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Non-destructive determination of anisotropic mechanical properties of pharmaceutical solid dosage forms

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ABSTRACT

The mechanical property anisotropy of compacts made from four commercially available pharmaceutical excipient powders (microcrystalline cellulose, lactose monohydrate, ascorbic acid, and aspartame) was evaluated. The speed of pressure (longitudinal) waves in the uni-axially compressed cubic compacts of each excipient in the three principle directions was determined using a contact ultrasonic method. Average Young's moduli of each compact in the axial (x) and radial (y and z) directions were characterized. The contact ultrasonic measurements revealed that average Young's modulus values vary with different testing orientations which indicate Young's modulus anisotropy in the compacts. The extent of Young's modulus anisotropy was quantified by using a dimensionless ratio and was found to be significantly different for each material (microcrystalline cellulose > lactose > aspartame > ascorbic acid). It is also observed that using the presented contact method, compacts at high solid fraction (0.857–0.859) could be differentiated than those at the solid fraction of 0.85 in their groups. The presented contact ultrasonic method is an attractive tool since it has the advantages of being sensitive to solid fraction ratio, non-destructive, requiring small amount of material and rapid. It is noteworthy that, since the approach provides insight into the performance of common pharmaceutical materials and fosters increased process knowledge, it can be applied to broaden the understanding of the effect of the mechanical properties on the performance (e.g., disintegration profiles) of solid oral dosage forms.

1. Introduction

Anisotropy is an attribute of a material with directionally dependent characteristics. In anisotropic materials, the mechanical properties vary with orientations or planes in which such properties are measured. In the pharmaceutical industry, there has been considerable interest on anisotropy and the difference in mechanical hardness and strength between the parallel (axial) and perpendicular (radial) compaction directions of tablets (Nyström et al., 1978; Ando et al., 1983; Alderborn and Nyström, 1984; Newton et al., 1992; Malamataris et al., 1996; Moe and Rippie, 1997; Edge et al., 2001; Galen and Zavaliangos, 2005; Mullarney and Hancock, 2006; Wu et al., 2008). These studies have provided that compacts produced via compaction process exhibit different mechanical property values (e.g., tensile strength and Young's modulus) when measured in different directions and therefore are mechanically anisotropic. Despite the widespread use of tablets as a dosage form, problems such as capping and lamination during tableting and with the produced tablets occur commonly. Predominantly, active pharmaceutical ingredients (APIs) exist as crystalline or amorphous solids and they are typically mixed with excipients (inert ingredients) and compacted into pharmaceutical tablets on a high-speed press. The blend of powders/granules is confined radially by a rigid die while being compressed axially by the moving punch or punches. When the compressional force is removed and the compact forced out of the die, it expands radially and shear deformation occurs as the elastic material rebounds, consequently, the process creates a heterogeneous internal tablet structure. The compaction of an anisotropic powder material, in terms of particle shape and particle size, would be also expected to generate an anisotropic compact (Edge et al., 2001), which further influences relevant tablet characteristics such as Young's modulus, tensile strength, porosity and dissolution rate. Such tablet characteristics are critical to the design of tablets and the performance evaluation of the relevant manufacturing processes. For instance, for an isotropic, homogeneous tablet the axial and radial Young's modulus values should

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be equal. However, non-uniform axial and radial compact recovery following compaction (Aulton et al., 1973) preferred particle orientation upon consolidation, particulate–die–punch interactions (Li and Puri, 1996), the distribution of compressional force, non-uniform density distributions within the compacts due to die wall friction (Eiliazadeh et al., 2003; Wu et al., 2005), and the properties of materials in the mixture contribute to the non-uniformity of the Young's modulus and to the non-homogeneity of the tablet. This non-uniformity may impact its disintegration profile (Indiran et al., 1998; Saravanan et al., 2002; Mizumoto et al., 2005) and the release rate of the medicament in the digestive tract, thus potentially affects its therapeutic response (Indiran et al., 1998; Saravanan et al., 2002; Mizumoto et al., 2005). In addition, it has been reported that (Nyström et al., 1978; Jarosz and Parrott, 1982; Moe and Rippie, 1997; Edge et al., 2001; Galen and Zavaliangos, 2005) anisotropic behaviour of a pharmaceutical powder may subsequently contribute to typical tablet manufacturing failures such as capping and/or lamination upon ejection of the tablets from the die.

In the pharmaceutical industry, for mechanical anisotropy assessment of pharmaceutical materials, various techniques, such as the flexure testing using both three- (Podczeck et al., 2006) and four-point beam bending (Eichhorn and Young, 2001), indentation testing (Kuppuswamy et al., 2001) and compression testing (Malamataris et al., 1996) have been introduced and discussed. These destructive tests not only damage the structure of the tablet and cause loss of product, but also provide limited information about the mechanical state of the tablet. Moreover, complicated sample preparations, demand for relatively large sample sizes and time-consuming procedures limit their use in the pharmaceutical industry. Therefore, for a better understanding of mechanical anisotropy in a tablet, analyzing the mechanical properties of a tablet as a function of the testing direction is rather useful.

