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Early Detection of Capping Risk in Pharmaceutical Compacts

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Abstract

Capping is a common mechanical defect in tablet manufacturing, exhibited during or after the compression process. Predicting tablet capping in terms of process variables (compaction pressure and speed) and formulation properties is essential in pharmaceutical industry. In current work, a non-destructive contact ultrasonic approach for detecting capping risk in the pharmaceutical compacts prepared under various compression forces and speeds is presented. It is shown that the extracted mechanical properties can be used as early indicators for invisible capping (prior to damage). Based on X-ray cross-section images and a large set of waveform data, it is demonstrated that the mechanical properties and acoustic wave propagation characteristics is significantly modulated by the tablet's internal cracks and capping at higher compaction speeds and pressures. In addition, the experimentally extracted properties were correlated to the directly-measured porosity and tensile strength of compacts of Pearlitol[®], Anhydrous Mannitol and LubriTose[®] Mannitol, produced at two compaction speeds and at three pressure levels. The effect compaction speed and pressure on the porosity and tensile strength of the resulting compacts is quantified, and related to the compact acoustic characteristics and mechanical properties. The detailed experimental approach and reported wave propagation data could find key applications in determining the bounds of manufacturing design spaces in the development phase, predicting capping during (continuous) tablet manufacturing, as well as online monitoring of tablet mechanical integrity and reducing batch-to-batch end-product quality variations.

Keywords: capping risk; continuous manufacturing; real-time compaction monitoring; solid dosage forms; porosity; compaction pressure; compaction speed.

1. Introduction

The physical properties and structural integrity of a pharmaceutical tablet may alter its therapeutic and structural functions. The imperfections and irregularities within a tablet may affect its mechanical, chemical and biological properties. Surface defects can directly modify the effectiveness and quality of tablet coatings that serve numerous purposes, such as controlling the release of active ingredients in the human body, ensuring the stability of the active ingredient, and extending product shelf-life by protecting its ingredients from degradation. Such imperfections and irregularities are in general related to (i) quality of incoming materials (excipients and actives), (ii) tableting (manufacturing) process parameters (e.g., compaction pressure, speed, and punch types), and (iii) handling systems for transport and processing. Consequently, defects may also be considered as early indicators for problems with manufacturing machinery, starting materials, and manufacturing parameters. Thus, predicting and monitoring tablets for defects is essential to the pharmaceutical industry for quality assurance purposes (Akseli et al., 2008).

Capping is a common mechanical defect in tablet manufacturing and formation, in which partial or complete cross-sectional segments are detached from the top or bottom face of a tablet during or after the compaction/compression process (Sarkar et al., 2015). Capping risk may be mitigated by modification of processing variables (e.g., compaction pressure and speed) or formulation changes. For a registered product, formulation change, however, is not a preferred alternative to resolve the capping problem. Moreover, particularly for a high-dose product, there is limited flexibility to adjust by making changes in the formulation. In compaction process, tablet capping has been identified to be caused by various mechanisms, such as air entrapment (Long and Alderton, 1960), mechanism of volume reduction during compression (Kuppuswamy et al.,

2001), compression speed (Garr and Rubinstein, 1991), viscoelastic recovery (Akseli et al., 2010; Malamataris et al., 1996; Nyström and Glazer, 1985), stress and density distribution (Han et al., 2008), and internal shear stress due to die wall pressure and friction (Sugimori et al., 1989). In order to prevent capping, numerous methods (e.g., lowering compression force, reducing compression speed, or decreasing ejection path in die (Garr and Rubinstein, 1991)) have been proposed and reported. However, at present the early detection of capping risk remains unexplored.

Previously a set of a non-invasive/non-destructive, wave propagation-based techniques for the characterization of tablet properties have been introduced and reported (I. Akseli et al., 2009; Ilgaz Akseli et al., 2009; Liu and Cetinkaya, 2010; Varghese and Cetinkaya, 2007; Smith et al., 2011; Vahdat et al., 2013). Current approach is based on the principle that the velocities of pressure (longitudinal) and shear (transverse) waves propagating in a medium depend on its elasticity (stiffness, hardness), and inertia (mass density and its spatial distribution) as well as its micro-granular structure. The wave dispersion relation of a medium is also expected to be modified by defects leading to capping, but it is outside the scope of current work. In general, the mechanical properties of a solid pharmaceutical compact correlate with its mechanical (tensile) strength, “hardness” and porosity. In addition to its mechanical and viscoelastic properties, the material texture of a tablet material (e.g., grain size and grain-to-grain stiffness coupling) determines the spectral dispersion of ultrasonic waves in the propagation medium material. By utilizing experimentally acquired spectral dispersion curves and fitting the parameters of a viscoelastic material model (including scattering effects), the physical-mechanical (such as mass density and distribution, material elasticity, and viscoelasticity) and micro-structural (such as

internal grain size distribution and inter-granular bonding) properties could also be extracted (Smith et al., 2011; Vahdat et al., 2013).

