bulk}$ / $cm^3$ | Pore volume $V_{pore}$ / $cm^3$ | Bulk density $\rho_b$ / $gcm^{-3}$ | Calculated specific pore volume $V_{pore\ calc}$ / $cm^3g^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1.1.3 | 10.0 | 1.3134 | 0.3024 | 0.3426 | 0.46 | 0.410 | 0.188 | 0.836 | 0.550 |
| 1.2.2 | 10.0 | 1.3122 | 0.3038 | 0.3566 | 0.44 | 0.411 | 0.181 | 0.868 | 0.507 |
| 1.3.2 | 10.0 | 1.3115 | 0.3026 | 0.3715 | 0.41 | 0.409 | 0.168 | 0.909 | 0.451 |
| 1.4.2 | 10.0 | 1.3098 | 0.3006 | 0.3852 | 0.38 | 0.405 | 0.154 | 0.951 | 0.400 |
| 1.5.2 | 10.0 | 1.3097 | 0.2986 | 0.3993 | 0.36 | 0.402 | 0.145 | 0.993 | 0.363 |
| 2.1.1 | 10.0 | 1.3084 | 0.2737 | 0.3617 | 0.36 | 0.368 | 0.132 | 0.978 | 0.368 |
| 2.2.1 | 10.0 | 1.3082 | 0.3343 | 0.4390 | 0.37 | 0.449 | 0.166 | 0.979 | 0.378 |
| 2.3.1 | 10.0 | 1.3071 | 0.3625 | 0.4767 | 0.36 | 0.486 | 0.175 | 0.987 | 0.365 |
| 2.4.1 | 10.0 | 1.3065 | 0.3927 | 0.5154 | 0.36 | 0.526 | 0.190 | 0.988 | 0.364 |
| 3.1.1 | 0.0 | 1.3104 | 0.3034 | 0.4113 | 0.36 | 0.409 | 0.147 | 1.003 | 0.359 |
| 3.2.1 | 3.8 | 1.3093 | 0.3032 | 0.4050 | 0.36 | 0.406 | 0.146 | 0.993 | 0.363 |
| 3.3.1 | 7.5 | 1.3107 | 0.3033 | 0.4038 | 0.36 | 0.408 | 0.147 | 0.988 | 0.364 |
| 3.4.1 | 8.8 | 1.3096 | 0.3000 | 0.4024 | 0.35 | 0.405 | 0.146 | 0.993 | 0.362 |
| 3.5.1 | 10.0 | 1.3095 | 0.3025 | 0.4007 | 0.36 | 0.406 | 0.146 | 0.987 | 0.365 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 3.6.1 | 11.3 | 1.3094 | 0.3030 | 0.3999 | 0.36 | 0.409 | 0.147 | 0.979 | 0.368 |
| 3.7.1 | 12.5 | 1.3104 | 0.3045 | 0.3999 | 0.37 | 0.409 | 0.147 | 0.978 | 0.368 |
| 3.8.1 | 15.0 | 1.3121 | 0.3062 | 0.4016 | 0.37 | 0.410 | 0.148 | 0.976 | 0.369 |
| 4.1.2 | 9.0 | 1.3084 | 0.2745 | 0.40633 | 0.29 | 0.369 | 0.107 | 1.101 | 0.263 |
| 4.2.1 | 9.5 | 1.3093 | 0.2971 | 0.40423 | 0.34 | 0.400 | 0.136 | 1.011 | 0.336 |
| 4.3.1 | 10.0 | 1.3094 | 0.3273 | 0.40567 | 0.40 | 0.441 | 0.176 | 0.920 | 0.435 |
| 4.4.1 | 10.5 | 1.3075 | 0.3642 | 0.40364 | 0.46 | 0.489 | 0.225 | 0.825 | 0.557 |
| 4.5.1 | 11.0 | 1.3076 | 0.3955 | 0.40402 | 0.50 | 0.531 | 0.266 | 0.761 | 0.657 |

