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Ultrasonic determination of Young's moduli of the coat and core materials of a drug tablet

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ABSTRACT

Many modern tablet presses have system controls that monitor the force exerted to compress the solid oral dosage forms; however this data provides only limited information about the mechanical state of the tablet due to various process and materials uncertainties. A contact pulse/echo ultrasonic scheme is presented for the determination of the local Young's moduli of the coat and the core materials of enteric-coated and monolayer coated tablets. The Young's modulus of a material compacted into solid dosage can be related to its mechanical hardness and, consequently, its dissolution rate. In the current approach, short ultrasonic pulses are generated by the active element of a delay line transducer and are launched into the tablet. The waveforms reflected from the tablet coat–core interface are captured by the same transducer and are processed for determining the reflection and transmission coefficients of the interface from partially overlapping echoes. The Young's moduli of the coat and the core materials are then extracted from these coefficients. The results are compared to those obtained by an air-coupled acoustic excitation study, and good agreement is found. The described measurement technique provides greater insight into the local physical properties of the solid oral dosage form and, as a result, has the potential to provide better hardness-related performance predictability of compacts.

1. Introduction

The most fundamental and critical objective of a solid oral dosage form (e.g. a drug tablet) is to deliver the active pharmaceutical ingredient(s) API(s) into the human blood stream accurately and reproducibly. Tablets are typically taken orally and disintegrate in the digestive tract. Many conventional film-coated tablets are coated with cellulosic polymer film, sugar or hybrid sugar layers. In recent years, sophisticated delivery systems with more complex mechanical forms and therapeutic functions, such as osmotic pumps (Wong et al., 2002), dry-coated tablets (Zerbe and Krumme, 2002; Ozeki et al., 2004) and multi-layered tablets, have also been introduced and adopted. In case of a simple compressed core, a measure of hardness (mechanical strength) is a useful tool for predicting the durability of the tablet to withstand subsequent processing, packaging, handling and shipping. It has been known that the Young's modulus of a material compacted into solid oral dosage form can often be related to its mechanical hardness (Fell and Newton, 1970; Michrafy et al., 2007), and tablet hardness affects its disintegration profile (Holgado et al., 1995; Indiran et al., 1998; Saravanan et al., 2002; Mizumoto, 2005) and the release rate of the medicament in the digestive tract, thus potentially affects its therapeutic response (Holgado et al., 1995; Indiran et al., 1998; Saravanan et al., 2002; Mizumoto, 2005). The described technique may be used to identify quality and performance problems related to the mechanical properties of the tablet early on the production process and, consequently, reduce associated cost and material waste.

A consumable tablet is a mechanical drug delivery system consisting of various bonded and compacted functional and structural parts (Cetinkaya et al., 2006). Though some coatings are simply for aesthetic or product identification purposes, many serve critical functions. Coatings that are insoluble at lower pH values are generally referred to as enteric or delayed-release coatings. Such coats protect the drug from acid degradation (as in enteric coats) and/or the patient from potential stomach irritation. Coatings that form a controlling barrier to the release of the active ingredient and impart a sustained release of the drug are valuable delivery systems that provide convenience as well as patient compliance. As these dosage forms can contain an entire days worth of drug, a defective coating could subject the patient to hyper therapeutic levels of drug. The criticality of the coating performance is paramount and exquisite control is essential to the production process. Therefore, monitoring the mechanical (physical) properties of coats are essential quality assurance tools. The described technique provides

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a means to measure physical properties about these coating layers and offers a greater degree of assurance of coat integrity and quality. The spatial distribution of APIs and excipients in a tablet as well as the properties of its coating layer(s) play critical roles in defining its performance as a drug delivery device. Since these components are tied together by mechanical means, mechanical properties of the coat and the core of a tablet can affect its therapeutic functions and their monitoring is essential to quality control.

Several techniques such as spectroscopy-based approaches (IR (infra-red), near-IR (NIR)) (Kirsch and Drennen, 1995, 1996, 1999; Morisseau and Rhodes, 1997; Chen et al., 2001; Donoso et al., 2003; Blanco and Alcala, 2006; Otsuka and Yamane, 2006), and short pulsed of electromagnetic radiation (e.g. TeraHertz pulsed spectroscopy) (Fitzgerald et al., 2005) have demonstrated potential with varying success for defect detection, coat thickness measurements and material characterization of tablets. NIR-based techniques are utilized to predict tablet hardness and porosity which rely on the observation that an increase in tablet hardness and a decrease in tablet porosity generate an increase in NIR absorbance (Morisseau and Rhodes, 1997; Blanco and Alcala, 2006). A nondestructive, but invasive method based on pulse photoacoustics (thermoelastic excitation and piezoelectric sensing) was proposed by Ketolainen et al. (1995) for evaluation of mechanical properties such as elasticity, porosity, density and sodium chloride content of pharmaceutical tablets. In this method, ultrasound is generated by means of pulsed laser beam and it was reported that such properties of tablets can be related to parameters extracted from the ultrasonic pulses transmitted through the tablets. Short pulses of electromagnetic radiation and its reflections from interfaces (e.g. TeraHertz pulsed spectroscopy) is based on the measurement of the time-of-flight of high-frequency electromagnetic waves inside the coating layer(s) of a tablet (Fitzgerald et al., 2005). The coating layer(s) thickness information is extracted for known speeds of light in the materials of the coat layers; therefore, it is an indirect method. Also, its size and high cost currently limit its widespread adoption. In the recent years, air-coupled acoustic excitation and ultrasonic methods (Varghese and Cetinkaya, 2007; Akseli and Cetinkaya, 2008a,b; Akseli et al., 2008a,b) are introduced for non-contact/nondestructive testing and characterization applications. In the air-coupled method, a tablet is mechanically vibrated in a frequency bandwidth by an air-coupled transducer and its vibrational response is acquired and processed for its spectral properties. The spectral properties (resonance frequencies and mode shapes) are related to the defect state and the mechanical properties of the tablet.

