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A material-sparing method for simultaneous determination of true density and powder compaction properties—Aspartame as an example

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Abstract

True density results for a batch of commercial aspartame are highly variable when helium pycnometry is used. Alternatively, the true density of the problematic aspartame lot was obtained by fitting tablet density versus pressure data. The fitted true density was in excellent agreement with that predicted from single crystal structure. Tablet porosity was calculated from the true density and tablet apparent density. After making the necessary measurements for calculating tablet apparent density, the breaking force of each intact tablet was measured and tensile strength was calculated. With the knowledge of compaction pressure, tablet porosity and tensile strength, powder compaction properties were characterized using tabletability (tensile strength versus pressure), compactibility (tensile strength versus porosity), compressibility (porosity versus pressure) and Heckel analysis. Thus, a wealth of additional information on the compaction properties of the powder was obtained through little added work. A total of approximately 4 g of powder was used in this study. Depending on the size of tablet tooling, tablet thickness and true density, 2–10 g of powder would be sufficient for characterizing most pharmaceutical powders.

Keywords: Aspartame; True density; Material sparing; Compaction; Porosity; Tensile strength

1. Introduction

True density is a fundamental material property critical for accurate characterization of powder mechanical properties. It is used to calculate tablet porosity, on which tablet hardness, tensile strength and elastic modulus depend exponentially for most powders (Ryshkewitch, 1953; Spriggs, 1961; Knudsen, 1962). An inaccurate true density can profoundly affect the accuracy of tableting data analysis (Sun, 2005). Thus, it is important to ensure accuracy of true density measurement in studying the compaction properties of any powder. Sweeteners such as aspartame are commonly used in chewable tablet formulations for taste modification. Recently, mechanical properties of aspartame as well as some other sweeteners were reported (Mullarney et al., 2003). It was observed in our laboratory that true density of a batch of commercial aspartame measured using helium pycnometry was highly variable and ranged from 1.266 to 1.381 g/cm^3 (Table 1). The root cause of the problem is likely the sensitivity of helium pycnometry to water released from the aspartame hydrate crystal lattice during the course of true density measurement (Sun, 2004). It is known that aspartame can exist in a number of crystal forms, including an 8/3 hydrate, a 2/3 hydrate, two forms of hemihydrate and the anhydrate (Hatada et al., 1985; Meguro et al., 2000; Leung et al., 1998). The 8/3 hydrate can be obtained by crystallizing aspartame from water. The 2/3 hydrate is obtained by drying the 8/3 hydrate with a dry nitrogen purge at room temperature. One of the hemihydrate polymorphs can only be obtained under extraordinary conditions and is normally not present in commercial aspartame powders (Leung et al., 1998). The commercial aspartame is produced by crystallizing from water followed by drying using nitrogen flow at room temperature. Under such conditions, the 8/3 hydrate is not stable and converts to a lower hydrate. The relative stability between the 2/3 hydrate and the common hemihydrate has not been established to this author's knowledge. However, it is clear that at ambient temperature and humidity the 2/3 or hemihydrates are more stable than the anhydrate since even prolonged drying under nitrogen purge does not yield the anhydrate. It is likely that anhydrate aspartame quickly converts to the lower hydrate

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Table 1
Physical properties of aspartame phases

Aspartame	Water (%)	True density (g/cm^3)	True density measured by helium pycnometry (g/cm^3)
2/3 hydrate	3.92	1.310[a]	N/A
Hemihydrate	2.97	1.363[a]	N/A
Lot R13348	3.65 (0.03)	1.310 (0.010)[b]	1.266–1.381

[a] Calculated from single crystal structures.
[b] Derived from fitting compaction data using Eq. (1).

when exposed to ambient conditions. In this study, the crystal form of the commercial aspartame lot was identified using powder X-ray diffractometry. One objective of this study is to show that the method of fitting compaction data to derive powder true density is valid for the problematic batch of aspartame (Sun, 2004). However, the main objective is to demonstrate how this material-sparing method may be used, through little added work, to characterize powder compaction properties to facilitate rapid early stage formulation screening and optimization.

2. Materials and methods

Aspartame, lot R13348, was purchased from Spectrum Quality Products (Gardena, CA, USA). Immediately before the compaction study, its water content was measured coulometrically and its polymorphic nature was identified using powder X-ray diffractometry. Under a polarized-light microscope, the particles were rod-shaped and birefringent. The length of most crystals was 1–10 μm. However, a small number of crystals with a length of 50–100 μm were also observed.

