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The Gurnham equation in characterizing the compressibility of pharmaceutical materials

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Abstract

Limitations of the Heckel equation in characterizing material compression behavior have been well reported. In this work, the Gurnham equation, which was first introduced in chemical engineering, is proposed as an alternate method of evaluating the compressibility of pharmaceutical powders. The Gurnham equation was adapted for tablet compression and the estimated slope parameter c was proposed to represent material compressibility. Data from the compression of four commonly used excipients (microcrystalline cellulose, corn starch, lactose monohydrate, and dibasic calcium phosphate dihydrate) and one drug (acetaminophen) were evaluated using the Gurnham equation. Using compression data at different peak pressures, linear relationships between porosity and ln Pressure of the five materials were obtained. The determined parameter c expresses the compressibility of materials. The analysis of previous experimental data, including granulations, mixtures and co-processed materials also indicates that c might be a representative parameter for material compressibility.
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1. Introduction

The compaction behavior of pharmaceutical powders has been shown to significantly influence the quality and commercial viability of a tablet formulation. Two of its important indices are compressibility (the ability of the material to undergo volume reduction under pressure) and compactibility (the ability of a material to yield a compact with adequate strength) (Celik, 1992). Compressibility reveals basic information about the compression process, which is fundamental for the understanding of compactibility.

The compressibility parameter of pharmaceutical powders is usually determined from the relationship between applied pressure and compact volume. As stated in a review article (Celik, 1992), various equations such as Walker and Bal'shin, Kawakita, Heckel and Cooper and Eaton have been developed to describe this relationship. However, it has proved difficult to find one relatively simple parameter from these equations that can differentiate the compressibility among different materials and be consistent under different experimental conditions.

This is no surprise because pharmaceutical powder compression is a complex process. It consists of several overlapping stages such as particle rearrangement, elastic/plastic deformation, and fragmentation during the process. Parameters derived from compression data obtained using different types of tablet machines often vary. At the same time, all pharmaceutical powders display different behaviors. Brittle materials such as dibasic calcium phosphate dihydrate, acetaminophen and lactose, compress mainly by fragmentation (Rowe and Roberts, 1996). Ductile materials such as microcrystalline cellulose and starch compress mainly by plastic deformation (Rowe and Roberts, 1996). It is well known that fragmentation and plastic deformation occur with all materials and it is the extent of the two processes taking place during compression that determines the volume reduction mechanism of a given material.

By far the most commonly used equation in the field of tablet manufacture is the Heckel equation (Heckel, 1961a,b). The constant, mean yield pressure, derived from the Heckel equation has been used to describe the plastic deformation ability of materials.

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Although the mean yield pressure has been widely used in the field, limitations of the Heckel equation have been well reported. Sonnergaard (1999) suggested that there is no evidence of a correlation between the mean yield pressure and the plasticity of a substance. There are groups that could not define the linear region on their Heckel plots (Rue and Rees, 1978; Celik and Marshall, 1989), which prevented them from determining any mean yield pressures of their materials. Large variations have been found among the reported mean yield pressures for a given material (Sonnergaard, 1999) as well as in calculated Heckel constants under different compression conditions. Because of these drawbacks, the use of the Heckel constant in describing complex tableting materials, such as granulations and mixtures is also limited. A new approach is needed that can provide more reliable and reproducible characterization of material compressibility during pharmaceutical powder compaction. In this work, we have evaluated the Gurnham equation as a means of characterizing the compressibility of pharmaceutical powders.

The Gurnham equation was first introduced in chemical engineering and has not previously been studied in pharmaceutical tableting. Gurnham and Masson introduced an equation to describe the expression of liquids from fibrous materials (Gurnham and Masson, 1946). They proposed that any increase in pressure, expressed as a fractional increase over the existing pressure, results in a proportional increase in the apparent density of the mass

$$\frac{\mathrm{d}P}{P} = A\,\mathrm{d}D \tag{1}$$

Where P is pressure, D is apparent density based on solid weight and total volume, and A is a constant.

By integration, Eq. (1) gives

$$D = a\ln(P) + b \tag{2}$$

Where a and b are constants.

Dry and wetted fibrous materials (soaked with water or oil) including cotton, wool, paper pulp, felt, sawdust, asbestos, sugar cane, and bagasse were studied. Linear relationships between apparent density and ln P were obtained for both dry and wetted materials except for a few cases.