In the current method, an acoustic wave pulse (in the bandwidth of ultrasonic frequencies) is generated by a contact transducer and

Table 1
Summary of the physical properties of the P-tablets. Dimensions, local coating thicknesses and masses of the enteric-coated P-tablets employed in the experiments.

Tablet ID	Tablet No.	Mass (mg)	Width (mm)	Length (mm)	Thickness (mm)	Coating Thickness (μm)
P-tablet	1	205.9	5.79	11.45	3.33	102.3
	2	209.1	5.78	11.47	3.35	102.1
	3	205.4	5.78	11.45	3.32	101.4
	4	207.2	5.78	11.45	3.32	101.7
	5	206.9	5.76	11.45	3.33	100.3
	6	210.9	5.77	11.45	3.34	102.3
	7	210.8	5.79	11.45	3.35	102.3
	8	203.4	5.78	11.45	3.31	101.2
	9	206.6	5.78	11.45	3.31	100.5
	10	202.8	5.78	11.45	3.31	100.6
	11	203.9	5.79	11.45	3.33	101.2
	12	202.4	5.78	11.45	3.35	100.1
	13	204.9	5.79	11.45	3.31	102.3
	14	205.7	5.78	11.45	3.32	101.4
	15	209.3	5.77	11.45	3.33	101.3
	16	201.9	5.77	11.45	3.33	100.8
	17	207.6	5.78	11.45	3.31	102.2
	18	201.8	5.79	11.45	3.31	102.1
	19	203.8	5.79	11.45	3.30	102.3
	20	202.6	5.78	11.45	3.33	101.9

Table 2
Summary of the physical properties of the A-tablets. Dimensions, local coating thicknesses and masses of the monolayer coated A-tablets employed in the experiments.

Tablet ID	Tablet No.	Mass (mg)	Thickness (mm)	Diameter (mm)	Coating Thickness (μm)
A-tablet	1	477.1	6.32	11.35	245.1
	2	477.8	6.31	11.36	245.8
	3	477.3	6.32	11.35	246.1
	4	476.9	6.33	11.34	246.2
	5	477.2	6.34	11.37	245.3
	6	477.3	6.33	11.33	245.3
	7	477.3	6.32	11.37	246.2
	8	476.7	6.32	11.34	245.7
	9	476.1	6.33	11.35	245.5
	10	476.8	6.31	11.34	245.2
	11	476.3	6.32	11.37	246.1
	12	476.9	6.31	11.33	245.2
	13	477.0	6.33	11.34	245.3
	14	477.8	6.35	11.36	245.4
	15	477.5	6.33	11.35	246.5
	16	476.4	6.31	11.38	245.2
	17	477.4	6.33	11.37	245.4
	18	477.8	6.33	11.36	245.4
	19	475.9	6.32	11.35	245.9
	20	476.6	6.33	11.36	245.3

its reflection from the coat–core interface is acquired by the same transducer. The propagation of ultrasonic waves is governed by the mechanical properties of materials and, therefore, methods based acoustic waves (wave packets) result in direct measurements of such properties. In what follows, a contact ultrasonic method for determination of the Young's moduli of the coat and the core materials of enteric-coated and monolayer coated tablets is presented and its application is demonstrated.

2. Materials and methods

2.1. Materials

In the reported experiments, two sample tablet groups (referred to as P-tablets and A-tablets) with different compositions and mechanical states are analyzed. P-tablets are enteric-coated tablets. Each P-tablet contains the following inactive ingredients: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide. A-tablets are monolayer coated commercial tablets with the Ibuprofen API of 200 mg and contain a nonsteroidal anti-inflammatory drug. Each A-tablet contains the following inactive ingredients: acetylated monoglycerides, colloidal silicon dioxide, corn starch, croscarmellose sodium, methylparaben, microcrystalline cellulose (MCC), pharmaceutical glaze, pharmaceutical ink, povidone, pregelatinized starch, propylparaben, sodium benzoate, sodium lauryl sulfate, stearic acid, sucrose, synthetic iron oxide, titanium dioxide, white wax. The dimensions, local coating thicknesses and masses of the both tablet groups are listed in Tables 1 and 2.