### *2.1 Terahertz time-domain spectropscopy*

Terahertz time domain spectroscopy (THz-TDS) (Li *et al.*, 2010; Parrott *et al.*, 2009) was employed to study the porosity of the powder compacts. Since pharmaceutical tablets are porous media, their effective (bulk) refractive index ($n_{\text{eff}}$) is governed by porosity ($f$), especially for tablets with uniform density distribution of the solid phase. The porosity dependent effective refractive index, $n_{\text{eff}}(f)$, is given as,

$$n_{\text{eff}}(f) = \frac{c\Delta t}{H} + 1 \,, \tag{3}$$

where $H$ is the height of the tablet and $c$ is the speed of light in vacuum. The terahertz pulse delay ($\Delta t$), which is obtained from the difference between the measured time-of-flight of a terahertz pulse after transmission through a reference and that of a sample, is used in Eq. (3). The different optical path length taken by the terahertz pulse traversing the reference (i.e., no specimen present in the transmission chamber) and sample (i.e., tablet) causes the relative delay. Due to the significant absorption of terahertz illumination by water vapour (Exter *et al.*, 1989), the sample compartment of the THz-TDS was purged with nitrogen during the reference and sample measurement.

The porosity, $f_{\text{THz}}$, can be derived also from the effective terahertz refractive index, $n_{\text{eff}}$, by knowing the mass fraction composition in respect to API and MCC, $\varphi$, and their respective

intrinsic refractive indices, $n_{MCC}$ and $n_{API}$, as derived from the zero porosity approximation, such that

$$f_{\mathrm{THz}} = \frac{n_{\mathrm{MCC}} - (n_{\mathrm{MCC}} - n_{\mathrm{API}})\varphi - n_{\mathrm{eff}}}{(n_{\mathrm{MCC}} - 1)} \quad (4)$$

More details about this relation of effective refractive index to porosity and intrinsic refractive indices of the components are given in Bawuah *et al.* (Bawuah *et al.*, 2016b).

### *2.2 Mercury porosimetry*

Mercury intrusion measurements were made using an Autopore V mercury porosimeter (Micromeritics Instrument Corporation, Norcross, GA, U.S.A.). The maximum applied pressure of mercury was 414 MPa, equivalent to a Laplace throat diameter of 4 nm. The equilibration time at each of the increasing applied pressures of mercury is set to 20 s. The tablets were measured as supplied.

By observing the behaviour under intrusion and extrusion at the highest pressures, it is possible to ascertain whether the sample displays the typical pore retention hysteresis or whether mercury is extruded at equal volumes to that during intrusion as a function of pressure. If the latter occurs, then it can be concluded that the skeletal material is being elastically compressed and the gradient of the elastic response to pressure provides a measure of the elastic bulk modulus of the skeletal material, i.e. the material bulk modulus of the pore wall when compressed equally from all directions. If the extrusion, however, exceeds the intrusion then the skeletal material is partially undergoing strong plastic deformation. The plastic deformation, however, is generally impossible to quantify as it is concurrent with the usual mercury retention hysteresis due to necking and filament snapping, and “ink bottle” shaped pore behaviour.

The bulk modulus of an homogeneous solid sample, $M_{ss}$, is derived from the inverse of its elastic compressibility, $C_{ss}$, which, in turn, is given by the rate of change of material volume, $V_{ss}$, as a function of pressure, $P$, per unit sample volume,

$$C_{ss} = \frac{1}{M_{ss}} = -\frac{1}{V_{ss}} \frac{dV_{ss}}{dP} \tag{5}$$

For the case of an incompressible sample, in the limit $C_{ss} = 0$ and the bulk modulus becomes infinite.