2.1. Karl Fischer titrimetry (KFT)

The water content of aspartame was determined coulometrically using a Karl Fischer titrimeter (Model C3000 Titrator, AquaStar, EM Science). Three blanks were run by removing the stopper from the titration cell and performing the step of adding a sample to the cell without using a powder. This step accounts for the effects of water in air on the measurement. The average blank value was automatically registered and sample water content was automatically corrected using the blank value. An overestimated blank value can cause the measured water content of a sample to fall below its actual water content. The relative humidity during the time of measurement was 30%. Three accurately weighed powder samples were analyzed and the average and standard error calculated.

2.2. Powder X-ray diffractometry

An aluminum sample holder with a 12 mm diameter cavity was used for collecting powder X-ray diffractometry (PXRD) data. PXRD was performed using a Scintag X2 Advanced Diffraction System operating under Scintag DMS/NT$^{\mathrm{TM}}$ and Microsoft Windows NT$^{\mathrm{TM}}$ 4.0 software. The system uses a copper X-ray source maintained at 45 kV and 40 mA to provide Cu KL3 (Kα1) emission of 1.5406 Å and a solid-state peltier cooled detector. Beam aperture was controlled using tube divergence and anti-scatter slits of 2 and 4 mm width and detector anti-scatter and receiving slits of 0.5 and 0.3 mm width. Data were collected using a step scan of 0.03° per step with 1 s dwell time at each step over a range of 2–35° two-theta. The powder was gently pressed using a clean glass slide and a piece of clean weighing paper to ensure coplanarity between sample surface and the surface of the sample holder.

2.3. Preparation of tablets

A set of round flat-faced tooling with a 10.00 mm diameter was used for compression. Punch faces and die wall were dusted with magnesium stearate prior to each compaction. About 300 mg of powder was transferred to the die cavity manually. Compaction force was applied using an instrumented hydraulic press. The valve of the hydraulic line was closed after the desired force was achieved. Subsequently, the compaction force slightly decreased with time as a result of continuous consolidation (volume reduction) of the powder bed under pressure. Thus, each compaction was maintained for 30 s to reduce the variability of powder consolidation, which can affect tablet density. Both peak compaction force and force after 30 s of compaction were recorded. Compaction pressure was calculated from the compaction force and area of the upper punch tip. Tablets were ejected manually after each compaction. Tablet weight, dimensions and breaking force were measured between 1 and 2 h after ejection. Each tablet was accurately weighed to 0.1 mg and the diameter and the thickness of each tablet were measured to 0.01 mm using a digital caliper (Model 62379-531, Control Company, Friendswood, TX, USA). To obtain more accurate measurements of tablet dimensions, loose particles on tablet surfaces were gently removed using a brush and flashing on the edge of each tablet was also carefully removed. Tablet density, ρ_{tablet}, was calculated from tablet diameter, thickness and weight. The peak pressure was used for subsequent non-linear regression to obtain the true density of the powder. The ability of the powdered material to be densified by an external pressure was represented using a plot of tablet density versus compaction pressure (Fig. 1).

2.4. Deriving powder true density

The tablet density approaches the true density, ρ_{true}, of the powder with increasing pressure (Fig. 1). The relationship between tablet density and compaction pressure follows Eq. (1) (Sun, 2004). To derive the true density, tablet density versus compaction pressure data of a total of 12 tablets was fitted to Eq. (1) using non-linear regression (Origin® V7.0, OriginLab Corp. Northampton, MA, USA).

$$p = \frac{1}{C}\left[(1-\varepsilon_{\mathrm{c}}) - \frac{\rho_{\mathrm{tablet}}}{\rho_{\mathrm{true}}} - \varepsilon_{\mathrm{c}} \ln\left(\frac{1-(\rho_{\mathrm{tablet}}/\rho_{\mathrm{true}})}{\varepsilon_{\mathrm{c}}}\right)\right] \quad (1)$$

where C (MPa^{-1}) and ε_{c} are the constants that can be used to describe how a powder consolidates under pressure (Sun, 2004; Kuentz and Leuenberger, 1999). In this study, the regres-