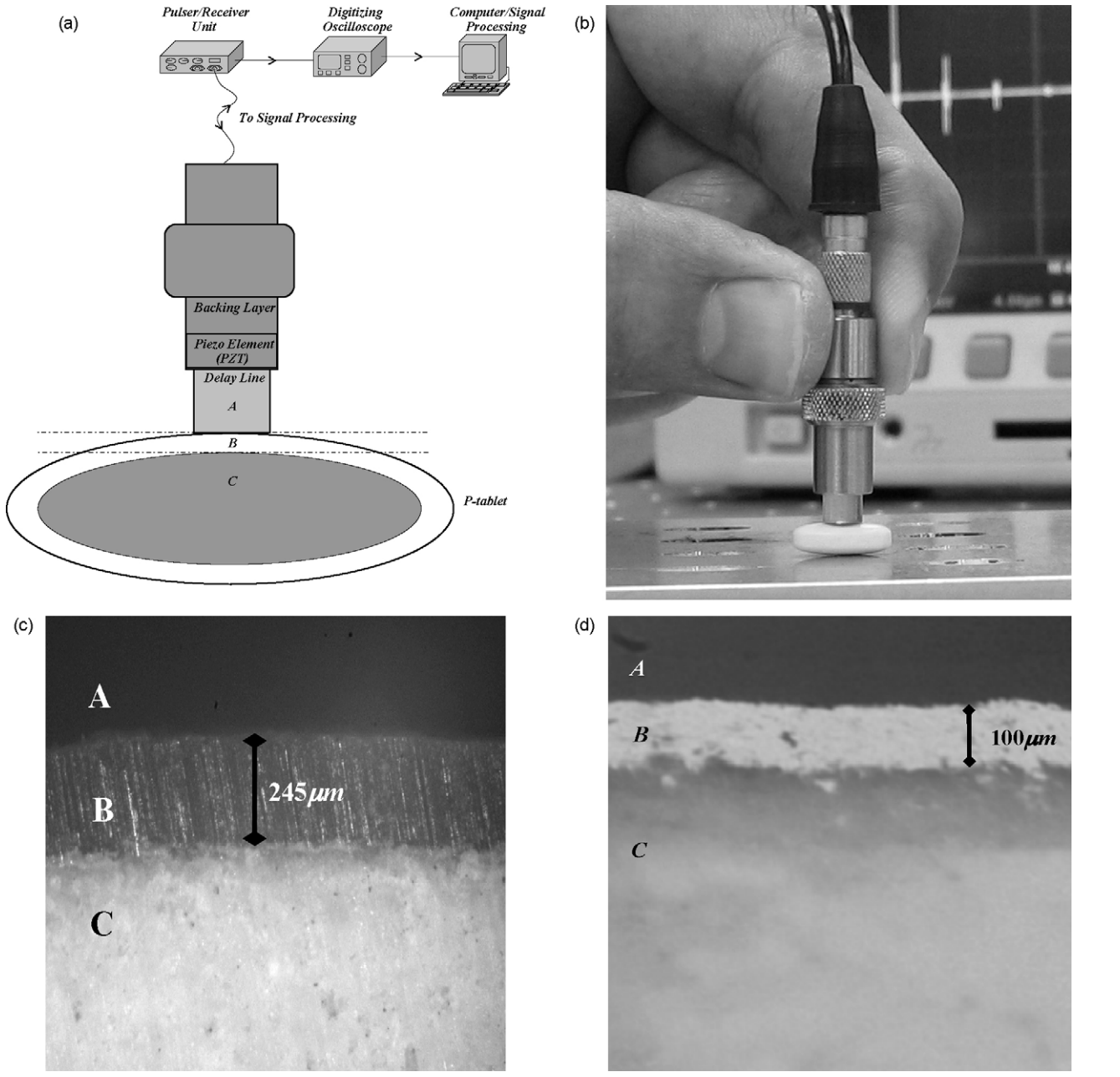

Fig. 1. (a) The schematics of the measurement set-up with a piezoelectric transducer (not-to-scale), the instrumentation diagram of the experimental set-up in the pulse-echo mode. (b) A photograph of the set-up (close-up). (c and d) The microscope images of the cross-section of the A-tablet at 5× and P-tablet at 10×.

2.2. Experimental set-up

The present measurement approach is based on the analysis of the propagation speed of an acoustic pulse launched into a tablet and its reflection from the coat–core interface of the tablet. Processing the acquired waveforms yields the acoustic impedances and, consequently, the Young's moduli of the coat and the core materials of the tablet (E_{coat} and E_{core}) in the locale of the measurement. The experimental set-up developed for the current study consists of an ultrasonic pulser/receiver unit (Panametrics 5077PR), a delay line transducer (Panametrics M208), a digitizing oscilloscope (Tektronix TDS3052) and the data acquisition is controlled by a computer. An instrumentation diagram of the experimental set-up is depicted in Fig. 1a. In the experiments reported, the delay line transducer with a central frequency of 20 MHz is placed on a surface of the tablet vertically to transmit acoustic pulses through the tablet (Fig. 1a and b). The key function of the delay line is to create a time lapse between the original acoustic pulse (i.e. incident wave) and the arrival of any reflected waves from the interface to avoid mixing (overlapping) of travelling wave packets. An acoustic couplant gel material (e.g. glycerin) is used for increasing acoustic transmission of the ultrasonic field of the transducer to the tablet substrate. It is observed that glycerin gel has caused no visible damage to the tablet coat when it is removed fairly quickly (i.e. less than a minute or so). In the experiments, the delay line transducer is put in contact with a surface of the tablet vertically to transmit acoustic pulses through the tablet (Fig. 1a and b). An electrical pulse from the pulser/receiver unit excites the transducer at a central frequency of 20 MHz. The acoustic pulse transmitted through the coat of the tablet and reflected from the delay line-coat and the coat–core (A-scan) interfaces is captured by the same transducer and acquired using the digitizing oscilloscope (Figs. 1 and 2). From an ultrasonic A-scan, the ultrasonic travel time (time-of-flight) through specimen and the amplitude of the received signal can be determined. In the reported contact ultrasonic experiments, the sampling resolution of the acquired acoustic signals is 50 ns and the oversampling rate of the digitizing oscilloscope is set to 512. A series of twenty P-tablets and twenty A-tablets are employed for this study. The results are compared to those obtained using the air-coupled acoustic excitation method for the same tablets (Akseli and Cetinkaya, 2008a). It is observed that Young's Moduli values of all twenty tablets are consistent for each tablet group. The Young's modulus variations observed over time for the same tablets were less than 0.2%. It is noteworthy that other material parameters affecting the acoustic impedances (i.e. mass densities of the coat and the core materials) of the tablet materials can also be predicted by using this approach.