For comprehensive quality assurance monitoring of solid dosage forms in the pharmaceutical industry the U.S. Food and Drug Administration (FDA) has initiated a now well-known guidance program entitled the Process Analytical Technology (PAT), which encourages the development and implementation of new technologies and procedures on how to characterize, evaluate and monitor the critical properties of pharmaceutical powders (Hussain et al., 2004). The purpose of the PAT guidelines is to increase the understanding and the control of different manufacturing processes to meet increased quality demands on pharmaceutical preparations in terms of efficacy, safety, cost and higher product reliability. The PAT guidelines are strong incentives for a "quality by design" approach in pharmaceutical research and development work, which requires an increased mechanistic understanding of critical raw material properties that determine product functionality. An increased understanding of the manufacturing processes and different process parameters that control the end-product and how indicators of these can be monitored real-time is also necessary in an adaptive tableting manufacture process. It is thus essential to implement a practical approach to make the development phase more effective, less time consuming and more material sparing is generated in the area of pharmaceutical formulation technology.

In the current work, a non-destructive contact ultrasonic method was employed for quantifying the level of mechanical property anisotropy in uni-axially compacted pharmaceutical compacts and to investigate the degree of average Young's modulus anisotropy in these compacts in parallel (axial) and perpendicular (radial) to the direction of compaction. Such information could be helpful to broaden the understanding of the effect of the mechanical properties on the disintegration profiles of solid oral dosage forms.

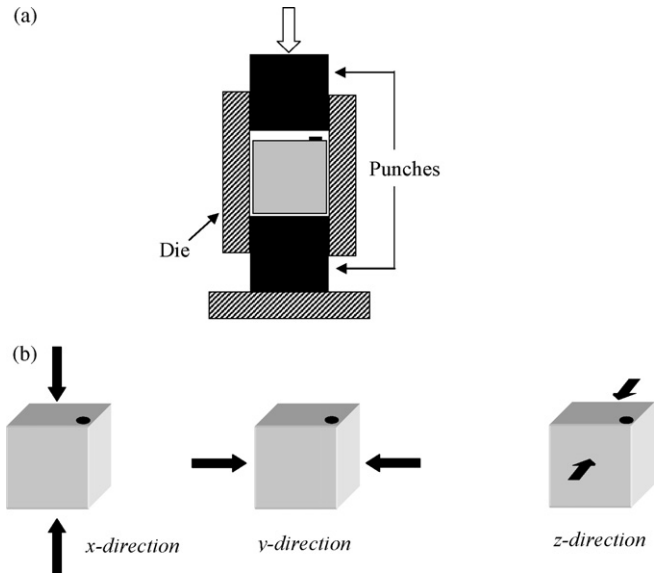

Fig. 1. Schematics of the (a) compaction apparatus, (b) contact ultrasonic measurement directions. Compacts were marked on the top surface with a dot (●) to enable testing of compacts in different directions to assess average Young's modulus anisotropy.

2. Materials and methods

2.1. Materials

In the reported study, a set of 11 cubic compact samples for each of four commercially available pharmaceutical excipient powders, namely, microcrystalline cellulose MCC (Lot # GM2008516, Avicel PH102, FMC Biopolymer, Newark, DE), lactose monohydrate (Lot # GR00827, FastFlo, Foremost, Rothschild, WI), ascorbic acid (Lot # E010004226, Spectrum, Gardena, CA), and aspartame (Lot # GR00528, Spectrum, Gardena, CA) was used.

2.2. Methods

2.2.1. Compact preparation

Cubic compacts (3/8″) were formed by uni-axial compression (~1 mm/s compression speed) using a custom built press that permitted gradual triaxial decompression of the samples. Prior to compression, the punch and die surfaces were sparingly lubricated

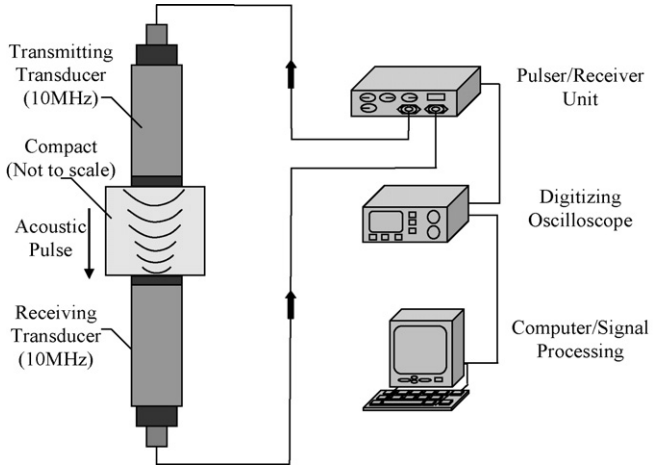

Fig. 2. Schematic of the acoustic experimental set-up with a pair of 10 MHz transducers operating in pitch-catch mode (not to scale).

with magnesium stearate suspended in methanol (5%, w/v). The bottom punch was stationary while the top punch was moving (similar to an eccentric tablet press). The compression dwell time was 1.5 min and triaxial decompression time was 2 min to enable the formation of high quality compacts. Each powder was compressed to a target solid fraction of 0.85 when possible, which is typical of pharmaceutical tablets (Hancock et al., 2003). The compacts were marked on the top surface in the direction of

