A dry-coated tablet is a solid dosage form with a controlled drug-release system, which consists of a core and an outer layer. The accuracy of its geometric (e.g. the outer layer wall and core thicknesses) and mechanical properties (e.g. Young's moduli and mass densities of associated materials) could be crucial to its therapeutic and structural functions. The objective of current study is to develop a non-destructive technique for determining the geometric and mechanical properties of dry-coated tablets. Two contact ultrasonic techniques (i.e. pitch-catch and pulse-echo measurement modes) are employed and the properties of all the structural components of a set of experimental tablets are measured and reported. The thicknesses of the outer layers of the sample tablets are used to obtain the eccentricity of the core tablets. The two approaches are compared for their effectiveness in obtaining these properties of the sample dry-coated tablets. The thicknesses of the outer layers obtained with the proposed approach and with the direct (destructive) measurements are also compared. A good agreement is found; there is an approximately 2% difference. The eccentricity and concentricity of a set of tablets are determined and it is concluded that the observed consistent anomaly in eccentricity can be attributed to the same root cause and its correction can be achieved by control input based on monitoring data. Potential of the approach for in-die real-time monitoring of compaction presses and its PAT (Process Analytical Technology) applications for the pharmaceutical manufacturing are also discussed.

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The chief objective of current study is to develop a systematic procedure for determining the geometric and mechanical properties of the individual components of a dry-coated tablet in a non-destructive, rapid manner. For verification purposes, the layer thicknesses of the same tablets are also destructively measured following the non-destructive measurements. Contact ultrasonic techniques based on the pitch-catch and pulse-echo modes of acoustic wave measurements are employed and utilized. The thicknesses of the outer layer and the longitudinal velocities and Young's moduli of the core and the outer layer are determined, and, based on this data, an evaluation of the eccentricity of the core tablet with respect to the outer boundaries of the entire tablet is conducted. The reflections of the longitudinal (pressure) elastic wave pulses from the interfaces of the core tablet and the outer layers are obtained in pulse-echo measurements. The effectiveness of the current setups was previously demonstrated for more typical tablet designs by Akseli et al., 2009a,b). A non-contact method based on the modal analysis of the acousto-vibrational responses of traditional tablets was also developed and utilized in Varghese and Cetinkaya, 2007; Akseli and Cetinkaya, 2008a,b). In addition to its potential uses in the formulation and research phases, this approach could also be adopted for the online monitoring and characterization of the geometric and mechanical properties of the parts outer layers of a dry-coated tablet with a known mass density and longitudinal speed of sound in the material of the outer layer. In this study, the measured properties are obtained by a direct (destructive) means.

Current approach supports the main objectives of the Process Analytical Technology (PAT) initiative of the U.S. Food and Drug Administration (FDA), which encourages manufacturers to analyze, and control manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (Hussain et al., 2004).

2. Materials and methods

2.1. Sample tablets

A set of 25 experimental dry-coated tablets are used in the reported geometric and mechanical characterization experiments. The sample dry-coated tablet consists of a core tablet and an outer tablet (Fig. 1). The core and coat of the experimental tablets were compacted especially for this investigation using a Manesty DryCota press (OYSTAR USA, Fairfield, NJ) from two undisclosed proprietary powder materials. The dry-coated tablet manufacturing typically involves the following three basic steps: (1) a sufficient amount of powder for the outer layer fills the inside of a die, (2) a core tablet which is compacted in a separate press unit is placed on the powder bed such that the powder engulfs the core tablet, and (3) the powder containing the core tablet is compressed into a thick solid layer (dry coat) containing the core tablet. The outer tablet is composed of three structural parts, namely the top outer layer, the bottom outer layer and the side outer layer. The top layer is distinguished by the location of the identification (brand) print on the tablet surface. As depicted in Fig. 1a and b, these three structural parts of the outer tablet with the core tablet form three interfaces (the top outer layer–core interface, the bottom outer layer–core interface and the side outer layer–core interface).

In dry-coated tablet manufacturing, due to substantial centrifugal and vibrational forces generated in the compaction presses, the positional control of the core tablet and the eccentricity monitoring of the final product is critically important for obtaining the required symmetry of the tablet geometry. In current study, using the monitoring approach based on ultrasound waves, the geometric and mechanical properties of each structural part of a dry-coated tablet from the sample set are separately characterized and reported.