2.3. Mathematical formulation for contact ultrasonic measurements

In calculating the velocities of propagation in the coat material, the time-of-flight (TOF), the coat thickness and the mass density of the coat material are required. In the current work, the properties of both materials in the measurement zone (the transducer contact area) are assumed linear, isotropic and homogenous in the relevant range of acoustic frequencies and amplitudes. The mass densities of the coat (ρ_{coat}) and the core (ρ_{core}) materials with known geometric attributes are determined from direct mass measurements and the coating layer thickness (h) of each tablet are destructively measured using an optical microscope at 5× and 10× magnification factors (Fig. 1c and d). When a propagating acoustic pulse impinges the interface between two media of different materials, a portion of the propagating pulse energy is reflected back and the remaining energy is transmitted across the interface depending on the mechanical (acoustic) impedances of the two media. As an acoustical pulse travels through various interfaces, its phase speed and amplitude attenuation are dependent on the material properties of the media, namely, the acoustic impedance (Z) of an acoustically homogenous material, defined by $Z = \rho \cdot c_L$, where ρ is the mass density of the propagation medium, and c_L the phase velocity of longitudinal stress wave in that medium. In terms of the acoustic impedances of the media, the reflection coefficient, defined as $C_r = A_r/A_i$ (the ratio of the stress wave amplitude of the reflected waveform which is related to the strain in the material A_r to that of the incident wave A_i) and transmission coefficient $C_t = A_t/A_i$ (the ratio of the stress wave amplitude of the transmitted waveform A_t to A_i) are expressed as

$$C_r = \frac{Z_2/Z_1 - 1}{Z_2/Z_1 + 1} \quad \text{and} \quad C_t = \frac{2Z_2/Z_1}{Z_2/Z_1 + 1} \tag{1}$$

where Z_1 and Z_2 are the acoustic impedance of the medium (1) in which the acoustic wave is incident and the acoustic impedance of the medium (2) from/into which the wave is reflected and/or transmitted (Achenbach, 1984), respectively.

As depicted in the ray tracing diagram of the propagation and reflection in a three-layer structure (A–B–C) (Fig. 2), the acoustic pulse (incident wave (1)) $f_1(t)$ generated by the active element of the transducer propagates into the delay line and reflects from the delay line (1′) (A)–air interface (no transmission into air is assumed) (Fig. 2a) is obtained by operating the transducer in air (Figs. 3a and 4a). The incident acoustic pulse is launched into

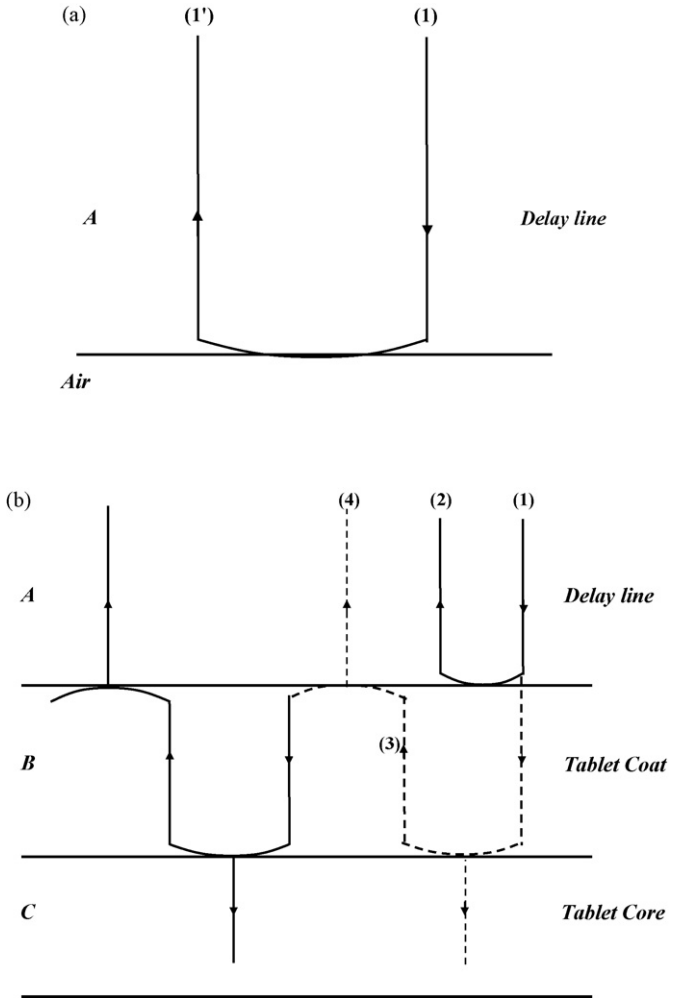

Fig. 2. (a) The path of the incident field reflected from the transducer delay line *A–Air* interface. (b) The paths of the reverberation of the incident wave from the interface between the delay line (A), the coat (B) and the core (C) of P-tablet01 and A-tablet01.