In current work, a non-destructive contact ultrasonic approach to detect capping risk in the pharmaceutical compacts prepared under various compression forces and speeds is introduced. The extracted mechanical properties can be used as early indicators of invisible capping effect on the compacts. The presented approach could find significant practical applications in the online/real-time monitoring of development processes and continuous manufacturing of pharmaceutical tablets. Acoustic waves directly interact with the physical/mechanical properties of compacts and their propagation velocities are extremely high compared to the characteristic time scales of production machinery and dwell times (milliseconds), thus their utilization is amenable to continuous *online* real-time monitoring of product quality.

Current study explores a monitoring mechanism for predicting the capping risk in solid dosage forms and aims to establish a high degree of correlation between the ultrasonically extracted parameters and the properties obtained from the off-line measurements (such as porosity, yield strength, breaking force, and “hardness”).

2. MATERIALS AND METHODS

2.1 Ultrasound Measurements

In the reported experiments, an ultrasonic experimental set-up based on an existing testing instrument (ATT2020, Pharmacoustics Technologies, LLC, Potsdam, New York, USA) was developed and employed. The ATT2020 instrument is a computer-controlled ultrasonic waveform acquisition and time-of-flight (ToF) analysis system consisting of two pressure

(compression) transducers (AT024, Valpey Fisher, Hopkinton, Massachusetts, USA) with a central frequency of 2.25MHz, two shear (transverse wave) transducers (E1574, Valpey Fisher, Hopkinton, Massachusetts, USA) with a central frequency of 1MHz, a pair of low attenuation delay-lines, an axial load monitoring system, a pulser/receiver board, and a tablet sample centering apparatus as well as a graphical user interface (GUI) based on the LabVIEW software (LabVIEW 15, National Instruments Corp., Austin, Texas, USA) for waveform acquisition and ToF analysis (Fig. 1.a). ATT2020 operates both in pulse-echo (reflection) and pitch-catch (transmission) ultrasonic modes for pressure and shear waves (Krautkrämer and Krautkrämer, 2013).

In current study, the set-up was utilized to acquire the ultrasonic responses for the characterization of the mechanical properties (at both macro and micro-scales) of the compact materials. Both pressure and shear data were acquired for characterizing the mechanical properties of the compacts. In the reported pressure and shear experiments, the ATT2020 instrument operated in pitch-catch mode, and the pulser/receiver parameters were set at a pulse width of 200ns, pulser voltage of 200V, a sampling rate of 100MHz, an amplification gain of 0dB, and an averaging (oversampling) rate of 512. In the pressure measurement station (left apparatus in Fig. 1.a), Transducer 1 was coupled with the delay-line and mounted into the upper transducer holder. The key function of the delay-line integrated into the experimental set-up was to separate the initial acoustic pulse (“main bang”) generated by Transducer 1 from interface reflections inside the tablet sample by creating a time lapse. Transducer 2 was directly mounted into the bottom transducer/sample holder. The sample holder apparatus is used to hold the sample securely in place while acquiring waveform and to allow two transducers approach to each other. The compact centering apparatus mounted on the transducer/sample holder was used

to accurately center and hold the compacts in place while acquiring acoustic waveforms. The transducer/sample holder is supported by a three-point structure-leveling platform that was utilized to calibrate the parallelism of measurement surfaces using a set of adjustment knobs. The surface contact between the transducer- compact interface is optimized for the transmission of travelling pulses. The load cells mounted at the bottom and connected to a liquid crystal display (LCD) was used to measure and monitor an applied axial load (on samples) during waveform acquisition to eliminate the effects of near-surface asperities on waveform quality. During current waveform acquisitions, the applied axial load was maintained at $1500 \pm 10\text{g}$ for ensuring repeatable transmission contact between the sample and the surfaces of the delay-line and transducer. Compared to the compaction pressure P_c levels ($P_1 = 50.06\text{ MPa}$, $P_2 = 150.18\text{ MPa}$, and $P_3 = 250.29\text{ MPa}$), the exerted axial force levels (on the order of few N) are extremely low, thus no substantial effect on compact deformation and microstructure is expected. The applied axial load can be read, saved and displayed on the LCD and/or the LabVIEW GUI of the ATT2020 instrument. In the shear (transverse wave) set-up (right apparatus in Fig. 1.a), the apparatus with a pair of shear transducers have the same configurations as the pressure set-up. An ultrasonic shear couplant gel (54-T04, Sonotech, Glenview, Illinois, USA) was used for increasing wave transmission between the sample and the surfaces of the delay-line and transducer in the shear wave experiments.