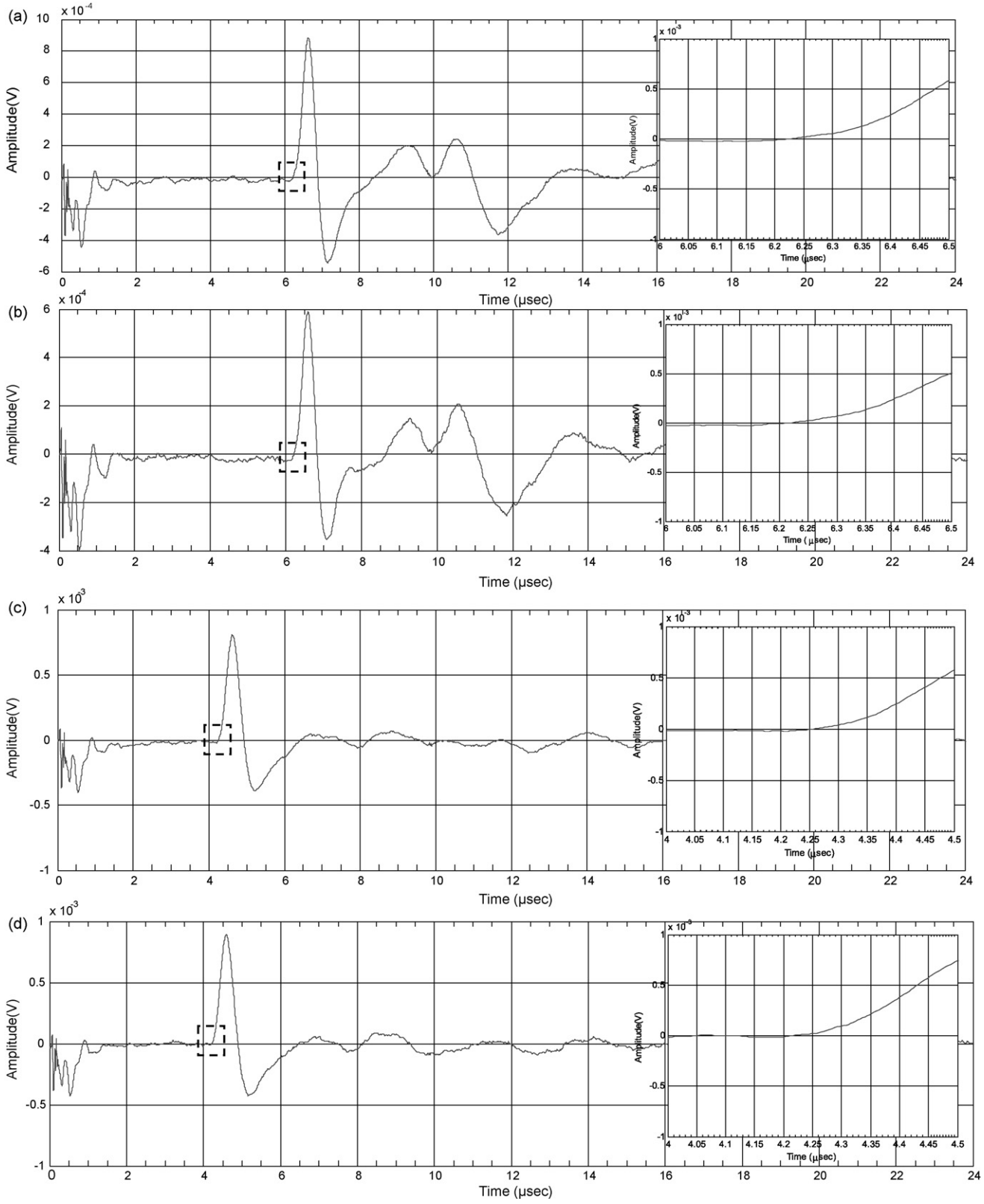

Fig. 3. (a–f) Longitudinal (pressure) acoustic waveforms for the two microcrystalline cellulose compacts in the axial (x) and radial (y and z) directions, respectively. Insets depict the TOF values of the longitudinal acoustic waves.