As mercury intrudes the pore volume of the tablet under pressure it eventually surrounds the solid phase making up the tablet skeletal structure at the point where all the accessible pores are filled with mercury, which, for a highly connected pore network such as a pharmaceutical tablet, can be assumed to a first approximation to be the case of complete pore filling. Beyond this point, corresponding to a pressure $P_{\text{pores filled}}$, as the intrusion pressure increases further, if the solid material is compressible, any further increase in mercury intruded volume is then related purely to the decrease in volume of the solid by compression. Thus, integrating Eq. (5) gives an expression for the volume change experienced by the skeletal material under compression, and, hence, the extra volume of mercury occupying this material volume change, $-\delta V_{\text{ss compression}}$

$$\int_{P_{\text{pores filled}}}^{P} dP = -M_{ss} \int_{V_{\text{ss pores filled}}}^{V_{\text{ss compressed}}} \frac{dV_{ss}}{V_{ss}}$$

$$\Rightarrow P_{\text{compression}} = P - P_{\text{pores filled}} = -M_{ss} \ln \frac{V_{\text{ss compressed}}}{V_{\text{ss pores filled}}}$$

$$\Rightarrow \frac{V_{\text{ss compressed}}}{V_{\text{ss pores filled}}} = \exp\left[\frac{-\left(P - P_{\text{pores filled}}\right)}{M_{ss}}\right]$$

$$\Rightarrow \delta V_{\text{ss compression}} = V_{\text{ss pores filled}} - V_{\text{ss compression}} = V_{\text{ss pores filled}}\left(1 - \exp\left[\frac{P_{\text{pores filled}} - P}{M_{ss}}\right]\right)$$

(6)

where $V_{ss\ compressed}$ is the solid material volume at the end of the compression experiment and $V_{ss\ pores\ filled}$ is the solid material volume at the start of the compression experiment when all the pores are filled. Eq. (6) is directly applied to the experimental intrusion data region where the mercury intrusion and subsequent extrusion lie coincident at high pressure, showing that the material behaviour is purely elastic. This, then, provides the measure for $M_{ss}$.

It is also convenient to use the skeletal material compressibility in terms of the extra mercury taken up by the compression, $\delta V_{ss\ compression}$, as a further correction for the intruded volume in addition to the generally used expressions describing the various corrections applied regularly in mercury porosimetry, i.e. including penetrometer vessel expansion as the mercury intrusion pressure increases ($\delta V_{blank}$) and the compression of mercury itself, the descriptions for which are given in detail by Gane *et al*. 1996. To do this, a further assumption is required in that the volume compressibility of the solid material is assumed constant over the whole pressure range, which for non-plastic materials can be considered reasonable. Furthermore, any source of error in this assumption is minimal at lower pressure due to the exponential term describing the response to pressure change (Eq. (6)), which shows its effect most strongly at the highest pressures, so that the solid material can be compressible throughout the intrusion process starting from its volume at atmospheric pressure, $V^1_{ss}$,

$$V^1_{ss} = V^1_{bulk}(1-f) \tag{7}$$

where $V^1_{bulk}$ is the known starting volume of the sample of known porosity, $f$, to give the whole intrusion correction expression shown in Gane *et al*. 1996, such that the true intruded volume into the pore structure, $V_{int}$, is given as

$$V_{int} = V_{obs} - \delta V_{blank} + \left[0.175 V^1_{bulk} \log_{10}(1 + P/1820)\right] - V^1_{bulk}\left(1 - \exp\left[\frac{P^1 - P}{M_{ss}}\right]\right) \tag{8}$$

measured intrusion volume, penetrometer expansion, compression of mercury, skeletal compression

This combination of elastic compression with the porosimetric corrections is performed by the authors using the software Pore-Comp (a software program developed by and obtainable from the Environmental and Fluids Modelling Group, University of Plymouth, U.K.).