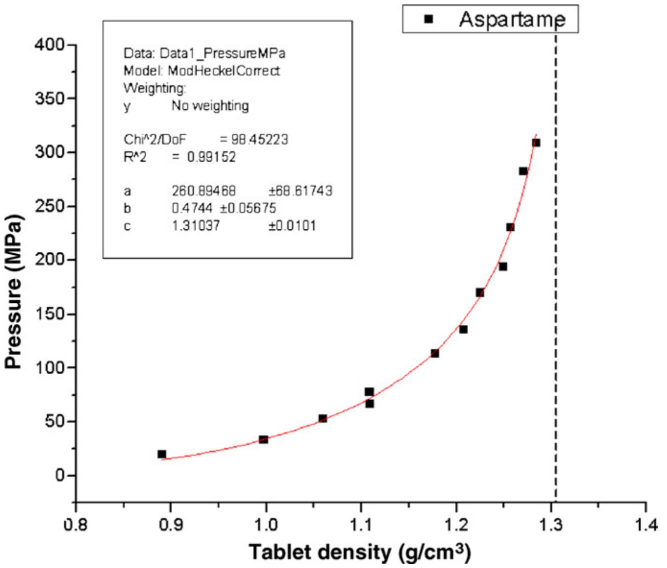

Fig. 1. A plot of compaction pressure vs. tablet density of aspartame. True density of the powder is obtained by fitting data to Eq. (1) using non-linear regression. The broken line indicates the true density of the powder calculated from single crystal structure.

sion was successfully performed with the initial values of $C = 0.003\ \text{MPa}^{-1}$, $\varepsilon_c = 0.4$ and $\rho_{\text{true}} = 1.4\ \text{g/cm}^3$ without any constraint imposed. This set of initial parameters has been found suitable for most powders. However, it is advisable to always visually check how well the line fits the data points. If the fit is less than satisfactory, individual initial values can be varied until a best-fit regression line is obtained.

The porosity of tablets, ε, was calculated using Eq. (2).

$$\varepsilon = 1 - \frac{\rho_{\text{tablet}}}{\rho_{\text{true}}} \tag{2}$$

2.5. *Measurement of tablet strength*

Breaking force of the tablets was measured using a tablet hardness tester (Tablet Tester 6D, Schleuniger Pharmatron Inc., Manchester). To eliminate the undesired effect of variable tablet thickness on measured breaking force, tensile strength was calculated using Eq. (3).

$$\sigma = \frac{2F}{10^6 \pi D T} \tag{3}$$

In Eq. (3), σ is the tensile strength (MPa), F the breaking force (N), D the tablet diameter (m) and T is the thickness of tablet (m) (Fell and Newton, 1970).

3. Results and discussion

3.1. *Powder true density*

To identify the crystal form of the aspartame under study, the experimental PXRD pattern was compared to PXRD patterns of the 2/3 hydrate and the common hemihydrate calculated from available single crystal structures (Hatada et al., 1985; Meguro et al., 2000) using a commercial software (Materials Studio, V3.1, Accelrys, San Diego, CA, USA). The experimental PXRD pattern matched well with that of the 2/3 hydrate (Fig. 2) and no characteristic diffraction peaks of the hemihydrate were observed. This suggests the commercial aspartame in this study is the aspartame 2/3 hydrate. The presence of any other crystal form is less than the limit of detection of PXRD, typically ~2% (wt%). The theoretical water content is 3.92% for the 2/3 hydrate and 2.97% for the hemihydrate. The water content of the tested aspartame was 3.65 ± 0.03% ($n = 3$; Table 1), very close to the theoretical water content for the 2/3 hydrate. This is in agreement with the PXRD results. The slightly lower water content than that of 2/3 hydrate may be caused by a slightly overestimated background water content value since the low relative standard error (<1%, $n = 3$) suggests good precision of the measurements. According to the single crystal data, the true densities are 1.310 and 1.363 g/cm^3 for perfect 2/3 hydrate and hemihydrate crystals, respectively. Considering the worst case scenario, the true density of a powder containing 98% 2/3 hydrate and 2% hemihydrate is 1.311 g/cm^3. By fitting tablet density versus pressure data, a true density of 1.310 ± 0.010 g/cm^3 was obtained ($R^2 = 0.992$; Fig. 1). The PXRD of the tablet compressed at the highest pressure did not show a crystal form change from the commercial aspartame. The fitted true density and the expected true density are in excellent agreement. In comparison to the problematic gas displacement measurement using helium pycnometry, the data-fitting method appears to be a good alternative for crystalline hydrates.