The volume reduction of dry fibrous material (particle slipping, deformation and disintegration) described in Gurnham and Masson's study may be considered similar to the events during tablet compression. Porosity is a commonly used parameter in powder compaction to describe the volume reduction process

$$\varepsilon = 1 - \left(\frac{D}{D_{\mathrm{true}}}\right) \tag{3}$$

Where ε is porosity, D_{true} is true density. Pycnometric density is used as the measure of true density in this work.

Replacing density with porosity in Eq. (2) yields:

$$\varepsilon = -c\ln(P) + d \tag{4}$$

Where c and d are constants. Eq. (4) describes a linear relationship between ln P and porosity for powder compression. When considering Eq. (4) in its differential form,

$$\mathrm{d}\varepsilon = \frac{-c\,\mathrm{d}P}{P} \tag{5}$$

The constant c expresses the effect of a change in pressure on compact porosity. A large value of c indicates a strong volume reduction ability of the material under compression.

The objective of this work is to verify whether the linear relationship described by Eq. (4) applies for pharmaceutical powders and if the constant c, thus determined, represents an appropriate compressibility parameter for pharmaceutical powders.

2. Materials and methods

2.1. Materials

The following five materials were used as received: acetaminophen USP (AC), 60% particles >38 μm, (Mallinckrodt Inc., St. Louis, MO, USA), microcrystalline cellulose NF-Avicel PH 102® (MCC), average particle size 90 μm, (FMC Corporation, Philadelphia, PA, USA), corn starch NF (CS), average particle size 50 μm, (Stanley Pharmaceutical, North Vancouver, BC), lactose monohydrate NF (LA), average particle size 100 μm (Kraft Inc., Norwich, NY, USA) and dibasic calcium phosphate dihydrate USP-Emcompress® (EM), average particle size 100 μM, (Edward Mendell, Patterson, NY, USA). True densities of AC, MCC, CS, LA and EM determined by a pycnometric method were 1.297, 1.549, 1.480, 1.538 and 2.353 g cm^{-3}, respectively.

2.2. Methods

Tablets were compressed using an instrumented Manesty Betapress (Manesty Machines Ltd., Liverpool, England). Details of press instrumentation, data acquisition and data analysis have been published previously. (Oates and Mitchell, 1989, 1990; Dwivedi et al., 1992) The press was fitted with 1.270 cm diameter round flat-faced TSM tooling (Thomas Engineering, Hoffman Estates, IL) at one station while the others were blanked off. The tablets were compressed at a fixed thickness setting with a press speed of 60 rpm. Different peak pressures were achieved by adjusting the amount of powder filled into the die cavity. A 5% solution of stearic acid in chloroform was applied before compaction to lubricate the die wall (and punch faces for acetaminophen). To observe trends in the data, individual series of approximately 20 tablets of each material were compacted at different peak pressures of up to 200 MPa. To determine the linear regression parameters, approximately 10 replicates of each material were compacted at four peak pressures: 50, 100, 150 and 200 MPa.

The porosity of the compacts was calculated using in-die measurements. Tablet thickness was calculated from punch displacement, which was determined indirectly from the measurements of punch force and its relationship to turret position during the compaction process. Deformation of the tooling and the press was taken into consideration when computing the punch displacement. The method of calculation was verified by direct

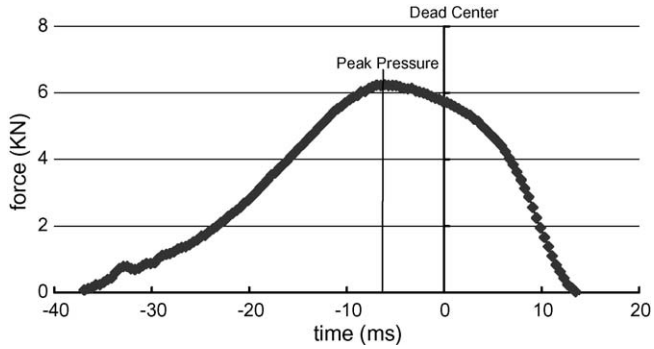

Fig. 1. A representative force–time curve for microcrystalline cellulose (MCC) at a peak pressure of 50 MPa.

measurements using a linear variable displacement transducer (LVDT) along with a series of slip rings mounted on the turret to transmit signals from the LVDT to the computer (Oates and Mitchell, 1990).

Force and time data were collected during the compaction process. A representative compaction profile for microcrystalline cellulose is given in Fig. 1. Linear regression analysis was performed to determine the slope parameter in Eq. (4) for each material.