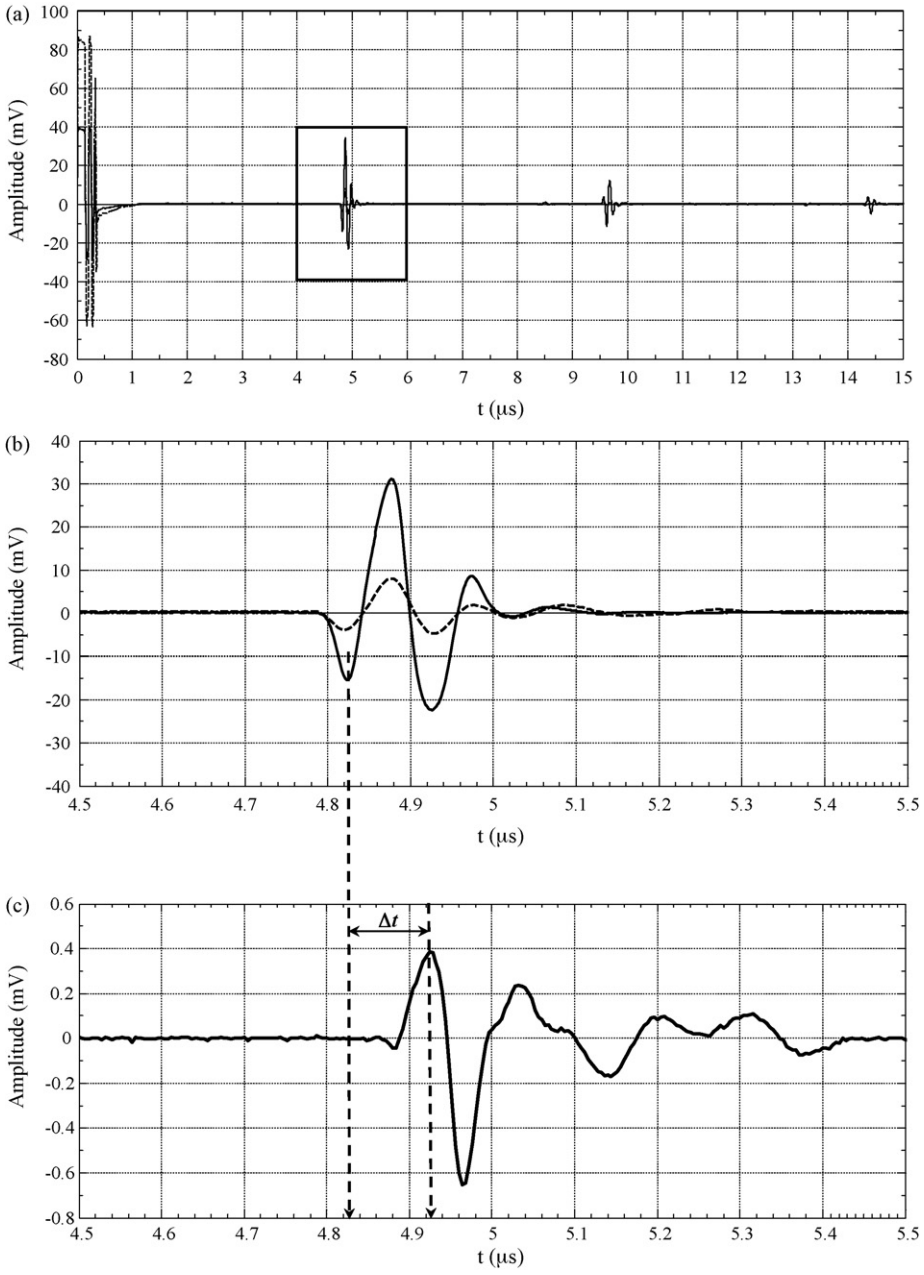

Fig. 3. (a) The waveform of the *A–Air* interface $f_{(1)}(t)$ (solid line) and the reflected waveform $f_{(4)}(t)$ (dashed line) for P-tablet01, the round trip TOF in the coating layer of the P-tablet01 $\Delta t = 98.9$ ns. (b) Close-up of the waveforms of the *A–Air* interface $f_{(1)}(t)$ (solid line) and the reflected waveform $f_{(4)}(t)$ (dashed line). (c) The first reflection $f_{(3)}(t)$ arriving at the sensing element of the transducer from the B–C interface.

the tablet reflected and transmitted (2 and 3) from media A–B–C (Fig. 2b) and received by the active element of the transducer (4) (Figs. 3b and 4b). In Fig. 2b, the acquired waveform ($f_4(t)$) reflected from and transmitted through A–B–C layers depends on the impedances of the media A (delay line), B (coating layer), and C (tablet core). Under the assumption of ideal reflection and propagation conditions (i.e. interface flatness, and coat thickness uniformity) in the measurement zone (under the transducer contact area), from the ray tracing, the response of the transducer in contact with the tablet can be approximated for the first reflection from the tablet coat–core interface as

$$f_4(t) \cong \underbrace{C_r^{B-C}.C_t^{A-B}.C_t^{B-A}.f_1(t-\Delta t)}_{f_3(t)} + \underbrace{C_r^{A-B}f_1(t)}_{f_2(t)} \quad (2)$$

where Δt is the round trip TOF in the coating layer, $f_3(t)$ the first reflection waveform from the B–C interface (Fig. 2b), C_r^{B-C} the reflection coefficient of the B–C interface, C_t^{A-B} the transmission coefficient from A to B, C_t^{B-A} the transmission coefficient from B to A, C_r^{A-B} the reflection coefficient of the A–B interface and $C_r^{A-B}f_1(t)$ the reflected waveform from B. As depicted in Figs. 3c and 4c, the overlapping $f_3(t)$ can be approximated from $f_2(t)$ and $f_4(t)$ as (Cepel and Neal, 2007)

$$f_3(t) \cong f_4(t) - f_2(t) \quad (3)$$

Since the amplitude of $f_2(t)$ is higher than that of $f_3(t)$, an approximate value for ${}^*C_r^{A-B}$ can be extracted from $f_1(t)$ and $f_4(t)$ as

$$f_3^*(t) \cong f_4(t) - {}^*C_r^{A-B}f_1(t) \quad (4)$$

where Z_A is obtained from $Z = \rho \cdot c_L$ and Z_B is determined substituting Z_A into Eq. (1). C_t^{A-B} and C_t^{B-A} are also calculated by substituting Z_A