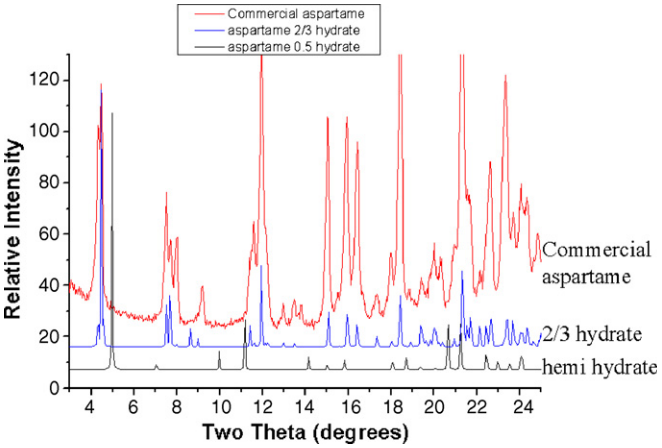

Fig. 2. Powder X-ray diffraction (PXRD) patterns of the commercial aspartame, the 2/3 hydrate and the hemihydrate. Positions of peaks in the PXRD pattern of the commercial aspartame match well with those of the 2/3 hydrate. No characteristic diffraction peak of the hemihydrate is observed.

3.2. *Compaction properties of aspartame*

Compaction properties were characterized using tabletability, compressibility and compactibility (Joiris et al., 1998; Sun and Grant, 2001a).

The tabletability plot of aspartame is shown in Fig. 3. Tablet tensile strength increases with increasing compaction pressure. The rate of increase in tensile strength gradually decreases with increasing pressure. For example, the rate is ~0.03 at below 50 MPa and ~0.01 at above 100 MPa. The change of slope in

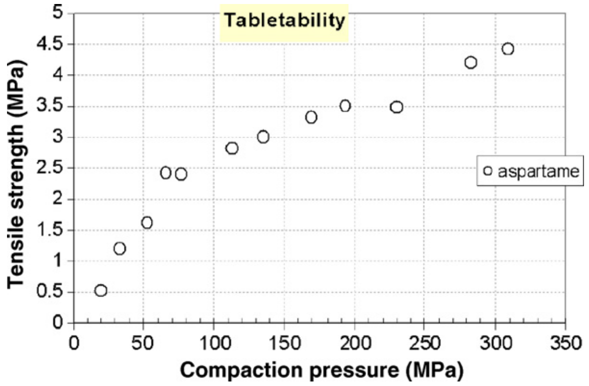

Fig. 3. Tabletability plot of aspartame.

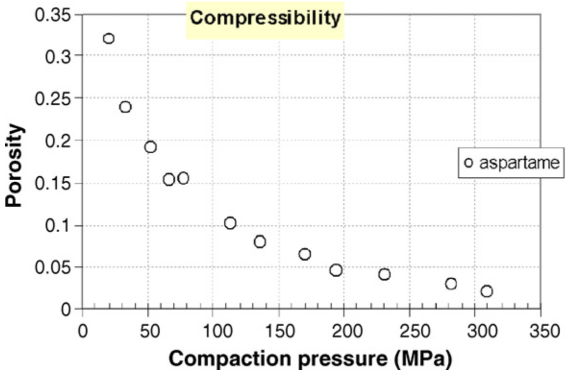

Fig. 4. Compressibility plot of aspartame.

the curve reflects the change in the rate at which the strength of overall interparticulate interactions increases with increasing compaction pressure. Initially, particles undergo rearrangement to achieve more efficient packing. The size of pores is reduced substantially and particles come together much closer during initial stages of compression, <50 MPa in this case. Consequently, significantly more bonding sites and therefore a significantly faster increase in total interparticulate interactions occur. However, at pressures >50 MPa, further increase of pressure only results in a slight increase in total interparticulate interactions in an ejected tablet since a large portion of the deformation during compaction is elastic in nature. Consequently, one observes a smaller increase in tablet strength.