2.2. Experimental set-up and procedures

The experimental set-up for the pitch-catch ultrasonic mode of measurements is devised to obtain the time-of-flight (TOF) of the acoustic pulses transmitted through each structural part of the sample tablet from one transducer to another (Fig. 2a). The set-up consists of an electrical pulser/receiver unit (Panametrics 5077PR), two piezoelectric transducers (Panametrics V129 and V112) with the central frequency of 10 MHz for converting the electrical pulse into an acoustic wave and vice versa, a digitizing oscilloscope (Tektronix TDS 3052) for data acquisition and digitizing waveforms, and a computer for signal processing and data storage. In the pitch-catch mode measurements, a pair of transducers are utilized. While one of the transducers is employed as the transmitting (pitching) transducer which launches an ultrasonic pulse into one side of the sample tablet, the other transducer is used as the receiving (catching) sensor which captures the ultrasonic pulse transmitted through the tablet on the other side and transmits it as an
electrical signal to the pulse/receiver unit. The oscilloscope digitizes the electrical signal as a waveform and saves it in its memory to be signal-processed by a computer. The sampling frequency of the oscilloscope was set to 100 MHz at the averaging rate of 252 and the pulse repetition frequency of 5 kHz. The experimental set-up for pulse-echo measurements (Fig. 2b) is developed to obtain the TOF of the longitudinal (pressure) pulse transmitted to and reflected from the interfaces of the sample tablet. The main difference between the two measurement configurations is that the pulse-echo measurement system employs only one transducer (Panametrics M129) with a central frequency of 10 MHz. The accuracy and effectiveness of the current instrumentation set-up were previously demonstrated for traditional tablet designs (Akseli et al., 2009a). All the experiments that are reported on the same day, and no systematic study on the aging of the samples and other long-term factors was conducted. Substantial amplitude attenuation is observed in the reported waveforms, however, due to the thinness of the samples, the waveforms were distinguishable at the frequency range of interest.

Following the non-destructive ultrasonic testing, the masses and geometric properties (thicknesses) of various structural parts of the sample tablets are destructively determined to form a baseline data set by systematically filing away the structural parts. As a tablet is filed down, its relevant dimensions and masses are directly measured with a digital caliper (Mitutoyo, Model CD-6) and a digital balance (Mettler-Toledo, Inc., Model A120S-L), respectively. The order of the filing sequence and the dimension and mass measurements are depicted in Fig. 3(a–e). Prior to the removal of each part of the tablet by filing, pitch-catch experiments are performed for obtaining the transmission TOF in the different parts of the tablet in two (z- and r-) directions (Fig. 4). Pulse-echo measurements are also performed to obtain the round-trip TOF data for the three outer layers of the tablets (Fig. 5). In Fig. 6, the waveforms and their arrival time close-ups for the first five tablets of the sample set obtained in pitch-catch measurements are presented. In Fig. 7, the waveforms and their arrival time close-ups of the sample tablet # 8 obtained in the pulse-echo measurements are shown. As observed in Fig. 7, the reflected pulse from the interface mixes with the response of the transducer only (without the sample), however, the difference between the transducer response only and the sample response yields the waveform of the reflected pulse (blue line) from the interface with a distinct arrival time.

The longitudinal (pressure) wave velocity and, consequently, the values of Young’s moduli of each part of a sample tablet can be obtained based on their dimensions, masses, transmission TOFs and round-trip TOFs. Using the directly measured dimensions (Fig. 8) and masses of the structural parts of a tablet, the mass densities of its components are obtained. In Fig. 9, the mass densities of each part of a tablet in the complete sample set (25 tablets) are summarized. Processing the acquired waveforms, as shown in Figs. 6 and 7, yields the longitudinal TOF, $\Delta t_L$, in the corresponding layer. The longitudinal wave velocity in each structural part of the sample tablet is determined by the relation $c_L = h / \Delta t_L$, where $h$ is the thickness of the structural part of the sample tablet, i.e. the distance through which the longitudinal wave travels. Because the longitudinal wave velocity $c_L$ in one-dimensional propagation is a function of the Young’s modulus $E$ and the mass density $\rho$, that is, $c_L = \sqrt{E/\rho}$, the Young’s modulus can be extracted accordingly. The longitudinal velocities and corresponding values of Young’s moduli from the pitch-catch and pulse-echo methods for all the tablets in the sample set are summarized in Figs. 10 and 11, and Figs. 12 and 13, respectively.
Fig. 4. Schematics of the paths of the pitch-catch TOF measurements in the order of waveform acquisition in (a) the entire tablet in the axial (z) direction, (b) the entire tablet in the radial (r) direction, (c) the core and the bottom outer layer in the axial direction, (d) the core in the axial direction, and (e) the core in the radial direction.