### *2.3 Environmental conditions*

The measurements made for THz time of flight, on the one hand as stated earlier, were made under conditions of dry nitrogen purging. In the mercury porosimetric analysis, the samples are first evacuated, and so, similarly to the THz measurement, a moisture free environment can be assumed. We recognise that the humidity condition might otherwise be important in respect to the behaviour of the MCC, which is to an extent hygroscopic. The physical dimensional analysis, was, on the other hand, made under ambient conditions, and so moisture might well be present in the tablet. However, the excellent correlation between the three methods of determining porosity suggest that moisture at the ambient conditions considered did not lead to any observable systematic structural change.

## 3. Results and discussion

### *3.1 Terahertz time-domain spectroscopy*

The effective refractive indices of the tablets from THz-TDS (see Eq. (3)), are given in Table 2. The effective refractive index was determined for every single tablet (in total 110 tablets). By combining the effective refractive index with the respective known porosity (calculated via density) for every single tablet it was possible estimate the intrinsic refractive indices of MCC ($n_{MCC}$ = 1.86) and of the API ($n_{API}$ = 1.73). The refractive index of MCC, $n_{MCC}$, found in this current work is almost the same as that derived earlier by Bawuah *et al*. (Bawuah *et al.*, 2016b),

but the refractive index of the API is different. Bawuah *et al*. used tablet set 3 to estimate $n_{API}$, whereas the current authors used all sets 1-4 to get a greater range of precise porosity, and, therefore, a more generalised value. We can, however, confirm that when using the same limited data set as Bawuah *et al*. the earlier found value can be fully replicated.

Figure 1 shows the porosity calculated from the terahertz measurement in comparison to the porosity via density calculation. Even though there are minor deviations between these two porosities for set $n$ = 3, the overall correlation ($R^2 \approx 1$) is very strong.

**Table 2** Average tablet porosity and effective refractive index. The average porosity $f_a$, (found from the values for $f$ calculated via density), and the average effective refractive index values, $n_{eff}$, were calculated from five tablets belonging to each tablet set number, $n.m$.

| | **Tablet set number, *n*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | |
| Formulation of production condition $m$ | average porosity *via density calculation* $f_a$ | average effective refractive index $n_{eff}$ | average porosity *via density calculation* $f_a$ | average effective refractive index $n_{eff}$ | average porosity *via density calculation* $f_a$ | average effective refractive index $n_{eff}$ | average porosity *via density calculation* $f_a$ | average effective refractive index $n_{eff}$ |
| 1 | 0.46 | 1.444 | 0.36 | 1.529 | 0.36 | 1.543 | 0.28 | 1.602 |
| 2 | 0.43 | 1.464 | 0.36 | 1.533 | 0.36 | 1.537 | 0.34 | 1.551 |
| 3 | 0.41 | 1.484 | 0.36 | 1.536 | 0.36 | 1.527 | 0.40 | 1.498 |
| 4 | 0.38 | 1.506 | 0.36 | 1.535 | 0.36 | 1.529 | 0.47 | 1.441 |
| 5 | 0.36 | 1.527 | | | 0.36 | 1.526 | 0.50 | 1.405 |
| 6 | | | | | 0.36 | 1.524 | | |
| 7 | | | | | 0.36 | 1.522 | | |
| 8 | | | | | 0.36 | 1.521 | | |

### *3.2 Mercury porosimetry*

The mercury porosimetry measurement is destructive to the tablet and so we show here one measurement per set, and not an average of five measurements as has been the case for the

non-destructive porosity and effective refractive index values. The existence of a correlation, however, across a wide parameter spread may be considered sufficient to identify outliers despite the limitation to single sample measurement in porosimetry, and so irreproducibility can be identifiable in a case where the correlation breaks down. The question of reproducibility in respect to the bulk modulus finding must be differently considered, in respect to whether it might be dependent on statistical sample size. Given that the mercury intrusion reaches a point of complete pore filling prior to the measurement analysis of elastic bulk modulus, the question centres on the reproducibility of the high pressure intrusion and subsequent extrusion data. The sample skeleton is elastically compressible if and only if the intrusion is coincident with the extrusion, and so this, by definition, is fully reversible and can be run back and forth in pressure many times. Thus, for a given sample, the measurement of bulk modulus is highly reproducible, unlike that of the pore structure at lower pressure which cannot be reproduced due to the one time intrusion and hysteresis of extrusion. Thus, pore structure will likely vary across samples, but provided the consistency of mix formulation quantities is assumed constant – always questionable in powder mixing of course – then the bulk modulus of the skeleton should report constant provided all pores are duly filled.