In the reported acoustic (pressure and shear) transmission experiments in the pitch-catch mode, a sample tablet was placed and centered on the bottom sample/transducer holder such a way that the bottom surface of the tablet contacted with Transducer 2 properly. Prior to experiments, the parallelism of the transducer faces was verified by a close examination of the contact area with an ordinary light source. Each compact was centered and fixed by an iris in its compact centering

apparatus during experiments. Transducer 1 integrated with the delay-line was vertically placed and centered in contact with the top surface of the sample tablet by manually lowering the upper transducer holder and exerting a constant axial load during measurements. An electrical pulse generated by the ultrasonic instrument first excites Transducer 1. The pressure (longitudinal) wave pulse transmitted through the delay-line and the tablet sample placed on the surface of Transducer 2, is eventually received by Transducer 2. The received pulse containing the ToF information was acquired, digitized, signal-processed and saved as a digital waveform data file via the ATT2020 GUI interface. Wave dispersion curves in medium materials could also be extracted and processed, yet no such information has been utilized in current work.

2.2 Compact Sample Sets

In the reported experiments, cylindrical compacts made of three materials: Pearlitol[®] (P), Anhydrous Mannitol (A) and LubriTose[®] Mannitol (L). Each material is compacted at two compaction dwell-time levels (corresponding to 4 milliseconds (high speed – HS) and 20 milliseconds (low speed – LS) peak compression dwell-time, respectively) (see Table 1 for measured tablet thicknesses, diameters, masses, apparent mass densities, average value of the tablet porosity and tensile strength). The resulting six material groups are referred to as PHS, PLS, AHS, ALS, LHS and LLS, respectively. To evaluate the effect of compaction pressure on capping risk, each resulting material group is compacted at three compaction pressure levels ($P_1=50.06$ MPa, $P_2=150.18$ MPa, and $P_3=250.29$ MPa). As a result, a three-dimensional design space for three material types (P, A, and L), two compaction speeds (HS and LS) and three compaction pressure levels (P_1 , P_2 and P_3) is formed. In total, the experimental sample set utilized in current study consists of 18 types of compacts.

In the reported experiments, for each compact type, 12 sample compacts were made and evaluated. The total number of compacts utilized in this study was 216. In Table 1, the compact masses measured by a digital scale (Model: A120S-L, Mettler-Toledo Inc., Columbus, Ohio, USA) with an error range of $\pm 50 \times 10^{-6}$ g, the heights and diameters of compacts measured by a digital caliper (CD-6 in CS Absolute Digimatic Caliper, Mitutoyo Inc., Aurora, Illinois, USA) with an error range of $\pm 5 \times 10^{-6}$ m are listed.

2.3 X-ray Computed Tomography (CT) Imaging

To study the internal micro-structures of samples and detect internal cracks in a non-destructive manner, an X-ray CT scanner using a CT-Scanner (Phoenix Nanotom[®] M, General Electric, Boston, Massachusetts, USA) with a maximum voltage of 180kV, a maximum power of 20W, and an image resolution of 3072×2400 pixels is employed. Images were saved and then reconstructed/post-processed using Phoenix datos|x CT software (General Electric, Boston, Massachusetts, USA). Using VGStudio MAX (Volume Graphics, Charlotte, North Carolina, USA) cross-section images are constructed (Fig. 1). As depicted in Fig.1.c, the cross-section of the compact LHS at P_1 shows a uniform microstructure with no visible cracks or breakage. In Fig. 1.d, the lateral internal cracks were observed in the compact LHS at P_2 , while the compact remained intact and no breakage was observed. As seen in Fig. 1.e, substantial material removal from the top and bottom surfaces of the compact was present and clearly visible in the compact LHS at P_3 .

2.3 Powder Preparation and Sample Compaction

Spray-dried mannitol (Pearlitol[®] SD) was obtained from Roquette America Inc. (Geneva, Illinois, USA). Anhydrous mannitol and co-processed mannitol (mannitol 96% + glyceryl

monostearate 4%, LubriTose[®] mannitol) were obtained from Kerry Functional Ingredients and Actives (Norwich, New York, USA). The powders were de-clumped by individually passing through a sieve (mesh # 40). Spray-dried mannitol and anhydrous mannitol were lubricated with Magnesium stearate (0.5 % w/w) by blending in a twin-shell blender (V-blender, Patterson-Kelley Company, East Stroudsburg, Pennsylvania, USA) without the use of intensifier bar, at 20 RPM (rotational per minute) for a period of two minutes. After blending, the powders were double-bagged, sealed and stored at room temperature (25°C) until used for the reported experiments. The true densities of the powders were measured using a helium displacement pycnometer (AccuPyc[™] 1340, Micromeritics, Norcross, Georgia, USA) using the method specified in the USP (United States Pharmacopeia) 38 – NF 33, general chapter <699> on the density of solids. All samples were tested in triplicate.