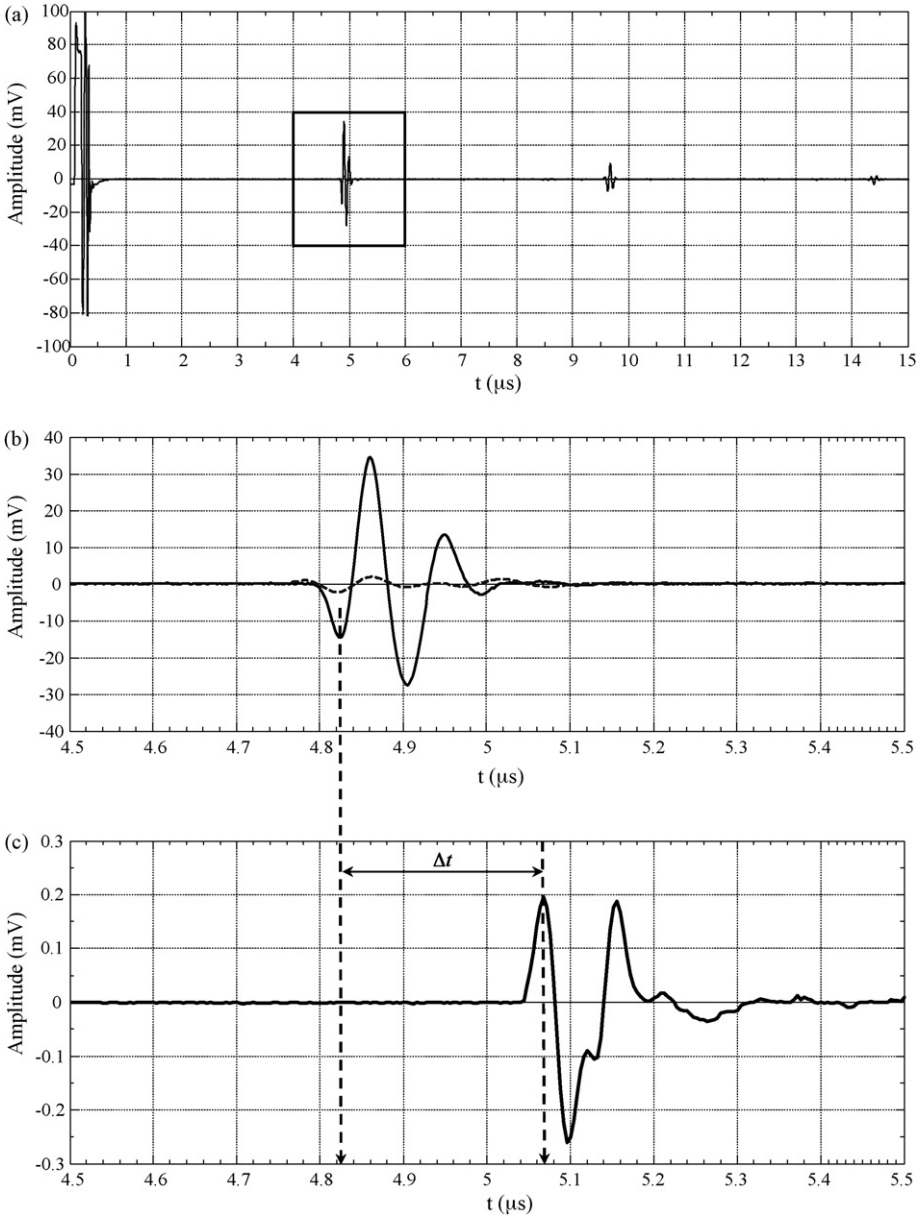

Fig. 4. (a) The waveform of the *A–Air* interface $f_{(1)}(t)$ (solid line) and the reflected waveform $f_{(4)}(t)$ (dashed line) for A-tablet01, the round trip TOF in the coating layer of the A-tablet01 $\Delta t = 245$ ns. (b) Close-up of the waveforms of the *A–Air* interface $f_{(1)}(t)$ (solid line) and the reflected waveform $f_{(4)}(t)$ (dashed line). (c) The first reflection $f_{(3)}(t)$ arriving at the sensing element of the transducer from the B–C interface.

and Z_B into Eq. (1):

$$\frac{f_3^*(t)}{f_1(t-\Delta t)} \cong C_r^{B-C}.C_t^{A-B}.C_t^{B-A} \tag{5}$$

The approximate value for C_r^{B-C} is obtained by substituting C_t^{A-B} and C_t^{B-A} into Eq. (5). Similarly, Z_C is determined using Eq. (1) and this information yields the value of the Young's modulus of the core material E_{core}. For a known coating layer thickness (h), the longitudinal velocity of sound c_L using $c_L = h/\Delta t$ of the coat material of the tablet can be determined. The Young's modulus of the coat material E_{coat} can then be calculated using $c_L = \sqrt{E/\rho}$. The mass densities of the coat and the core are obtained from direct mass measurements since the tablet geometry and coat thickness are known.

3. Results and discussion

The Young's modulus values of the P-tablets and A-tablets are extracted using the contact pulse/echo ultrasonic method described above in detail. For example, in P-tablet01 and A-tablet01 the TOF values in their coat layers are determined as $\Delta t = 98.9\,ns$ and $\Delta t = 245\,ns$ (Figs. 3 and 4), respectively. From Eq. (5) and the acquired waveforms $f_{(1)}(t)$ and $f_{(3)}(t)$ (Figs. 3 and 4), using known values of δ_{coat}, ρ_{core} and ρ_{coat} for P-tablet01 and A-tablet01, E_{coat} and E_{core} of the P-tablet01 and A-tablet01 are extracted as $3{,}030.42 \pm 1.21$ MPa, $2{,}619.98 \pm 1.43$ MPa and $3{,}054.11 \pm 1.74$ MPa, $2{,}382.27 \pm 1.16$ MPa, respectively, as tabulated in Tables 3 and 4. For the set of P-tablets and A-tablets, used in the experiments, it is determined that uncertainties in the arrival time measurements of the pressure wave Δt_L are ±0.8% and ±0.9%, respectively. This level of measurement uncertainly results in associated calculation errors of ±4.82 MPa, ±13.40 MPa and ±1.11 MPa, ±1.71 MPa in the

Table 3
Comparison of the values of Young's moduli obtained by the air-coupled and contact methods. $\bar{p}^n$ is the mechanical parameter vector obtained with the air-coupled excitation method. $\bar{p}^c$ is the Young's modulus and mass density (obtained from direct mass density measurements) values of the coat and the core material of twenty P-tablets (based on the values of E_{core}, ρ_{core}, ρ_{coat}, E_{coat}, δ_{coat} from $\bar{p}^n$). C.V. denotes the coefficient of variation.