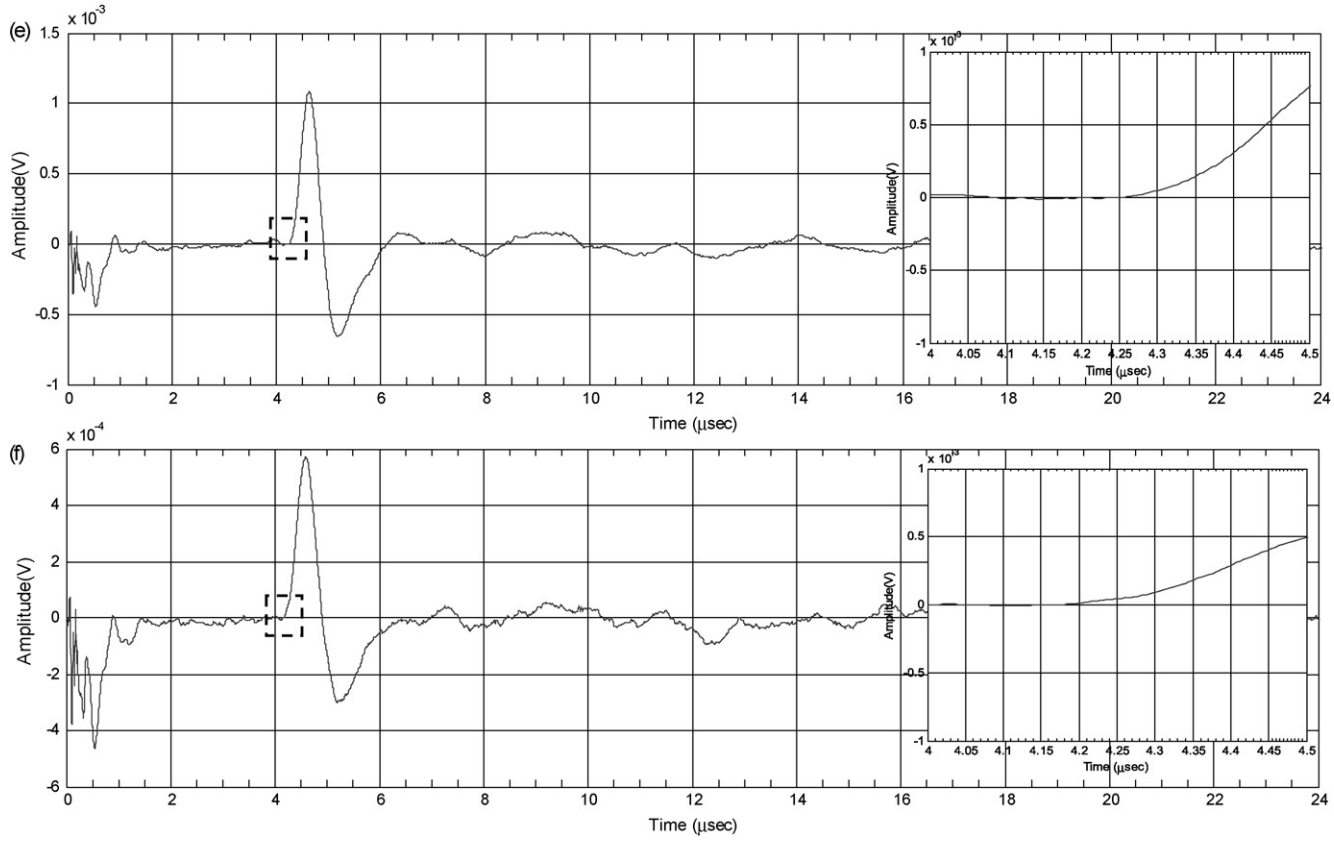

Fig. 3 (*Continued*).

compaction with a dot (●) to enable testing of compacts in different directions to assess average Young's modulus anisotropy (Fig. 1).

2.2.2. Contact ultrasonic measurements: mechanical property characterization

Various mechanical and elastic properties of a material (e.g., Young's modulus E and Poisson's ratio ν) can be extracted by measuring the acoustic properties of a pressure pulse (longitudinal waves) propagating in the material as the propagation of elastic waves in a material is governed by such parameters (Achenbach, 1984). The experimental set-up developed for the reported ultrasonic evaluation consists of a pulser/receiver unit (Panametrics 5077PR), a pair of piezoelectric transducers with a central frequency of 10 MHz (Panametrics 1807076), a digitizing oscilloscope (Tektronix TDS3052) and a computer controlling the data acquisition (Fig. 2). The contact ultrasonic measurement approach is based on the measurement of the time-of-flight (TOF), the time for a pulse of ultrasound to travel through the compact from the transmitting transducer to the receiving one (Fig. 2). For the Young's modulus extraction, the two piezoelectric transducers were placed in direct contact with the top and bottom surfaces of each flat-faced compacted sample. A thin, adhesive plastic tape layer ($d \ll \lambda$, where d is layer thickness of the tape and λ denotes the shortest wavelength in the ultrasonic pulse) was used as an acoustic couplant instead of glycerin gel in order to prevent damage to the compact. A square electrical pulse from the pulser–receiver unit was launched into the pitching transducer with a central frequency of 10 MHz. The acoustic field transmitted through the compact was captured by the receiving transducer in contact with the opposite face of the compact, and digitized as a waveform by the oscilloscope (Fig. 3). As can visually be identified, processing of the acquired waveforms yields the TOF values of the longitudinal (acoustic) waves Δt_L in the compacts (Fig. 3). Contact ultrasonic measurements were performed in the axial (x) and radial (y and z) directions (Fig. 1) of the same compact to assess the plane-to-plane TOF value variations. In other words, experiments were conducted in different orientations to evaluate the possible Young's modulus anisotropy. The acquired waveforms in the axial and radial testing directions of two MCC compacts were included in Fig. 3. The longitudinal phase velocity c_L is determined from the TOF of the longitudinal (acoustic) wave Δt_L component in the medium by $c_L = h/\Delta t_L$, where h is the distance travelled in the sample. The longitudinal phase velocity c_L is a function of the mass density ρ of the propagation medium, and the Young's modulus E of the medium, that is, $c_L = \sqrt{E/\rho}$. The average mass densities of compacts were determined from direct mass measurements (Table 1). For the compacts tested, to determine the times-of-flight of pressure waves, a numerical routine was used to record the time instants at which the signal amplitude exceeded a certain limit slightly above the noise floor (Figs. 3–7); these values were saved as the one-way arrival times Δt_L of the pressure waves (Tables 2 and 3). For known compact thicknesses h and arrival times Δt_L of the pressure waves, longitudinal phase velocity c_L values were determined for each compact as listed in Tables 2 and 3. Using values of the longitudinal phase velocity c_L and mass density ρ, the average Young's modulus E values of compacts were calculated (Tables 2 and 3). In the reported contact ultrasonic measurements, the TOF in the plastic tape, 0.23 μs, was subtracted from the determined TOF of each compact. In addition, the sampling periods of the acquired signals were 200 ns and the oversampling rate set on the digitizing oscilloscope was set to 512.

Table 1
Volumes, masses and mass densities of the compacts.