The compacts of individual powders were prepared on an instrumented, R&D single stroke tablet press (STYL'ONE Evolution, MEDELPHARM S.A.S, Beynost, France). The powders were compacted *via* single direct compression using round, flat-faced, TSM-D tooling (11.28 mm diameter). The target compact weight was set at 500 mg. The powders were individually fed to the die *via* installed gravity feed shoe. The powders were compressed at 5, 15, or 25 KN peak compression force (corresponding to compaction pressure levels of $P_1=50.06$, $P_2=150.18$, and $P_3=250.29$ MPa, respectively) with compression speeds v_c of 10 % (low) or 90 % (high) of the equipment's capacity. The low and high v_c translated to an average of 20 milliseconds (Low Speed – LS) and 4 milliseconds (High Speed – HS) peak compression dwell-time, respectively. The compaction parameters were acquired and analyzed by the ANALIS software integrated with the tablet press.

2.4 Direct Evaluation of Tablet Samples

Based on the true mass density of the porous material ρ_t determined by pycnometry (AccuPyc II 1340, Micromeritics Instrument Corp., Norcross, GA, USA), the mass porosity (ϕ^m) of the prepared compacts in percentage (%) was calculated using the bulk density of the compacts by:

$$\phi^m(\%) = (1 - \varepsilon) \times 100 \quad 1$$

where the compact solid fraction of the material, $\varepsilon = \rho_b / \rho_t$, ρ_b is the compact bulk density (compact bulk density = compact mass/table volume). Utilizing the test method described in USP 38 – NF 33, general chapter < 905 > on the uniformity of dosage units, the mass variations of the sample tablets were obtained and evaluated. A set of sample compacts ($n=12$) were randomly selected from each batch, and individually weighed on an electronic balance, and the weight recorded and listed in Table 1. The breaking force (diametrical crushing strength) of each tablet was tested according to the method described in USP 38 – NF 33, *General Chapter: Tablet Breaking Force < 1217 >*. Prior to waveform acquisition, ten samples were randomly selected from each test batch, and were tested using an automatic hardness tester (VK 200, Varian, Inc., Cary, North Carolina, USA). The compact breaking force is also obtained and recorded in kiloponds (kP) and further converted into tablet tensile fracture strength (force/tablet cross-sectional area). The mean tensile strength σ_b^m and porosity ϕ^m values for each sample are also reported in Table 1.

3. RESULTS AND DISCUSSIONS

The acquired ultrasonic pressure (longitudinal) and shear (transverse) waveforms for the six sample sets (PLS, PHS, ALS, AHS, LLS and LHS) at each compaction pressure P_c level ($P_1 = 50.06$ MPa, $P_2 = 150.18$ MPa and $P_3 = 250.29$ MPa) are depicted in Fig. 3. In Fig. 3.a, for all the sample sets (except LHS), the arrival of pressure pulses shortens with increasing P_c (from P_1 to P_3). Note that no shifting trend was observed in LHS due to the capping effects on the surface of the compacts at P_3 (Fig.1.b-c). In all three sample groups, the arrival time of pressure waves is sensitive to the compact P_c level, indicating that the compaction speed modulates the pressure wave propagation velocity (Fig. 3.a). In Fig. 3.b, a similar trend is observed for shear waves as well. The acquired pressure and shear waveforms are processed to obtain the pressure and shear ToF (Δt_L and Δt_T) determined by two time-frequency techniques, namely, the STFT (short-term Fourier Transform) and Gabor wavelet transform. In determining the ToFs (Δt_L and Δt_T) of a travelling pressure and shear wave pulses in a dispersive medium (material), a time-frequency technique is utilized, which requires the arrival time of wave (strain) energy at a particular frequency rather than the amplitude of arriving waves (Drai et al., 2002). In this approach, for a tablet with a thickness of h , the corresponding average pressure and shear wave velocities (c_L , and c_T) in the tablet material are determined by

$$c_L = h / \Delta t_L \quad c_T = h / \Delta t_T \quad 2$$

where h is also the one-way wave travel distance in a compact. The average measured compact thicknesses (h), diameters (d), masses (m), apparent mass densities (ρ_A), average value of the compact porosity (ϕ^m) and tensile strength (σ_b^m) from direct measurements, and the acoustically extracted parameters: pressure (c_L) and shear (c_T) wave velocities, average apparent Young's moduli (E_A) for the three levels of compaction pressure P_c ($P_1 = 50.06$ MPa, $P_2 = 150.18$ MPa

and $P_3 = 250.29$ MPa) are summarized in Table 1 for the sample sets (PLS, PHS, ALS, AHS, LLS and LHS).