Method used	Tablet ID: P-tablet	E_{core} (MPa)	ρ_{core} (kg/m^3)	ν_{core}	E_{coat} (MPa)	ρ_{coat} (kg/m^3)	ν_{coat}	δ_{coat} (μm)
$\bar{p}^n$ Air-coupled acoustic	Tablet01	2600.77	1313.59	0.33	3041.85	742.40	0.43	99.96
$\bar{p}^c$ Contact ultrasonic	Tablet01	2619.98	1321.95	–	3030.42	743.41	–	–
	Tablet02	2604.12	1310.05	–	3042.21	741.84	–	–
	Tablet03	2613.04	1308.83	–	3037.82	742.15	–	–
	Tablet04	2612.17	1314.41	–	3039.14	743.07	–	–
	Tablet05	2597.28	1307.98	–	3042.29	742.31	–	–
	Tablet06	2598.11	1309.56	–	3040.76	742.26	–	–
	Tablet07	2594.38	1309.13	–	3033.91	742.17	–	–
	Tablet08	2590.64	1308.71	–	3036.07	742.07	–	–
	Tablet09	2619.98	1308.28	–	3037.22	741.97	–	–
	Tablet10	2604.12	1307.86	–	3039.38	741.88	–	–
	Tablet11	2613.04	1307.43	–	3039.54	741.78	–	–
	Tablet12	2612.17	1307.01	–	3041.69	741.68	–	–
	Tablet13	2597.28	1310.05	–	3041.85	741.59	–	–
	Tablet14	2602.92	1310.78	–	3041.10	741.49	–	–
	Tablet15	2612.52	1312.09	–	3037.16	741.39	–	–
	Tablet16	2604.12	1313.40	–	3037.32	741.29	–	–
	Tablet17	2605.72	1314.71	–	3042.47	741.20	–	–
	Tablet18	2607.32	1316.02	–	3032.63	741.10	–	–
	Tablet19	2608.92	1317.33	–	3033.21	741.00	–	–
	Tablet20	2605.52	1318.64	–	3036.38	740.91	–	–
C.V.	–	0.31	0.32	–	0.12	0.09	–	–

extracted values of Young's modulus E for the coat and the core materials of the P-tablets and A-tablets, respectively. The coefficient of variations of the Young's modulus values of the coat and the core materials are 0.12% and 0.31% for the P-tablet set and 0.12% and 0.09% for the A-tablet set, respectively.

The extracted Young's modulus values for the twenty P-tablets tested (Table 3) are in good agreement with those obtained for the coat and the core materials using the air-coupled acoustic excitation method (Akseli and Cetinkaya, 2008a). Also, the Young's modulus values of the twenty A-tablets tested are determined using the air-coupled acoustic excitation method for comparison purposes with the contact ultrasonic method. It is found that the extracted values of Young's modulus from the contact ultrasonic experiments agree well with those determined using the air-coupled acoustic excitation method as tabulated in Table 4. Acoustic impedances, reflection and transmission coefficients of the media A–B–C of P-tablet01 and A-tablet01 based on the mechanical properties approximated from the air-coupled acoustic and contact ultrasonic method are also calculated and listed in Tables 5 and 6.

In the reported experiments, a series of contact pulse/echo ultrasonic experiments are conducted for the same P-tablet and A-tablet sets at random dates in order to establish repeatability and to monitor the variations in the mechanical properties of the coat and the core due to external effects (e.g. couplant gel). It is found that the coefficient of variation is calculated as 0.13%, 0.28% and 0.15%, 0.17% for the Young's moduli of the coat and the core materials of the P-tablets and A-tablets, respectively. It is confirmed that, since the tablets are coated, the effect of the couplant gel is irrelevant to

Table 4
Comparison of the values of Young's moduli obtained by the air-coupled and contact methods. $\bar{p}^n$ is the mechanical parameter vector obtained with the air-coupled excitation method. $\bar{p}^c$ is the Young's modulus and mass density (obtained from direct mass density measurements) values of the coat and the core material of twenty A-tablets (based on the values of E_{core}, ρ_{core}, ρ_{coat}, E_{coat}, δ_{coat} from $\bar{p}^n$). C.V. denotes the coefficient of variation.

Method used	Tablet ID: A-tablet	E_{core} (MPa)	ρ_{core} (kg/m^3)	ν_{core}	E_{coat} (MPa)	ρ_{coat} (kg/m^3)	ν_{coat}	δ_{coat} (μm)
$\bar{p}^n$ Air-coupled acoustic	Tablet01	2379.82	1004.40	0.28	3050.28	760.41	0.36	245.21
$\bar{p}^c$ Contact ultrasonic	Tablet01	2382.27	1006.53	–	3054.11	762.38	–	–
	Tablet02	2381.55	1005.23	–	3052.95	760.18	–	–
	Tablet03	2378.18	1004.68	–	3051.22	761.03	–	–
	Tablet04	2381.05	1003.63	–	3055.56	760.92	–	–
	Tablet05	2382.08	1002.71	–	3052.72	761.88	–	–
	Tablet06	2383.12	1003.68	–	3052.89	760.85	–	–
	Tablet07	2381.15	1004.96	–	3043.05	762.81	–	–
	Tablet08	2382.27	1004.91	–	3057.22	760.78	–	–
	Tablet09	2381.55	1003.87	–	3049.39	763.75	–	–
	Tablet10	2380.18	1004.82	–	3053.55	760.71	–	–
	Tablet11	2379.24	1004.77	–	3053.72	761.68	–	–
	Tablet12	2378.20	1005.73	–	3058.88	762.64	–	–
	Tablet13	2377.15	1005.68	–	3054.05	760.61	–	–
	Tablet14	2381.41	1003.64	–	3053.22	761.58	–	–
	Tablet15	2376.37	1006.59	–	3051.38	760.54	–	–
	Tablet16	2383.86	1003.54	–	3051.55	763.51	–	–
	Tablet17	2381.18	1002.50	–	3047.71	760.47	–	–
	Tablet18	2379.24	1005.45	–	3053.88	760.44	–	–
	Tablet19	2378.31	1004.41	–	3059.05	762.41	–	–
	Tablet20	2379.11	1005.12	–	3051.22	761.18	–	–
C.V.	–	0.09	0.11	–	0.12	0.14	–	–

Table 5
Comparison of acoustic impedances (Z). Acoustic impedances of the media A (delay line), B (coat), and C (core) are determined with the air-coupled excitation and contact methods for the P-tablet01 and A-tablet01 mechanical properties listed in Tables 3 and 4.