3. Results and discussion

3.1. Non-linear powder densification relationship between porosity and pressure

Porosity versus pressure relationships for the five pharmaceutical powders are shown in Fig. 2. These non-linear relationships between in-die porosity and peak pressure seem to correspond with the exponential relationships predicted by Eq. (5). As shown in Fig. 2, for a material under compression, the amount of further densification to be achieved depends on how much more pressure is to be applied as well as its current pressure. For the same material, to achieve the same amount of porosity change, a larger amount of pressure increase would be required for compacts under higher pressures. The plots of the five materials in this study seemed to fall into two groups. The plots of

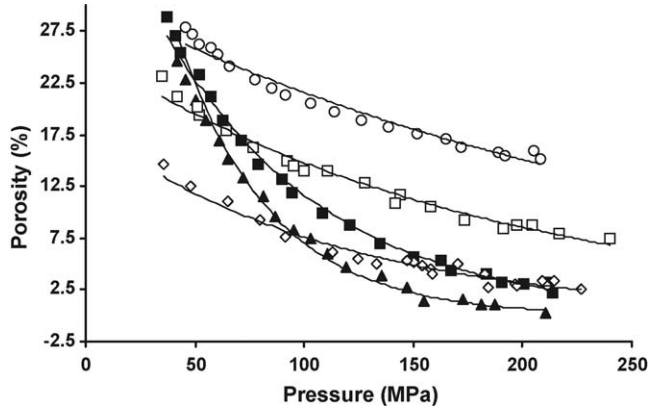

Fig. 2. Porosity vs. peak pressure for (■) microcrystalline cellulose, (▲) corn starch, (◯) emcompress, (□) lactose, and (◊) acetaminophen using series data.

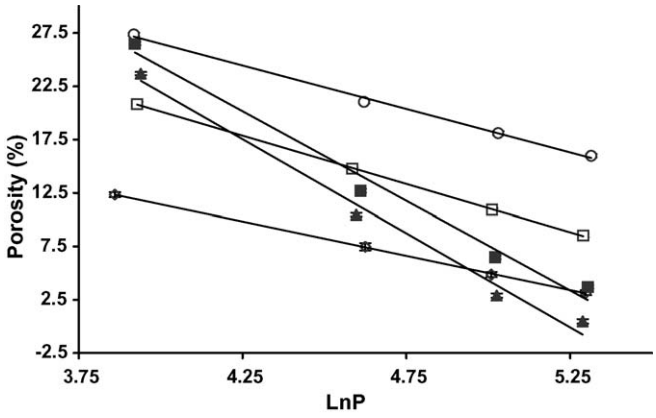

Fig. 3. Porosity vs. ln P for (■) microcrystalline cellulose, (▲) corn starch, (◯) emcompress, (□) lactose, and (◊) acetaminophen. Each point is the average of ~10 compactions.

the three brittle materials (AC, LA and EM) showed similar tendency, while the plots of the two ductile materials (MCC and CS) showed much stronger tendency to change porosity with pressure.

It is observed in Fig. 2 that at pressures higher than those used in this study, the porosity of corn starch compact may reach or drop below zero. Similar phenomena have been reported previously for pregelatinized potato starch and spray-dried sorbitol by Van der Voort Maarschalk et al. (1997) and Zuurman et al. (1999), and have been attributed to a reversible increase in true density with storage of elastic energy as the particles deform at high pressure.

3.2. Linear plots of the Gurnham equation (Eq. (4)) and their slope constants c

When plotting the data in Fig. 2 according to Eq. (4), using porosity versus ln P, five straight lines were obtained. To get a better estimate of the relationship for each material, the average of 10 replicate compactions of each material at four peak pressures: 50, 100, 150 and 200 MPa were employed for linear regression analysis. The plots using the average data are shown in Fig. 3.

Linear plots with regression coefficients ≥0.98 were obtained for all five materials. The parameter c, for each material was the slope from each linear regression analysis and is listed in Table 1. The two ductile materials corn starch and microcrystalline cellulose, which are highly compressible (Rowe and

Table 1
Parameter c for brittle and ductile materials

Materials	Parameter c	Mean c
Brittle materials		
Acetaminophen (AC)	6.41	7.87
Emcompress (EM)	8.16	
Lactose (LA)	9.06	
Ductile materials		
Microcrystalline celluose (MCC)	16.78	17.20
Corn starch (CS)	17.62	

Table 2
Materials re-evaluated by the Gurnham equation (Eq. (4))