Compact no.	Microcrystalline cellulose (Avicel PH102) ID# GM2008-516			Lactose monohydrate (FastFlo) ID# GM2008-512			Ascorbic acid ID# GM2008-511			Aspartame ID# GM2008-510		
	V (mm^3)	M (mg)	ρ (kg/m^3)	V (mm^3)	M (mg)	ρ (kg/m^3)	V (mm^3)	M (mg)	ρ (kg/m^3)	V (mm^3)	M (mg)	ρ (kg/m^3)
1	956.20	1256.4	1313.95	922.08	1203.1	1302.60	925.89	1334.0	1438.08	928.76	1050.4	1126.45
2	954.19	1256.2	1316.51	922.08	1201.1	1300.43	925.89	1336.6	1440.88	931.62	1052.1	1124.81
3	958.09	1254.2	1309.06	922.08	1195.2	1294.03	926.83^T	1340.9	1444.06	931.62	1055.3	1128.25
4	960.93	1256.4	1307.48	923.04	1198.3	1296.04	927.78	1329.9	1430.73	932.57	1045.9	1117.02
5	960.02	1255.3	1307.58	924.94	1204.6	1300.19	922.08	1322.6	1431.65	926.86^T	1055.5	1134.26
6	951.20	1257.1	1321.59	922.08	1196.7	1295.66	925.89	1337.1	1441.42	928.76	1050.6	1126.66
7	959.98	1255.9	1308.26	912.55^T	1193.1	1305.24	927.79	1337.8	1439.23	931.62	1051.4	1124.06
8	963.77^T	1305.1	1354.16	922.08	1198.3	1297.39	927.79	1333.6	1434.70	930.67	1044.6	1117.90
9	958.09	1259.5	1314.59	923.98	1201.6	1298.30	926.84	1328.3	1430.45	930.67	1050.1	1123.81
10	957.14	1254.5	1310.68	923.03	1196.9	1294.54	913.48^T	1341.7	1466.04	927.81	1034.3	1110.25
11	957.14	1258.1	1314.44	924.94	1202.2	1297.60	929.69	1340.3	1438.97	932.57	1049.8	1121.20
C.V.	0.34	1.12	0.97	0.35	0.29	0.25	0.45	0.42	0.65	0.20	0.54	0.54

Superscript T denotes the compacts at high solid fraction (>0.85%; that is, <15% porosity). C.V. denotes the coefficient of variation.

3. Results and discussion

A non-destructive contact ultrasonic technique to determine the average Young's modulus values and evaluate the possible Young's modulus anisotropy levels in commercially available pharmaceutical excipient powders was developed. The current technique was based on the extraction of average Young's modulus values of the compacts in the axial and radial testing directions. All the compact samples were tested on the same day to reduce effects of aging and ambient conditions on the measurements.

The comparison of the acoustic waveforms for the MCC, lactose, ascorbic acid, and aspartame compacts acquired in the axial and radial directions is depicted in Figs. 4–7, respectively. Corresponding TOF and longitudinal phase velocity c_L values are listed in Tables 2 and 3. Among the four compact groups, the lactose compacts exhibited a relatively high axial average Young's modulus values (Fig. 8), while the MCC compacts exhibited a relatively low average Young's modulus values ($E_{lactose} > E_{aspartame} > E_{ascorbic\ acid} > E_{MCC}$). In contrast, as depicted in Fig. 8, in the radial direction (y- and z-direction) MCC compacts demonstrated a relatively high average Young's modulus values than the other compacts, that is, $E_{MCC} > E_{aspartame} > E_{lactose} > E_{ascorbic\ acid}$. For each compact group, the radial average Young's moduli were comparable in the y- and z-directions; however, the axial average Young's moduli were relatively different (Fig. 8). These observations suggest that average values of the Young's moduli depend on the testing orientations, and, therefore, the compact materials are anisotropy. This is not surprising because uni-axially