Fig. 5. Schematics of the paths of the round-trip TOF pulse-echo measurements of (a) the top outer layer in z-direction, (b) the bottom outer layer in z-direction, and (c) the right side (with respect to the brand printed on the top surface of the tablet) of the side outer layer in r-direction.

3. Results and discussions

3.1. Geometric properties

In realizing the designed drug-release action and dissolution profiles of dry-coated tablets in a repeatable manner, it is widely accepted that the core tablet must be placed in the geometric center of the tablet with minimal eccentricity (Ozeki et al., 2004; Lin et al., 2004). In the current study, the horizontal cross-section of the tablet, which is the cross-section perpendicular to the thickness direction (z-direction) shown in Fig. 1b, was examined to confirm the eccentricity of the core tablet on the radial plane (r-direction) and the thicknesses of the top outer layer and the bottom outer layer (Fig. 1a) are determined to verify the eccentricity of the core tablet in the thickness direction (z-direction). From the horizontal cross-section of the sample tablet (Fig. 1b), it is observed that the core tablet is concentric, that is, it is nearly perfectly placed in the center of this tablet on the horizontal plane.

The directly measured thicknesses of the top outer layers and the bottom outer layers of the tablets in the sample set are summarized in Fig. 8. It is clear that the thickness of the top outer layer of each tablet in the sample set is consistently and substantially different from those of its bottom outer layer. For the sample tablets 1, 4, 5, 6, 8, 9, 11, 13, 14, 16, 17, 18, 21, and 25, the thicknesses of the top outer layers are greater than that of the bottom outer layer, while for the sample tablets 2, 3, 7, 10, 12, 15, 19, 20, 22, 23, and 24, the top outer layers are thinner than the bottom outer layers. For the convenience of describing and analyzing the mechanical properties of each structural part of the tablets, all the outer layers of the sample tablets (top outer layers and bottom outer layers) are grouped into two sub-sets, namely, the tablets with the thick outer layers and those with the thin outer layers. This is apparently the result of randomness in choosing the branding side of a tablet in this particular compaction press. It can be observed from the data depicted in Fig. 8 that the thicknesses of the thick outer layers of the sample tablets lay in the range of 1.50–1.66 mm (a variation of 10.7%) while those of the thin outer layers are in the range 1.10–1.31 mm (a variation of 19.1%). It is consequently concluded that for all the sample tablets the core tablets are significantly off from their geometric centers in the axial (z) direction.
Fig. 6. The waveforms captured in pitch-catch mode (with the close-ups in inset) for the first five tablets of the sample set of (a) the top outer layer, the core and the bottom outer layer in $z$-direction, (b) the core and the bottom outer layer in $z$-direction, (c) the core in $z$-direction, (d) the side outer layer and the core in $r$-direction, and (e) the core in $r$-direction.

Fig. 7. The pulse–echo waveforms (with their close-ups in inset) of the sample tablet # 8 for (a) its top outer layer, (b) bottom outer layer, and (c) right side of the side outer layer. The transducer acoustic response only (without the sample) is used to extract the reflected pulse from the interface (blue line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 8. Directly measured thicknesses of the top outer layer (■) and the bottom outer layer (△) of the sample tablet set. These two outer layers can be naturally grouped into thick outer layers (the top outer layers of tablets: 1, 4, 5, 6, 8, 9, 11, 13, 14, 16, 17, 18, 21, and 25 and the bottom outer layers of tablets: 2, 3, 7, 10, 12, 15, 19, 20, 22, 23, and 24) and the thin outer layers.
3.2. Mechanical properties

Directly measured mass densities of various parts of the tablets in the sample set are summarized in Fig. 9. The mean mass densities of the thick outer layer, the thin outer layer, the core, and the side outer layer for all the sample tablets are 1139.1 kg/m³, 1147.7 kg/m³, and 1091.5 kg/m³, respectively. The layer-to-layer density variations are up to 6%. The longitudinal velocities based on the TOF obtained in the pitch-catch experiments and the corresponding Young’s modulus of each part of the sample tablets are summarized in Figs. 10 and 11, respectively. The same types of data obtained from pulse-echo measurements are depicted in Figs. 12 and 13, respectively. Based on the pitch-catch measurements, the means of longitudinal wave velocities in the thick outer layers and the thin outer layers in z-direction, which are 1663.60 m/s and 1648.55 m/s respectively, are close to each other, and these velocities are 22.26% and 22.97% lower than the mean of the longitudinal wave velocities in the side outer layer in r-direction, which is 2140.1 m/s. The mean values of Young’s moduli of the thick outer layer and the thin outer layers, which are 3.19 GPa and 3.13 GPa, respectively, are close to each other, and they are 36.96% and 38.14% lower than the mean of Young’s modulus of the side outer layer in r-direction, which is 5.06 GPa.