Acoustic impedances (Z)			
Medium	$\bar{p}^n$ Air-coupled method ($\times 10^6$ kg/m^{2}s)	$\bar{p}^c$ Contact method ($\times 10^6$ kg/m^{2}s) P-tablet01	$\bar{p}^c$ Contact method ($\times 10^6$ kg/m^{2}s) A-tablet01
A (delay line)	2.428	2.428	2.428
B (coat)	1.502	1.499	1.525
C (core)	1.848	1.861	1.548

the analysis and its results. Also, to study the possible plasticization effect of couplant gel on the coating, and, consequently, to the extracted Young's modulus values of the coating and the core materials, a thin, adhesive plastic tape layer ($d \ll \lambda$, where d is layer thickness of the tape and λ denotes the ultrasonic wavelength) is used as an acoustic couplant instead of glycerin gel (acoustic impedance of the coat material is much higher than the acoustic impedance of soft plastic layer; therefore the loading of the surface is minimal). It is found that the percentage differences between the extracted Young's modulus values of the coat and the core materials using glycerin gel and adhesive plastic tape are in the range of $\pm$0.1% for both of the tablet groups. This suggests that the glycerin gel has no effect on the plasticization of the coating on the tablet surface when removed fairly quickly.

The reported contact pulse/echo ultrasonic method has a potential to be utilized as a mechanical characterization tool for enteric-coated, dry-coated, multi-layered (coated as well as uncoated) and multi-layer coated tablets when high-frequency delay line transducers (e.g. 10–20 MHz) are employed. Using such a transducer, ultrasonic wavelengths are short enough to penetrate through the initial and final coating layers and final coat–core interface and reflect back to the active element of the transducer. In case of dry-coated tablets, the coat thickness is greater, thus the measurement of arrival time in the coating layer is simple. In case of coated multi-layered tablets and multi-layer coated tablets, since the layer thicknesses are typically in the micron-level range, a numerical bandpass filter can be applied to remove high- and low-frequency noise associated with the ambient conditions such as mechanical vibrations to acquire consistent results. Using this deconvolution process, mechanical properties of the coat and the core materials of a tablet can be extracted.

In contrast to other methods for the analysis of mechanical properties such as diametrical compression test (Michrafy et al., 2007) and NIR spectroscopy (Kirsch and Drennen, 1995, 1996, 1999), contact pulse/echo ultrasonic method provides a direct measurement of the Young's modulus rather than a calibrated estimate of the tablet hardness based on diametrical crushing load and a chemometric model. Diametrical compression testers experience difficulty with in measuring the properties of unusual or asymmetric tablet shapes. Also, unlike NIR spectroscopy, no model calibration is required for the contact ultrasonic measurements. The advantage of the NIR spectroscopic method lies in its applicability for real time at-line monitoring (Kirsch and Drennen, 1995, 1996, 1999). Such NIR measurements rely on reflectance measurement from the tablet surface and do not interrogate the entirety of the tablet volume. However, the acoustic technique cannot measure chemical compositions in a tablet and the size of the transducer, local contact area and the shape of the tablet are key parameters to acquire consistent results.

Table 6
Comparison of the values of the reflection C_r and transmission coefficients C_t. C_r and C_t values are determined for various interfaces based on Tables 3 and 4 for P-tablet01 and A-tablet01.

Reflection and transmission coefficients			
C_r and C_t	$\bar{p}^n$ Air-coupled method	$\bar{p}^c$ Contact method P-tablet01	$\bar{p}^c$ Contact method A-tablet01
C_t^{A-B}	0.764	0.764	0.771
C_r^{B-C}	0.103	0.104	0.095
C_t^{B-A}	1.235	1.236	1.228
C_r^{A-B}	−0.236	−0.236	−0.228

4. Conclusions and remarks

A contact pulse/echo ultrasonic method based on the propagation of high-frequency acoustic pulses in enteric-coated and monolayer coated tablets is developed for determination of the Young's moduli of their coat and the core materials. Two sample tablet groups with different compositions and mechanical states are analyzed. From the measured reflection and transmission coefficients of the corresponding materials, the acoustic impedances of the delay line–coat–core interfaces are obtained. The Young's moduli of the coat and the core materials of the sample tablet sets are extracted from their acoustic impedance data. The extracted Young's moduli of the coat and the core materials agree well with those measured from the air-coupled acoustic excitation method.

The hardness of a tablet is related to the Young's moduli of the coat and the core materials, therefore it is possible that manufacturing process of tablets and mechanical properties of tablet materials can affect the therapeutic functions of the drug. The presented contact pulse/echo ultrasonic method has the potential to be used as a nondestructive tablet Young's modulus tester with the capability to isolate individual tablets with coat or core integrity problems. In addition, with the reported scheme it is possible to estimate the thickness of the coating layer of a tablet if the calibration for the speed of sound in the coat medium is available. Equipment employed in the introduced scheme is considerably more cost-effective than those used in the air-coupled acoustic excitation set-up and other commercially available systems, however since this is a contact pulse/echo method, permanent damage and/or contamination to the tablet is a possibility but this can be eliminated using an adhesive tape rather than an acoustic couplant gel. Unlike the air-coupled acoustic excitation methods, the contact technique requires no numerical simulations using finite element (FE) analysis or any calibration measurements. It is noteworthy that, since the presented technique fosters increased process knowledge, it can be applied to broaden the understanding of the effect of formulation and process on the physical properties of tablets.

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