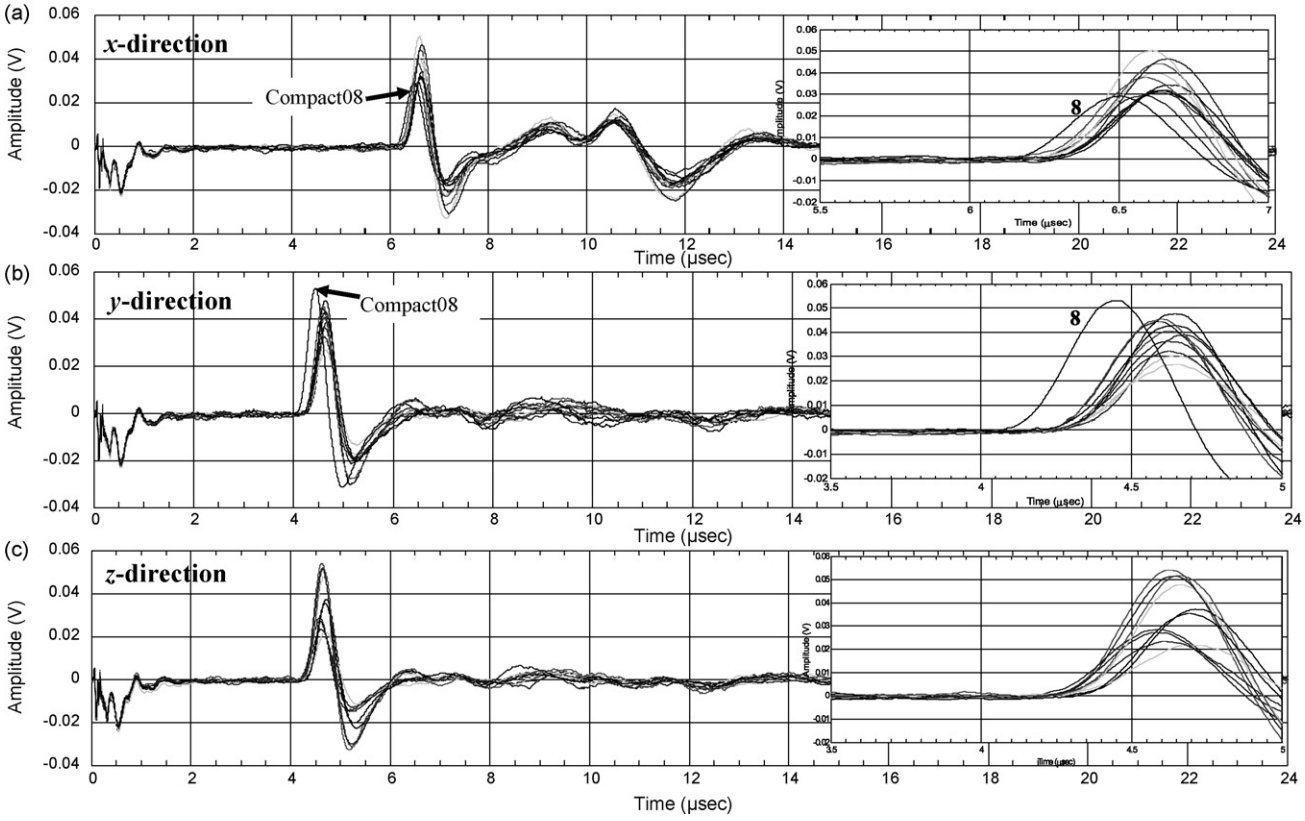

Fig. 4. (a–c) Comparison of the acquired acoustic waveforms for the 11 microcrystalline cellulose compacts in the axial (x) and radial (y and z) directions, respectively. (a, b) Inset depicts the compact08 with high solid fraction.

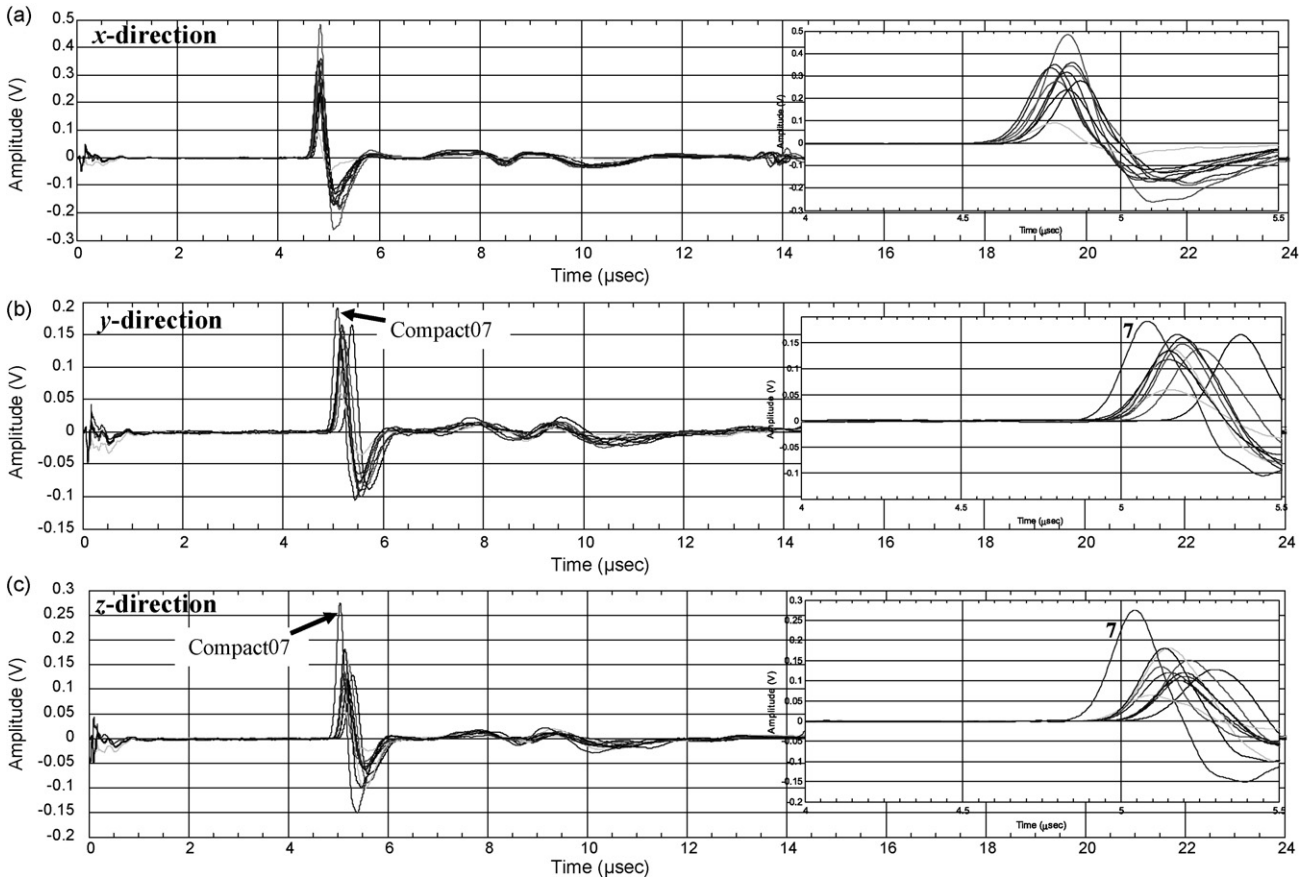

Fig. 5. (a–c) Comparison of the acquired acoustic waveforms for the 11 lactose monohydrate compacts in the axial (x) and radial (y and z) directions, respectively. (b, c) Inset depicts the compact07 with high solid fraction.