All the data for the mercury intrusion curves for the tablet samples have been corrected using Pore-Comp for mercury and penetrometer effects and also where applicable for obtaining the bulk modulus from the sample elastic skeletal compression (Gane *et al.*, 1996), as described in Materials and Methods.

For all tablets the mercury started to penetrate into the tablets initially at 0.14 MPa (20 μm). To aid comparison across the samples, the data have, therefore, been zeroed at this initial intrusion measurement point.

The cumulative intrusion curves for set $n$ = 1, Figure 2a), show a decreasing specific pore volume for the samples, as would be expected due to the increased compaction. The samples

show no or negligible elastic skeletal compression under the highest pressures, and so we conclude that the compression is either fully plastic and/or that the elastic bulk modulus is immeasurably high. As we shall see in sets $n$ = 3 and $n$ = 4, it is more likely that when the elastic compression cannot be identified, it is swamped by the plastic deformation of the MCC excipient. This plastic behaviour may, for example, be related to the moisture history of the MCC.

The peak of the set $n$ = 1 samples in Figure 2b) decreases as the porosity of the samples decreases and, in relation, the bulk density of the samples increases. The peak diameter decreases progressively from 6.2 µm to 5.0 µm, 4.4 µm, 3.9 µm and finally to 3.5 µm. There is a secondary step in the pore size distribution curves to the left of the main peak at ~1.3 µm.

The cumulative pore volume curves for set $n$ = 2 in Figure 3a) display only a slight difference in the total pore volume for the four samples measured. This shows there is some variation in the tablets made but that the target of constant porosity has generally been reproducibly met. The samples, as for set $n$ = 1, show no or negligible elastic skeletal compression under the highest pressures.

The pore size distribution peaks for the set $n$ = 2 samples, Figure 3b), lie all at the same pore diameter of 3.9 µm. The samples have a secondary step to the left of the peak at ~1.3 µm as was also seen for set $n$ = 1.

The cumulative intrusion curves for set $n$ = 3 are shown in Figure 4a). Samples 3.3.1, 3.6.1, 3.7.1 and 3.8.1 have all been corrected for elastic skeletal compression. With the exception of 3.3.1, these are the samples with the higher loadings of API, and so we may conclude that the API shows some measurable elastic compressibility. Figure 4a) shows samples 3.8.1 with 15 % API have the lowest specific total pore volumes. Samples 3.2.1 and 3.5.1 have the highest total specific pore volumes. The samples do not follow any specific ordered trend between

these values. It is noted that the calculated specific pore volume appears to be targeted to a more or less constant value, and, if so, this would explain the “randomised” small variation in intrusion volume data.

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The set *n* = 3 samples all have one main peak in their pore size distributions at a pore diameter of 4.0 μm, Figure 4b). The peak is highest for sample 3.1.1 with no added API and sample 3.2.1 with the lowest addition of API. As the amount of API is increased, the height of the peak at this diameter decreases and a trend is clear, with the exception of sample 3.4.1 which has
380 the lowest peak.

There is an area where differences can be seen to be occurring in the pore structure as the API loading amount is increased over the pore diameter range 0.9 - 2.5 μm, Figure 4c). We see, therefore, that following the sample trend in Fig. 4c) there is a distinctly more compact
385 packing as the API amount increases. Considering the particle size of the API (~13 μm) we can conclude that the combination with the MCC (~50 μm) leads to a tighter structure packing. Also, the API itself resists deformation due to its rigidity, whereas the MCC is likely to compact tightly around it as the tablet porosity is reduced under tablet compression during forming.