Based on the pulse-echo measurements, the means of longitudinal velocities of the thick outer layers and the thin outer layers in z-direction, which are 1690.38 m/s and 1645.86 m/s, respectively, are close to each other, and these wave velocities are 16.31% and 18.51% lower than the mean of longitudinal velocities in the side outer layer in r-direction, which is 2019.7 m/s. The mean values of Young’s modulus of the thick outer layers and the thin outer layers, which are 3.27 GPa and 3.22 GPa, respectively, are close to each other, and these values are 27.49% and 28.60% lower than
the mean of Young’s moduli of the side outer layer in r-direction, which is 4.51 GPa. Therefore, although the thick outer layers and the thin outer layers have the same material as the side outer layers, their longitudinal velocities and Young’s modulus in z-direction are substantially different from those of the side outer layers in r-direction. The mean value of the longitudinal (sound) velocity of the core in z-direction, which is 1405.4 m/s, differs by 57.59% from that of the core in r-direction, which is 2214.7 m/s. The mean value of Young’s modulus of the core in z-direction, which is 2.20 GPa, differs 148.18% from that of the core in r-direction, which is 5.46 GPa. Thus, it is concluded that the longitudinal wave velocity and Young’s modulus of the tablet are substantially anisotropic, as also observed and reported in (Mullarney and Hancock, 2006; Akseli et al., 2009b) for cubic compacts.

3.3. Comparison of ultrasonic transmission modes

From the pitch-catch mode measurements, the TOF and the corresponding longitudinal velocities and Young’s moduli of the thick outer layer in z-direction, the thin outer layer in z-direction, the side outer layer in r-direction, the core in z-direction and in r-direction can be obtained. The pulse-echo measurements provide only the TOF and the corresponding longitudinal velocities and Young’s moduli of the thick outer layer in z-direction, the thin outer layer in z-direction, the side outer layer in r-direction. Thus, in this particular application, with the pitch-catch method, a more complete understanding of the mechanical properties of the sample tablets can be gained.

In this study, the ratio of the standard deviation and the mean is used to quantify the variations of the longitudinal velocities and Young’s moduli of each part of a sample tablet. The longitudinal velocities and Young’s moduli of the three outer layers and the side outer layers obtained in the pitch-catch mode measurements have less significant variation than those based on the pitch-catch measurements, and that in the extraction of the mechanical properties such as the longitudinal velocity and Young’s modulus, the pulse-echo method provides more reliable data than the pitch-catch method.

3.4. Wall thickness estimates for outer layers

In this study, the reflections of longitudinal acoustic pulses from the outer layer–core interfaces are obtained in the pulse-echo mode, and, accordingly, the round-trip TOF in each outer layer is determined. This approach makes it possible to use the pulse-echo mode to estimate the thicknesses of the outer layers of a dry-coated tablet and, consequently, to determine the geometric position of core tablet with respect to the entire tablet. The following equation is used for estimating the layer thickness: 
\[ h = \frac{c_L \Delta t}{2} \]
where \( h \) is the thickness estimate of the outer layer, \( c_L \) is the longitudinal wave velocity of the outer layer and \( \Delta t \) is the round-trip TOF in the outer layer. The mean wave velocities in the thick outer layers, the thin outer layers, and the side outer layers obtained in the pitch-catch mode measurements (Table 1) are used as the longitudinal wave velocities of the corresponding outer layers for the purpose of estimating their thicknesses. The round-trip TOF in each outer layer is obtained from the pulse-echo mode measurements. The thickness estimates for the three outer layers and the thicknesses of the corresponding outer layers obtained with the destructive method

![Fig. 14. Comparison of the coat thicknesses obtained by destructive means (direct measurements) of the thick outer layers (●), the thin outer layers (▲), and the side outer layers (■), and the thicknesses obtained by the non-destructive pulse-echo method of the thick outer layers (○), the thin outer layers (△), and the side outer layers (□).](Author's personal copy)
of the geometric and mechanical properties of dry-coated tablets. By integrating the traditional die-punch set with an ultrasonic system based on the experimental configurations and methods presented in this study, a real-time online tablet quality monitoring system as a PAT tool could be developed for pharmaceutical manufacturing. Further research is underway in this direction.

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References