It may be expected that tablets manufactured using regular tooling contain a substantial number of defects and their strength can be highly variable (Hiestand and Smith, 1984; Roberts et al., 1995). However, literature data often suggest acceptable variability of tablet tensile strength for different types of powder. Low relative standard deviation in tablet tensile strength, typically less than 5%, for many powders including drugs, excipients and formulations, has been observed in this author's laboratory. Thus, a single tablet at each of 12 pressures is considered acceptable for outlining the overall tabletability of most powders. If much larger variation in a tabletability plot is observed, an additional set of 12 tablets can be used. For some drugs, tablet lamination occurs during tablet ejection, especially if compaction pressure is high. Therefore, it is imperative to inspect individual tablets before and after strength testing for signs of lamination. Lamination of a tablet must be reported to accompany the subsequent data analysis. It should also be pointed out that a split die that allows tri-axial decompression has been successfully used to manufacture square-shaped tablets of problematic powders (Hiestand and Smith, 1984). The uniform relaxation of tablets during decompression is thought to minimize the generation of macro-scale defects (Hiestand and Smith, 1984). At a minimum, the use of a split die can eliminate the tablet ejection step after compaction. In principle, a similar split die may be constructed for round tablets to obtain intact tablets of powders with poor compaction properties. The split die was originally designed for manufacturing large tablets, and thus requires the use of a significant amount of powder. However, miniaturized tablets, square or round, can in principle be manufactured using a small split die.

With increasing pressure, tablet densities of different powders approach their corresponding true densities. These can be significantly different from material to material. Thus, it is difficult to compare plots of tablet density versus pressure for different powders. Because tablet porosity is calculated from the ratio of tablet density to true density, it always assumes a value between 0 and 1. In practice, porosity is typically in the range 0.05–0.4. Therefore, compressibility plots (Fig. 4) of different powders may be conveniently used to compare consolidation properties of different powders. For aspartame, the tablet porosity is initially reduced from 0.32 to 0.2 when the pressure is increased from 20 to 50 MPa. However, only a 0.01 reduction in tablet porosity (from 0.05 to 0.04) is observed when the pressure is increased from 200 to 230 MPa. The different rates of pore size reduction and elimination by increased pressure are consistent with the effect of pressure on tablet strength, as pointed out in the previous discussion.

On a compactibility plot (Fig. 5), tablet tensile strength often increases exponentially with decreasing porosity, obeying the Ryshkewitch relationship (Eq. (4)) (Ryshkewitch, 1953).

$$\sigma = \sigma_0 \, e^{-b\varepsilon} \tag{4}$$

where σ is the tensile strength (MPa), σ_0 the tensile strength at zero porosity (MPa), ε the porosity of tablets and b is a constant.

Thus, the maximum tablet strength of a powder at zero porosity may be predicted from the compactibility plot. For aspartame in this study, the maximum strength is 5.2 MPa. This value is

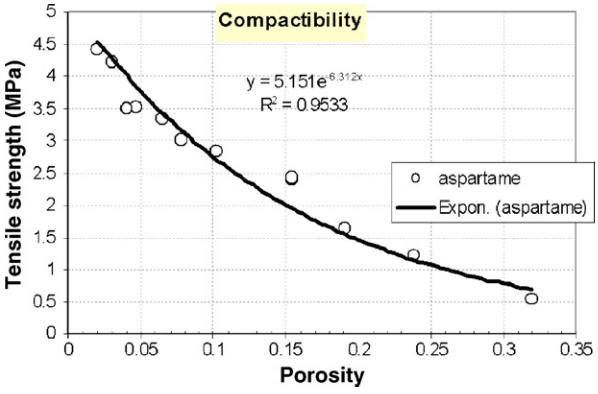

Fig. 5. Compactibility plot of aspartame.

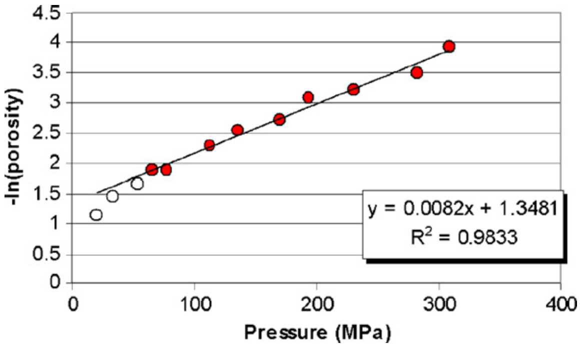

Fig. 6. Heckel plot of aspartame. Only points presented as solid circles are used for linear regression.

comparable with that of a typical lot of spray-dried lactose, a common tablet filler. It therefore appears that the use of a small amount of aspartame in a formulation is unlikely to impair tabletability of the formulation.