Reviewing the acquired pressure and shear waveforms (Fig. 3) reveals that the reflections (peak) of the compact samples shift to the left with the increase in the compaction pressure P_c (from P_1 to P_3), indicating a decrease in the ToF values. The pressure wave ToF values for the sample set PLS were obtained as $\Delta t_L = 3.32, 1.87$ and 1.44 μsec for each P_c , respectively (Fig. 3.a), the shear wave ToF values were also determined as $\Delta t_T = 4.85, 2.80$ and 2.31 μsec for each P_c , respectively (Fig. 3.b). Note that this shifting trend is not observed in LHS, as capping effect was observed on the surface of the compacts with compaction pressure $P_3 = 250.29$ MPa (Fig. 1.b), indicating pressure and shear ToF was modulated by the observed capping effect. In general, ToF is sensitive to the change in the compaction pressure P_c . In Fig.3, it also can be observed that the pressure and shear arrivals of the compact vary between low speed group (LLS, ALS and PLS) and high speed group (LHS, AHS and PHS) at each P_c level (implying a change in ToF). This variation is evident between ALS and AHS. For example, pressure $\Delta t_L = 3.30, 2.11$ and 1.78 μsec in ALS and $\Delta t_L = 4.85, 2.80$ and 2.31 μsec in AHS for each P_c , respectively. As included in Table 1, the pressure (c_L) and shear (c_T) velocities as well as apparent density (ρ_A), and Young's moduli (E_A) of the sample set increase with the increasing compaction pressure P_c . For example, in the sample set PLS, $c_L = 1414.88, 2134.39$ and 2617.05 m/sec, $c_T = 969.64, 1432.13$ and 1624.77 m/sec, and $E_A = 2.13, 5.70$ and 9.12 GPa, respectively.

In Fig. 4, the superimposed plots for c_L , c_T and E_A for each sample set as a function of P_c are depicted. It is observed that the c_L , c_T , and E_A curves for all the sample sets (except LHS and AHS) monotonically increased with an increase in P_c . However, in the sample set LHS and AHS, the c_L , c_T , and E_A curves decreased from $P_2 = 150.18$ MPa to $P_3 = 250.26$ MPa, indicating

the visible (Fig. 1.e) and invisible (Fig. 1.d) capping effect on the mechanical properties of the compacts with high manufacturing speed and compaction pressure P_c .

3.1 Mechanical Property Analysis of the Sample Compacts

Using the well-known relationships, i.e. compressibility and tableability, the mechanical performance of the prepared compacts was analyzed and reported. *Compressibility* is defined as the ability of a tableting material to experience a reduction in volume, because of an applied compaction pressure with punches in a die, and quantified by Heckel plots (Joiris et al., 1998; Sun and Grant, 2001). Namely, compressibility is the extent to which a powder bed experience a volume reduction under axial force (pressure) in a confined space (e.g., in a die). *Compressibility* is often represented by a plot of the calculated compact porosity versus compression pressure (i.e, P_c/A_T with A_T is the area of the tablet horizontal cross-section). *Tableability*, defined as the capacity of a powder material to be transformed into a compact form of given strength under the effect of compression pressure (force), is often represented by a plot of compaction pressure (P_c) versus the tensile strength of the compact (σ_b^m) (am Ende et al., 2007; Joiris et al., 1998; Sun and Grant, 2001).

The compressibility profiles of all the sample sets (PLS, PHS, ALS, AHS, LLS and LHS) are included in Fig. 2.a. In general, the porosity ϕ^m decreased with an increase in compaction pressure in all the sample sets (except LHS). In the sample set LHS, the porosity ϕ^m increased from compaction level P_2 to P_3 , shown an inconsistent trend compared with the other sample sets (Fig. 2.a). This effect known as capping is often observed in the compacts with relatively higher proportion of lubricants at higher speeds, and higher compaction pressure, as lubricants in a formulation are known to reduce the tensile strength of compacts. The capping effect on the

compacts in LHS is clearly observed in Fig. 1.b. Thus, these observations are consistent with the fact that lubricant can cause to capping at higher compaction pressure and speed levels.

The tableability profiles of the sample sets (PLS, PHS, ALS, AHS, LLS and LHS) are depicted in Fig. 2.b. Pearlitol[®] (PLS and PHS) shows higher tableability profile due to its plastically deforming behavior, (namely, compact tensile strength σ_b^m at a given compaction pressure level P_c), compared to that of Agglomerated Mannitol (ALS and AHS) and LubriTose[®] Mannitol (LLS and LHS). Similar to that observed with compressibility (Fig. 2.a), all sample sets (except AHS and LHS) show an increase in the compact tensile strength σ_b^m with increasing compaction pressures P_c . In the sample set LHS, as expect, the tensile strength (σ_b^m) decreased from compaction level P_2 to P_3 due to the visible capping effect on the compact surface (Fig. 1.d). Note that in sample set AHS, a decrease in tensile strength (σ_b^m) was also observed from compaction level P_2 to P_3 , indicating invisible capping (Fig. 1.b) tendency that modulates the tensile strength σ_b^m of the compacts at higher speed and compaction pressure level.