390 The cumulative intrusion curves for set *n* = 4 are shown in Figure 5a). Sample 4.1.2 has the lowest total specific pore volume. Sample 4.5.1 has the highest total specific pore volume. All 5 measurements for this set *n* = 4, once again, have all been corrected for elastic skeletal compression.

395 The samples 4.*m*.*x* all have one main peak in their pore size distributions, Figure 5b). The diameter at which this peak falls is largest for sample 4.5.1 at 7.8 μm. The peak for this sample is also the highest among the tested samples in this series. This corresponds with the highest specific pore volume seen for this sample in Figure 5a). The peaks reduce in height and pore diameter through the sample set *n* = 4: 4.4.1, 4.3.1, 4.2.1, and 4.1.2, and this corresponds with

the experimentally designed trend order for the total specific pore volume values seen in Figure 5a). These samples, like all the previous samples, have a slight bump to the left of the main peak. We can only speculate as to the meaning of this small mercury intrusion volume, but it might relate to API intra agglomerate pore volume.

The total cumulative intrusion, bulk moduli and tablet porous properties, as determined from the porosimetry measurement, are summarised in for all the tablet sets Table S1 (supporting information).

## 4. Discussion

This is a unique study in the sense that porosity is detected both by Hg porosimetry and THz detection. Furthermore, we consider this to be the first study that is devoted to skeletal bulk modulus in the frame of THz. Therefore, the importance of the porosity comparisons is that we can show that the physically dimension-determined porosity and mercury intrusion porosity are comparable, and thus extending the analysis to new structure parameters, such as skeletal bulk modulus and pore size distribution, can be considered reliable.

Excellent correlation ($R^2$ = 0.91) is indeed seen when comparing the porosity values between those of mercury intrusion, $f_{mp}$, and those from direct physical parameter calculation, $f$, and THz determination, $f_{THZ}$, respectively (Figures 6a) and 6b)). The intercept of the fits on the $y$-axis is at -0.014 for the physical porosity comparison and at -0.012 for the THz porosity comparison, respectively, which can be interpreted as 1.2 % of the total pore space is either not accessible using mercury porosimetry or, more likely, the choice of the true initial intrusion point was subject to a small systematic error, which could be related to an earlier intrusion start or more plausibly a slight compression of the compact before actual intrusion occurred.

Even more so, the porosity comparison is highly valuable in the light of the fact that we can conclude that the connectivity of the pore network structure in the tablet is very high, i.e. all pores are found to be accessible by the mercury intrusion method due to the good coincidence with the porosity found from the physical dimensions and density calculation. This is an important finding in two ways: (i) it shows that the permeability of the tablet is high, which is a vital factor for disintegration and dissolution, as well (ii) it proves that, due to the coincidence with the THz porosity, any derivation of structural arrangement arising separately from each of the two methods must *per force* show agreement. This latter information will prove critical in any future structure modelling work.

The skeletal material elastic bulk modulus values are shown graphically in Figure 7, in which the experimental design for each series of tablets manufactured is explained schematically. The skeletal bulk modulus values show that set $n$ = 1 and set $n$ = 2 display no discernible elastic compression for the skeletal material of the tablets. With the exception of sample 3.3.1, the first 5 samples of set $n$ = 3 also show no elastic compression. As the amount of API content increases, or relative MCC content decreases, at the higher API loadings, elastic compressibility starts to be seen. Set $n$ = 4 shows an overall increasing trend of bulk modulus with an increasing amount of API (not including the two previously excluded tablet samples).