Materials[a]	Abbreviation	Source	True density (g cm^{-3})
Calcium carbonate powder	CC	CalEssence® Specialty Minerals Inc., Bethlehem	2.596
Calcium carbonate granulation	CC Gran.	Delavau Co., Philadelphia[b]	2.562
Calcium carbonate powder and microcrystalline cellulose 1:1 physical mixture	CC and MCC Phy. Mix.	CalEssence® and Avicel PH 102®[c]	1.982
Calcium carbonate granulation and microcrystalline cellulose 1:1 physical mixture	CC Gran. and MCC Phy. Mix.	CC Gran. and Avicel PH 102®[c]	1.966
Calcium carbonate and microcrystalline cellulose 1:1 co-processed mixture	CC and MCC Co Pro.	Endurance Plus®, FMC Corp., Philadelphia	1.928

[a] Materials from an earlier study (Miller et al., 2000) compressed under the same experimental settings.
[b] A proprietary wet granulation containing 96% calcium carbonate.
[c] The physical mixtures were prepared by blending the materials in a cube blender, passing the mixtures by hand through a # 16 mesh screen, then re-blending the screened mixtures in the cube blender.

Roberts, 1996), have higher c values compared to the three brittle materials. From high to low, c values for the five materials were in the following order: corn starch, microcrystalline cellulose, lactose monohydrate, dibasic calcium phosphate dihydrate and acetaminophen. The order of the first four materials was consistent with their reported mean yield pressures (Rowe and Roberts, 1996). The reported mean yield pressure of acetaminophen falls between lactose and microcrystalline cellulose. However, in this study, acetaminophen has the lowest c value, which is consistent with its poor compressibility parameter reported by Celik and Marshall (1989) and Sonnergaard (1999).

As seen in Table 1, mean c values of the ductile materials and the brittle materials were clearly different. The mean c for ductile materials (17.2) is much higher than the mean c for brittle materials (7.87).

3.3. c values of complex materials from an earlier study compressed under the same conditions

Experimental data from an earlier study (Miller et al., 2000), compressed under the same experimental settings were also analyzed using Eq. (4). The pharmaceutical materials re-evaluated in this study are listed in Table 2.

Linear plots of porosity versus ln P were also obtained for these materials listed in Table 2. c values for all materials that were analyzed in this work including the five materials and these previous materials are shown in Fig. 4. It seems that c not only reflects the compressibility of single component materials, but also reflects the compressibility of more complex systems. The effect of granulation, mixing technique, and spray drying on the compressibility of the brittle material—calcium carbonate has also been reflected by the gradual increase of c from 6.29 to 14.73 (Fig. 4). The compression behavior of the co-processed (spray dried) microcrystalline cellulose and calcium carbonate was more like the compression behavior of pure microcrystalline cellulose than that of the physical mixture. c values obtained in this work reflected their reported (Miller et al., 2000) differences as shown in Fig. 4.

The compressibility parameter determined in this work represents the volume reduction ability of a material during the dynamic compaction process. This c value may or may not be directly connected with the compactibility of a material, because other factors such as elastic recovery during decompression and bonding character of the material may also influence the final strength of the tablet.

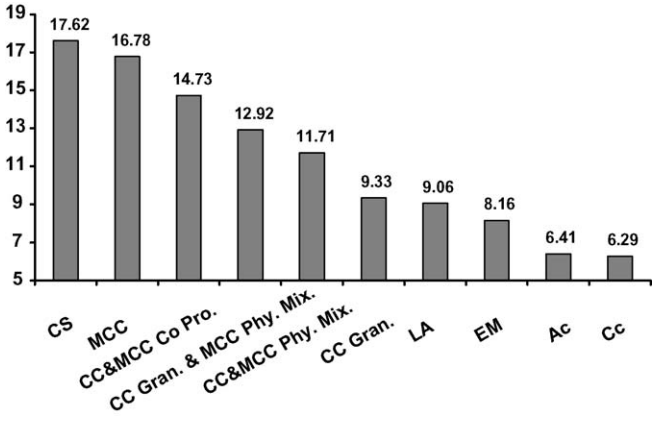

Fig. 4. Parameter c for various pharmaceutical materials.

4. Conclusions

The Gurnham equation (Eq. (4)) has been investigated as a new tool to characterize pharmaceutical powder compression. Linear plots of porosity versus ln P were obtained for the five experimental materials in this work as well as materials from a previous study. Parameter c determined using Eq. (4) seemed to provide a good representation of material compressibility, not only for single component materials, but also more complex pharmaceutical materials. Higher c values indicated better compressibility.

The Gurnham equation shows great potential in providing a quantitative description of the compression behaviors of pharmaceutical powder systems. It would be interesting to see in future work that this compressibility parameter is being used along with other parameters such as elastic recovery and bonding index for tablet formulation design and optimization.

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