3.2 Correlation of the Tensile Strength σ_b^m with c_L , c_T , and E_A

In establishing the predictability and reliability of the proposed approach in measuring the physico-mechanical properties of the pharmaceutical *compacts*, correlations between the direct-measured properties of sample compacts and the acoustic parameters obtained from the temporal response waveform set for each sample were calculated and reported (Fig. 5). In Fig. 5.a, the correlations between the tensile strengths of compacts (σ_b^m) for the sample set (PLS, PHS, ALS, AHS, LLS and LHS) at various compaction pressures and the pressure and shear velocities (c_L and c_T) are depicted. It is observed that, for all sample sets (except LLS, LHS and AHS), the

pressure and shear velocities (c_L and c_T) increase with increasing the compact tensile strengths σ_b^m , whereas c_L in sample set LHS and c_T in LLS, LHS and AHS are not in correlation due to the capping effect on the compacts at higher speed and compaction pressure levels (Fig. 1.c-e). Moreover, c_L and c_T are also a distinct and separated for each sample set and appeared to reflect the relative mechanical properties of the materials (Fig.5.a).

The established correlations between the compact tensile strengths (σ_b^m) for the sample set (PLS, PHS, ALS, AHS, LLS and LHS) and the apperant Young's modulus (E_A) calculated using the acoustically obtained parameters are shown in Fig. 5.b. The E_A values of the reported sample set were found to directly correlate with the measured compact tensile strengths σ_b^m (except LHS and AHS). Similar to the correlations with c_L and c_T (Fig. 5.a), E_A in the sample set AHS and LHS are not in correlation with tensile strengths σ_b^m , as capping effect was observed (Fig. 1.b). In general, the E_A values rise with increasing tensile strength.

3.3 Correlation of Compact Porosity ϕ^m with c_L , c_T , and E_A

Compact porosity ϕ^m has been previously reported to correlate with the tensile strength σ_b^m (Dave et al. 2013). In addition to correlating the sample tensile strengths with the acoustic parameters, the directly measured porosity with the acquired acoustic parameters, i.e. c_L , c_T , and E_A are also compared. In Fig. 6.a, the correlations between the measured porosities (ϕ^m) for the complete sample set (PLS, PHS, ALS, AHS, LLS and LHS) at various compaction pressure levels (P_c) and the pressure and shear velocities (c_L and c_T) are depicted. An inverse correlation was observed between the measured compact porosity ϕ^m and c_L for each sample set (except

LLS, LHS and AHS). As shown in Fig.6.a, c_L and c_T in sample set LHS were not in correlation with ϕ^m due to invisible internal cracks (Fig. 1.d) and visible capping (Fig. 1.e) observed at P_2 and P_3 . The trend lines of c_L for PLS, PHS and ALS, AHS were distinct or separated, whereas the trend lines of c_T for PLS PHS and ALS, AHS were found to be overlapping (Fig.6.a).

The correlations between the porosities of compacts (ϕ^m) for the sample set (PLS, PHS, ALS, AHS, LLS and LHS) at various compaction pressures (P_c), and the Young's modulus (E_A) calculated using the acoustically obtained parameters are shown in Fig. 6.b. An inverse correlation was established between the measured compact porosity ϕ^m and E_A for each sample set of the reported study. As expected, the estimated E_A values of the tested samples were found to directly correlate with the measured compact porosities (ϕ^m). In general, the E_A values (Table. 3) appeared to decrease with increasing porosity (ϕ^m). The trend lines of E_A for compacts with different material were found to be distinct and separated for each sample set (Fig. 6.b).

In summary, the reported observations made using a non-destructive ultrasonic technique and presented results quantify the sensitivity and correlation of the extracted properties (c_L , c_T , and E_A) with the directly measured quantities (tensile strength (σ_b^m) and porosity (ϕ^m)) of the compressed samples. This comparison is often regarded as an experimentally quantifiable physical property benchmark.