The bulk modulus of the sets 3 and 4 depends on the API concentration as well as the porosity of the powder compact, as illustrated in Figure 8. The dependence of the bulk modulus on the API concentration can be clearly seen in Figure 8b), whereas the contribution of the porosity is not apparent as, in set 4, both variables were varied simultaneously. MCC is well known to exhibit plastic deformation during compaction, and so we may conclude that the skeletal elastic bulk modulus is thus strongly affected by the API particles. However, in order to evaluate the impact of porosity on the bulk modulus, we compare the changes in $M_{SS}$ between the minimum and maximum concentrations. To compare these variations relative to their concentration

ranges, we normalised the change in $M_{SS}$ by their respective concentration range. The relative change is significantly (6 times) larger for set 4 than for set 3, indicating a strong contribution to the porosity in relation to the $M_{SS}$. Therefore, increasing porosity as well as increasing API concentration causes an increasing bulk modulus. Since porosity *per se* is not a controlling parameter of the physical nature of the skeletal component materials, this finding can only be interpreted in the light of the positional relationship between API and MCC. The plastic deformability of the MCC could allow API to become embedded within the MCC matrix under the highest tablet compaction pressures. In essence this leads to a strengthening of the MCC and essentially a masking of the hardness of the API, which can only be fully manifest by a discrete separate packing between the API and the MCC without any structural embedment of the API in the excipient.

A similar effect of the porosity on the bulk modulus was discussed by Adolfsson and Nyström for different materials (Adolfsson and Nyström, 1996). Adolfsson and Nyström studied the tensile strength and elasticity depending on the porosity for different pharmaceutical materials. They observed that an increase in compaction load increases the elastic deformation of the particles, which is in line with the results of this study, i.e., increasing porosity (i.e., decreasing compaction load) causes an increasing bulk modulus (i.e., decreasing elasticity). In general, structural changes of a powder compact affect the bonding mechanisms as well as the effective bonding surface area, which further strongly impact the mechanical properties, such as tensile strength, of the tablet (Nyström *et al.*, 1993).

A major question, which, within the scope of this analysis cannot be answered directly, is the degree of likely uniformity/homogeneity of the tablets. However, we consider that many of these characteristics are indeed answered in a novel way indirectly using the analytical methods applied in this work. For example, the content uniformity, although not directly mapped by, for example, spectroscopy, and thus not describable as homogeneous versus heterogeneous and/or non-uniform, it is very well described in respect to construct uniformity

of pore size distribution and pore structure reproducibility (good and poor are demonstrated according to the differing series) within the various tablet sets. Thus, the claim is merely that the techniques could identify changes in structure, not absolute confirmation of original homogeneity, and this was the target of the exercise here.

Similarly, tensile strength will be greatly determined not only by structure but also constituent formulation as well as its consistency. Therefore, it would be impossible using the data in this work to separate out these parameters sufficiently reliably to make any comment with confidence on the further role of the changes seen with any regard to tensile strength. We also draw attention to the unknown nature of the structure, where it would be necessary to stress that the interaction of materials and their respective arrangement both contribute compositely to tensile strength, as well as the mechanical properties of the single components. Therefore, a measure of constituent bulk modulus alone, which is the topic here, is certainly insufficient to link singly with tensile strength.

## 5. Conclusions

Mercury porosimetry measurements were performed on 4 differing sets ($n$ = 1 - 4) of MCC/API tablets to attain their porosity and elastic bulk moduli. The porosity values from mercury porosimetery, terahertz measurements and from density calculations were compared to each other revealing a very high correlation between the terahertz measurements and the calculated porosity. The correlations with the porosity from mercury porosimetry is weaker, but still very high. However, porosimetry provides much more details about the pore structure, which cannot be assessed by terahertz.

One of the major quality control factors for pharmaceutical tableting is the ability to determine structure consistency. However, this is a challenge since many factors control the pore structure including material changes and production changes. The strong correlation of the

elastic bulk modulus of the tablet solid skeleton with the mix state of excipient and API content, according to overall compaction level, provides a novel means of controlling these two factors. The structural impact of API content in this case could also be tracked separately at constant porosity following the elastic bulk modulus of the tablet skeletal material determined using mercury intrusion porosimetry.