Table 2
Summary of the acoustic and mechanical properties of the microcrystalline cellulose and lactose monohydrate compacts. Percentage differences of the average Young's moduli extracted in the axial and radial directions are shown for each compact.

	$\Delta t_L{}^x$ (μs)	$\Delta t_L{}^y$ (μs)	$\Delta t_L{}^z$ (μs)	$c_L{}^x$ (m/s)	$c_L{}^y$ (m/s)	$c_L{}^z$ (m/s)	E_x (GPa)	E_y (GPa)	E_z (GPa)	% Maximum difference E	Solid fraction (SF)
MCC											
1	5.991	4.022	4.014	1685.86	2419.19	2424.01	3.734	7.689	7.720	106.75	0.85
2	5.978	3.982	3.934	1691.21	2435.96	2473.31	3.765	7.812	8.053	113.89	0.85
3	6.017	3.878	3.990	1681.90	2509.03	2438.60	3.703	8.241	7.785	122.55	0.85
4	5.966	3.952	3.874	1701.31	2462.04	2511.62	3.784	7.926	8.248	117.97	0.85
5	5.942	4.011	3.986	1704.81	2428.32	2441.04	3.800	7.710	7.791	105.03	0.85
6	5.914	4.038	3.946	1711.19	2409.61	2448.05	3.870	7.673	7.920	104.65	0.85
7	5.962	3.990	3.962	1700.77	2438.60	2455.83	3.784	7.780	7.890	108.51	0.85
8[T]	5.874	3.806	3.854	1733.06	2556.49	2524.65	4.067	8.850	8.631	117.61	0.857
9	5.882	3.902	4.022	1720.50	2493.59	2419.19	3.891	8.174	7.694	110.07	0.85
10	6.002	4.014	3.942	1684.44	2424.02	2468.29	3.719	7.701	7.985	114.71	0.85
11	6.018	3.938	4.062	1679.96	2470.80	2395.37	3.710	8.024	7.542	116.28	0.85
C.V.	0.85	1.81	1.57	1.00	1.84	1.57	2.81	4.46	3.79		
Lactose											
1	4.354	4.758	4.730	2218.65	2053.38	2065.54	6.412	5.492	5.557	16.75	0.85
2	4.322	4.686	4.698	2237.39	2084.93	2077.48	6.510	5.653	5.613	15.98	0.85
3	4.368	4.866	4.766	2190.93	2005.75	2049.94	6.212	5.206	5.438	19.32	0.85
4	4.346	4.686	4.678	2227.34	2082.80	2088.50	6.430	5.622	5.653	14.37	0.85
5	4.366	4.694	4.714	2219.42	2081.38	2072.55	6.405	5.633	5.585	14.68	0.85
6	4.358	4.688	4.718	2216.61	2084.04	2070.79	6.366	5.627	5.556	14.58	0.85
7[T]	4.364	4.682	4.642	2215.86	2086.72	2102.54	6.414	5.682	5.771	12.76	0.859
8	4.368	4.711	4.752	2213.83	2071.75	2055.98	6.359	5.569	5.484	15.96	0.85
9	4.346	4.712	4.652	2227.34	2073.43	2100.17	6.441	5.582	5.726	15.39	0.85
10	4.282	4.698	4.734	2258.29	2079.61	2063.79	6.602	5.599	5.514	19.73	0.85
11	4.386	4.683	4.678	2209.30	2086.27	2088.50	6.334	5.648	5.660	12.15	0.85
C.V.	0.65	1.16	0.85	0.76	1.16	0.83	1.54	2.37	1.81		

C.V. denotes the coefficient of variation.
[T] denotes the compacts with high solid fractions (>0.85%; that is, <15% porosity).