CONCLUSIONS AND REMARKS

A compaction pressure (P)- and speed (v_c)-based design space of solid dosage compacts is explored for capping risk. Three types of powder materials (Pearlitol (P), Agglomerated mannitol (A) and LubriTose[®] mannitol (L)) at three compaction pressure levels ($P_1=50.06$ MPa, $P_2=3 P_1$

=150.18 MPa, and $P_3=5 P_1 = 250.29$ MPa) and two compaction speeds v_c (4 and 20 msec peak compression dwell-time) were evaluated. Employing an X-ray CT scanner, the internal microstructures of the compacts were obtained at micro-meter scale, and evaluated for texture uniformity, internal cracks and defects. The X-ray images indicated formation of internal cracks leading to visible capping behavior at higher compaction pressures. With the presented acoustic set-up, the acoustic and mechanical properties of the compacts (c_L , c_T and E_A) were extracted in a non-destructive manner from ultrasonic waveforms. It is shown that these acoustic parameters can be adopted as early indicators for capping risk. Pressure (longitudinal) and shear (transverse) waves (Fig. 3) propagating in the axial directions of compacts, along with the wave arrival times (i.e. ToF) are strongly modulated by the internal cracks (prior to visible damage) (Fig. 1.c) and substantial material damage and removal due to capping (Fig. 1.d). The analysis of the experimental data indicates that the ultrasonic wave velocities and elastic experimental properties (c_L , c_T and E_A) correlated with resulting physical properties (ϕ^m and σ_b^m) for sample set PLS, PHS, ALS and LLS, whereas in sample set AHS and LHS, due to the invisible internal cracks and visible capping, no clear correlations were observed. Based on the ToF (Δt_L) measurements of pressure (longitudinal) waves in the sample sets, E_A of the compact materials was extracted and analyzed. It is found that the E_A values of PLS, PHS, ALS, AHS and LLS rise with an increasing P_c (Fig. 4.b), whereas in sample sets LHS at P_2 and P_3 , E_A values decrease. This reduction is attributed to lateral internal cracks (Fig. 1.d) and substantial material removal (Fig. 1.e). Also, the E_A values for the samples compacted at Low Speed (LS) (namely, PLS, ALS and LLS) differ from those at High Speed (HS) (PHS, AHS and LHS, respectively). For example, at $P_1 = 50.06$ MPa, ΔE_A (difference of E_A between LS group and HS group) is 1.41, 5.17 and 2.28%, at $P_2 = 150.18$ MPa, $\Delta E_A = 2.23, 14.23$ and 29.89%, at $P_3 = 250.29$ MPa, ΔE_A is

6.91, 36.41 and 78.95%, respectively. Along with the high-resolution X-ray CT images indicating internal cracks at P_2 and P_3 for LHS, it is concluded that the mechanical properties (c_L , c_T and E_A) correlate with P_c and v_c . Also, E_A can be used as an early indicator for detecting capping effect (prior to visible capping damage to compacts). In PHS, PLS, ALS, and LLS, E_A and σ_b^m are directly correlated, whereas E_A and ϕ^m are inversely correlated. In AHS and LHS, E_A was not in correlation with ϕ^m or σ_b^m due to visible capping and invisible cracks in compacts.

Current study presents a compact powder and compression parameters based design space, and a non-invasive, practical, and easy-to-use approach for characterizing the physical-mechanical properties of pharmaceutical tablets. This time- and material-sparing approach can be utilized at many key stages of pharmaceutical manufacturing research and solid dosage product development as well as manufacturing. For instance, during pre-formulation and formulation stages, the physical-mechanical characterization of neat materials and complex (mixture) formulations is a critical process. Utilizing the wave propagation approach described here as a non-invasive characterization technique can assist in optimizing the formulation and process variables with minimal material loss. During solid dosage manufacturing, the approach can further minimize the time required for product quality checks and corrective actions. In short, this approach supports the QbD (Quality-by-Design)-PAT (Process Analytic Technology) paradigm developed and recommended by the U.S. FDA (United States Food and Drug Administration). Finally, we note that the wave dispersion relation of medium is also likely to be altered by internal defects leading to capping, yet it is outside the scope of current work. Further study on the effects of defects on dispersion curves should shed additional light on predicting capping risk in pharmaceutical solid dosage forms.

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Table 1. Directly measured parameters: the average measured tablet thicknesses (h), diameters (d), masses (m), apparent mass densities (ρ_A), average value of the tablet porosity (ϕ^m) and tensile strength (σ_b^m). The acoustically extracted parameters: pressure (c_L) and shear (c_T) wave velocities, average apparent Young's moduli (E_A), and Poisson's ratio (ν), with corresponding standard deviations for the six sample sets of cylindrical tablets (i.e., PLS, PHS, ALS, AHS, LLS and LHS) for the three levels of compaction pressure P_c (in the range of P_1 , P_2 and P_3).