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## Supporting Information

**Table S1** Porosimetric analysis: porosity, bulk volume, pore volume, bulk density, total specific pore volume and skeletal elastic bulk modulus ("-" reports no distinguishable elastic behaviour) of the complete tablet samples. The specific pore volume in Table 1 derived from the physical dimensions of the tablets is shown for comparison.

| | Mercury porosimetry | | | | | | |
|---|---|---|---|---|---|---|---|
| **Tablet identification** | **Porosity** | **Bulk volume** | **Pore volume** | **Bulk density** | **Total specific pore volume** | **Skeletal *elastic* bulk modulus** | ***Calculated specific pore volume from Table 1*** |
| ***n.m.x*** | $f_{mp}$ | $V_{bulk}$ | $V_{pore}$ | $\rho_b$ | $V_{pore\ total}$ | ***M*ss** | $V_{pore\ calc}$ |
| | | **/ $cm^3$** | **/ $cm^3$** | **/ $gcm^{-3}$** | **/ $cm^3g^{-1}$** | **/ MPa** | **/ $cm^3g^{-1}$** |
| 1.1.3 | 0.454 | 0.398 | 0.179 | 0.850 | 0.529 | - | **0.550** |
| 1.2.2 | 0.453 | 0.396 | 0.177 | 0.888 | 0.505 | - | 0.507 |
| 1.3.2 | 0.430 | 0.397 | 0.169 | 0.923 | 0.460 | - | 0.451 |
| 1.4.2 | 0.391 | 0.396 | 0.153 | 0.961 | 0.402 | - | 0.400 |
| 1.5.2 | 0.322 | 0.469 | 0.149 | 0.841 | 0.377 | - | 0.363 |
| 2.1.1 | 0.376 | 0.348 | 0.129 | 1.016 | 0.365 | - | 0.368 |
| 2.2.1 | 0.382 | 0.431 | 0.162 | 0.999 | 0.377 | - | 0.378 |
| 2.3.1 | 0.379 | 0.465 | 0.174 | 1.005 | 0.372 | - | 0.365 |
| 2.4.1 | 0.363 | 0.510 | 0.183 | 0.991 | 0.361 | - | 0.364 |
| 3.1.1 | 0.360 | 0.423 | 0.152 | 0.952 | 0.378 | - | 0.359 |
| 3.2.1 | 0.371 | 0.417 | 0.155 | 0.949 | 0.391 | - | 0.363 |
| 3.3.1 | 0.366 | 0.402 | 0.147 | 0.991 | 0.370 | 15 047 | 0.364 |
| 3.4.1 | 0.370 | 0.405 | 0.150 | 0.983 | 0.376 | - | 0.362 |
| 3.5.1 | 0.371 | 0.426 | 0.158 | 0.931 | 0.399 | - | 0.365 |
| 3.6.1 | 0.366 | 0.410 | 0.150 | 0.966 | 0.379 | 16 000 | 0.368 |
| 3.7.1 | 0.367 | 0.405 | 0.149 | 0.975 | 0.376 | 16 729 | 0.368 |
| 3.8.1 | 0.347 | 0.413 | 0.143 | 0.953 | 0.364 | 16 322 | 0.369 |
| 4.1.2 | 0.265 | 0.380 | 0.101 | 1.047 | 0.253 | 15 125 | 0.263 |
| 4.2.1 | 0.345 | 0.379 | 0.131 | 1.044 | 0.330 | 15 373 | 0.336 |
| 4.3.1 | 0.392 | 0.419 | 0.164 | 0.947 | 0.414 | 15 157 | 0.435 |
| 4.4.1 | 0.472 | 0.467 | 0.220 | 0.846 | 0.558 | 15 954 | 0.557 |
| 4.5.1 | 0.496 | 0.509 | 0.252 | 0.779 | 0.637 | 17 325 | 0.657 |