Compaction data are often analyzed using the Heckel analysis (Heckel, 1961a,b) The linear portion of the −ln(porosity) versus pressure curve is fitted to Eq. (5).

$$-\ln(\varepsilon) = KP + A \quad (5)$$

The reciprocal of the slope of the regression line, *K*, is termed the mean yield pressure and is believed to be three times the yield strength of the powder (Heckel, 1961b). *A* is a constant. In this study, the Heckel plot appears linear at pressures above 50 MPa (Fig. 6). The linearity is good considering the sensitivity of −ln(porosity) to small errors in porosity when it approaches zero (Sun and Grant, 2001b) The mean yield pressure of the aspartame is 122 MPa from the Heckel analysis. The mean yield pressure is high compared with most pharmaceutical powders (Rowe and Roberts, 1996), suggesting that aspartame is a relatively hard material and should undergo mainly brittle fracture, rather than plastic deformation, under pressure. This result is consistent with a previous study where aspartame was found to be brittle (Mullarney et al., 2003).

The powder-sparing method works well for aspartame. We have used this method successfully for characterizing a number of common tablet excipients using both a hydraulic press (low strain rate) and a tableting emulator (high strain rate). It is possible that some drugs may not form intact tablets, even using a split die, due to poor mechanical properties. In those cases, one can characterize mechanical properties of the problematic powders by studying compaction properties of mixtures with a well-characterized tablet excipient, e.g., microcrystalline cellulose.

4. Conclusions

This study shows that the method of fitting compaction data to derive powder true density is accurate for a hydrated commercial aspartame sample. After completing the experiments necessary to determine true density, a wealth of additional information on the compaction properties of aspartame is obtained through little added work. Generally, 12 tablets compressed under different pressures are sufficient for characterizing compaction properties and for obtaining true density. This procedure is relatively powder sparing. A total of approximately 4 g of powder was used in this study. If available sample is limited, smaller tablet tooling can be used for data collection. Depending on the size of tablet tooling and the thickness of tablets, 2–10 g of powder would be sufficient for characterizing most pharmaceutical powders. Fig. 7 summarizes the testing procedure and data analysis that is presented above. It may be useful to implement the experimental procedures described here to facilitate rapid formulation screening and optimization for good compaction properties. Since a number of powder mechanical properties are characterized, this

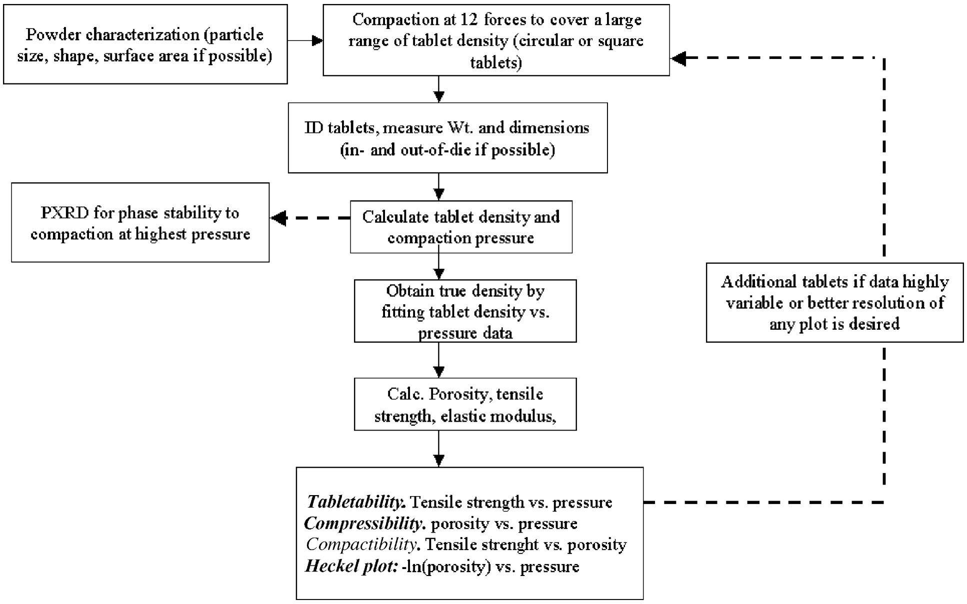

Fig. 7. Schematic presentation of the data collection and analysis process of the proposed powder-sparing method.

method can possibly be used to distinguish lot-to-lot variation of incoming exicipients and drugs. It should be pointed out that good powder flow, good release from punch faces, acceptable weight and content uniformity and some other requirements must be met for successful commercial manufacture of any formulation. These properties should be evaluated separately, in addition to careful evaluation of powder compaction properties, during the course of formulation development before large-scale manufacture.

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