Sample Set	Compression Pressure P_c (MPa)					
		ϕ^n (%)	σ_b^m (MPa)	h (mm)	d (mm)	m_A (g)
PLS	P_1	27.20 ± 0.22	1.20 ± 0.03	4.70 ± 0.03	11.26 ± 0.01	0.498 ± 0
	P_2	14.28 ± 0.33	3.87 ± 0.07	4.00 ± 0.02	11.26 ± 0.02	0.499 ± 0
	P_3	8.95 ± 0.43	5.52 ± 0.08	3.76 ± 0.02	11.28 ± 0.01	0.500 ± 0
PHS	P_1	28.09 ± 0.41	0.89 ± 0.03	4.75 ± 0.04	11.27 ± 0.01	0.498 ± 0
	P_2	15.46 ± 0.83	3.12 ± 0.13	4.01 ± 0.02	11.29 ± 0.02	0.496 ± 0
	P_3	11.03 ± 0.33	4.74 ± 0.06	3.81 ± 0.02	11.29 ± 0.01	0.496 ± 0
ALS	P_1	21.92 ± 0.21	1.14 ± 0.06	4.37 ± 0.05	11.27 ± 0.01	0.501 ± 0
	P_2	12.72 ± 0.11	1.84 ± 0.04	3.88 ± 0.05	11.29 ± 0.01	0.499 ± 0
	P_3	8.41 ± 0.14	2.21 ± 0.09	3.75 ± 0.04	11.30 ± 0.01	0.507 ± 0
AHS	P_1	20.28 ± 0.27	0.81 ± 0.03	4.34 ± 0.02	11.27 ± 0.01	0.510 ± 0
	P_2	13.86 ± 0.14	1.72 ± 0.06	4.01 ± 0.06	11.29 ± 0.01	0.511 ± 0
	P_3	9.81 ± 0.26	1.74 ± 0.04	3.80 ± 0.03	11.29 ± 0.01	0.506 ± 0
LLS	P_1	16.34 ± 0.95	0.52 ± 0.02	4.08 ± 0.04	11.29 ± 0.01	0.503 ± 0
	P_2	6.76 ± 0.41	1.28 ± 0.04	3.61 ± 0.04	11.29 ± 0.01	0.496 ± 0
	P_3	5.09 ± 0.48	2.11 ± 0.11	3.59 ± 0.03	11.30 ± 0.01	0.503 ± 0
LHS	P_1	11.82 ± 0.73	1.11 ± 0.06	3.87 ± 0.03	11.28 ± 0.01	0.502 ± 0
	P_2	9.07 ± 0.83	1.09 ± 0.04	3.76 ± 0.06	11.29 ± 0.01	0.504 ± 0
	P_3	10.49 ± 0.65	0.91 ± 0.05	3.79 ± 0.03	11.28 ± 0.01	0.499 ± 0

Figure 1.a

Fig.1.b

Inset to Figure 1.b

Fig.1.c

1
m
m

Fig.1.d

1
m
m

Fig.1.e

Figure 1. (a) Instrumentation diagram of the experimental set-up operating in the pitch-catch mode. (b) The sample tablet with capping surface in sample set LHS with compaction pressure P_3 of 250.29 MPa, the damage to the tablet surface is clearly visible. Inset: The sample tablet with complete surface (no visible damage). The X-ray CT cross-sectional (side views) images of (c) the compact LHS at $P_1 = 50.06$ MPa shows a uniform microstructure with no visible cracks or breakage, (d) the lateral internal cracks observed in the compact LHS at $P_2 = 150.18$ MPa, (e) substantial material removal from the top and bottom surfaces of the compact in sample set LHS at $P_3 = 250.29$ MPa.

Figure 2.a

Figure 2.b

Figure 2. Relationship between the compaction pressure (P_c) and the directly measured properties: (a) tensile strength (σ_b^m) and (b) porosity ratio (ϕ^m) for the sample sets.

Figure 3.a

Figure 3.b

Figure 3. Normalized pressure (a) and shear (b) waveforms for the six sample sets (PLS, PHS, ALS, AHS, LLS and LHS) with the delayline response (dotted lines) at corresponding compaction pressure levels ($P_1 = 50.06$ MPa, $P_2 = 150.18$ MPa and $P_3 = 250.29$ MPa).

Figure 4.a

Figure 4.b

Figure 4. Relationship between the compaction pressure (P_c) and the measured material properties: (a) pressure (c_L) and shear wave velocities (c_T), and (b) average Young's moduli (E_A), of the compact materials acquired using the pitch-catch experimental configuration for the six sample sets (PLS, PHS, ALS, AHS, LLS and LHS).

Figure 5.a

Figure 5.b

Figure 5. Relationships between the directly measured tensile strength (σ_b^m) and acoustically obtained material parameters: (a) c_L and c_T , and (b) E_A (extracted) for the six sample sets.

Figure 6.a

Figure 6.b

Figure 6. Relationships between the directly measured porosity ratio ϕ^m and acoustically determined parameters: (a) c_L , (b) c_T , and (c) E_A (extracted) for the six sample sets.