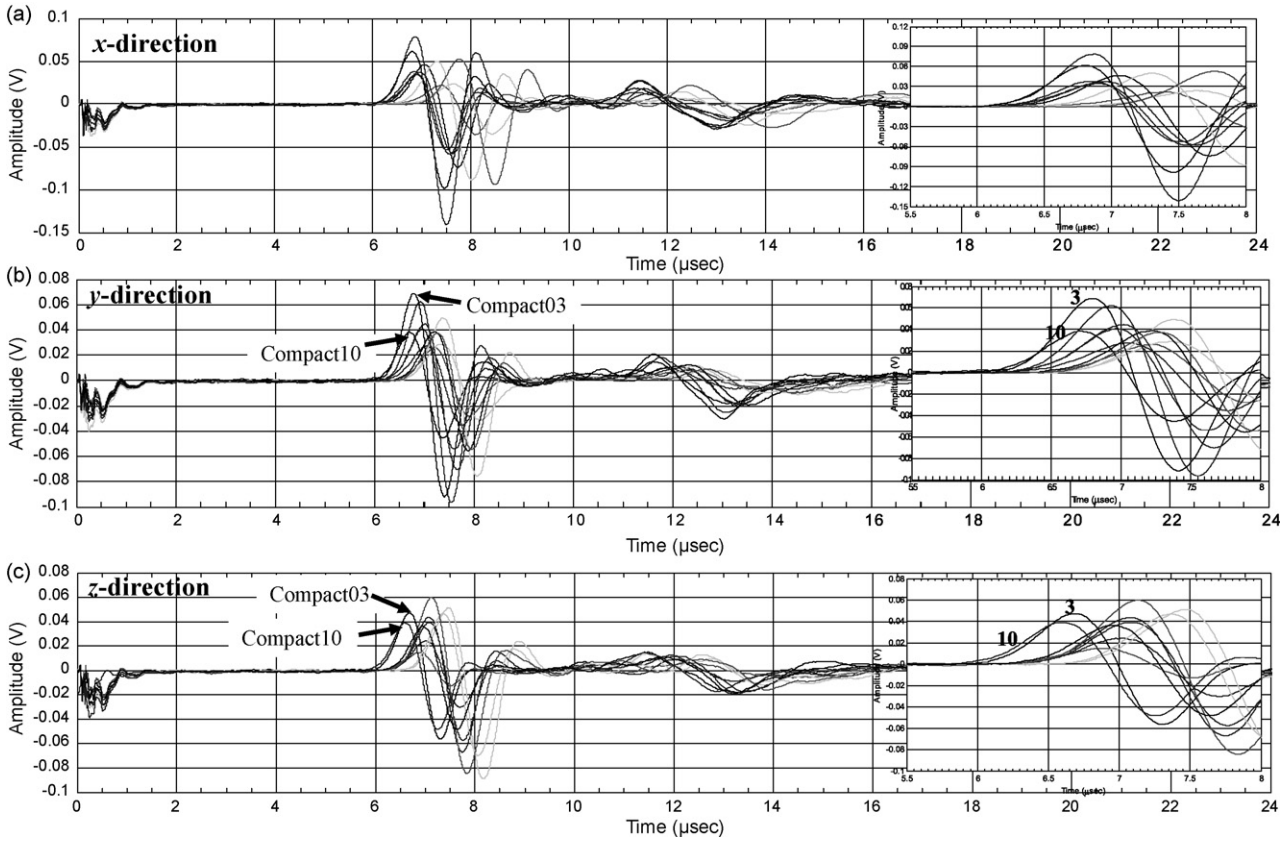

Fig. 6. (a–c) Comparison of the acquired acoustic waveforms for the 11 ascorbic acid compacts in the axial (x) and radial (y and z) directions, respectively. (b, c) Insets depict the compact03 and compact10 with high solid fraction.

Table 3
Summary of the acoustic and mechanical properties of the ascorbic acid and aspartame compacts. Percentage differences of the average Young's moduli extracted in the axial and radial directions are shown for each compact.

	$\Delta t_L{}^x$ (μs)	$\Delta t_L{}^y$ (μs)	$\Delta t_L{}^z$ (μs)	$c_L{}^x$ (m/s)	$c_L{}^y$ (m/s)	$c_L{}^z$ (m/s)	E_x (GPa)	E_y (GPa)	E_z (GPa)	% Maximum difference E	Solid fraction (SF)
Ascorbic											
1	6.322	6.206	5.962	1534.32	1574.28	1638.71	3.385	3.564	3.862	14.09	0.85
2	5.914	5.998	5.973	1640.18	1628.88	1635.69	3.876	3.823	3.855	1.39	0.85
3[T]	5.682	5.666	5.678	1707.15	1724.32	1720.68	4.208	4.294	4.275	2.02	0.858
4	6.214	6.189	6.291	1540.07	1578.61	1553.01	3.477	3.653	3.536	5.06	0.85
5	5.874	5.974	6.062	1644.54	1635.42	1611.68	3.872	3.829	3.719	4.11	0.85
6	5.411	5.942	5.994	1790.80	1645.91	1631.63	4.631	3.912	3.844	20.47	0.85
7	6.131	6.352	6.346	1582.12	1539.67	1541.13	3.603	3.412	3.418	5.60	0.85
8	5.714	6.151	6.018	1697.58	1589.99	1625.12	4.135	3.627	3.789	14.01	0.85
9	6.598	6.122	5.974	1470.14	1595.88	1637.09	3.092	3.643	3.834	23.99	0.85
10[T]	5.766	5.738	5.694	1682.28	1706.17	1719.35	4.149	4.267	4.334	4.47	0.857
11	5.794	5.902	5.714	1672.42	1658.76	1711.59	4.002	3.937	4.191	6.45	0.85
C.V.	5.69	3.44	3.68	5.69	3.49	3.68	11.37	7.30	7.43		
Aspartame											
1	4.258	4.091	4.114	2289.81	2385.72	2372.39	5.906	6.411	6.340	8.55	0.85
2	4.286	4.134	4.122	2279.51	2360.91	2370.21	5.845	6.270	6.319	8.11	0.85
3	4.306	4.098	4.082	2268.93	2381.65	2393.43	5.808	6.400	6.463	11.28	0.85
4	4.314	4.138	4.126	2264.72	2361.04	2367.91	5.729	6.227	6.263	9.32	0.85
5[T]	4.194	4.038	4.022	2322.37	2417.04	2424.17	6.117	6.626	6.666	8.97	0.858
6	4.215	4.082	4.114	2313.17	2390.98	2372.39	6.028	6.441	6.341	6.85	0.85
7	4.342	4.178	4.174	2252.42	2333.65	2340.68	5.703	6.122	6.158	7.98	0.85
8	4.318	4.124	4.122	2262.62	2366.63	2367.78	5.723	6.261	6.267	9.51	0.85
9	4.322	4.154	4.106	2260.53	2349.54	2377.01	5.743	6.204	6.350	10.57	0.85
10	4.306	4.042	4.034	2266.60	2412.17	2416.96	5.704	6.460	6.486	13.71	0.85
11	4.302	4.091	4.126	2273.36	2388.17	2365.49	5.795	6.395	6.274	10.35	0.85
C.V.	1.08	1.07	1.06	0.98	1.07	1.01	2.37	2.27	2.16		

C.V. denotes the coefficient of variation.

[T] denotes the compacts with high solid fractions (>0.85%; that is, <15% porosity).

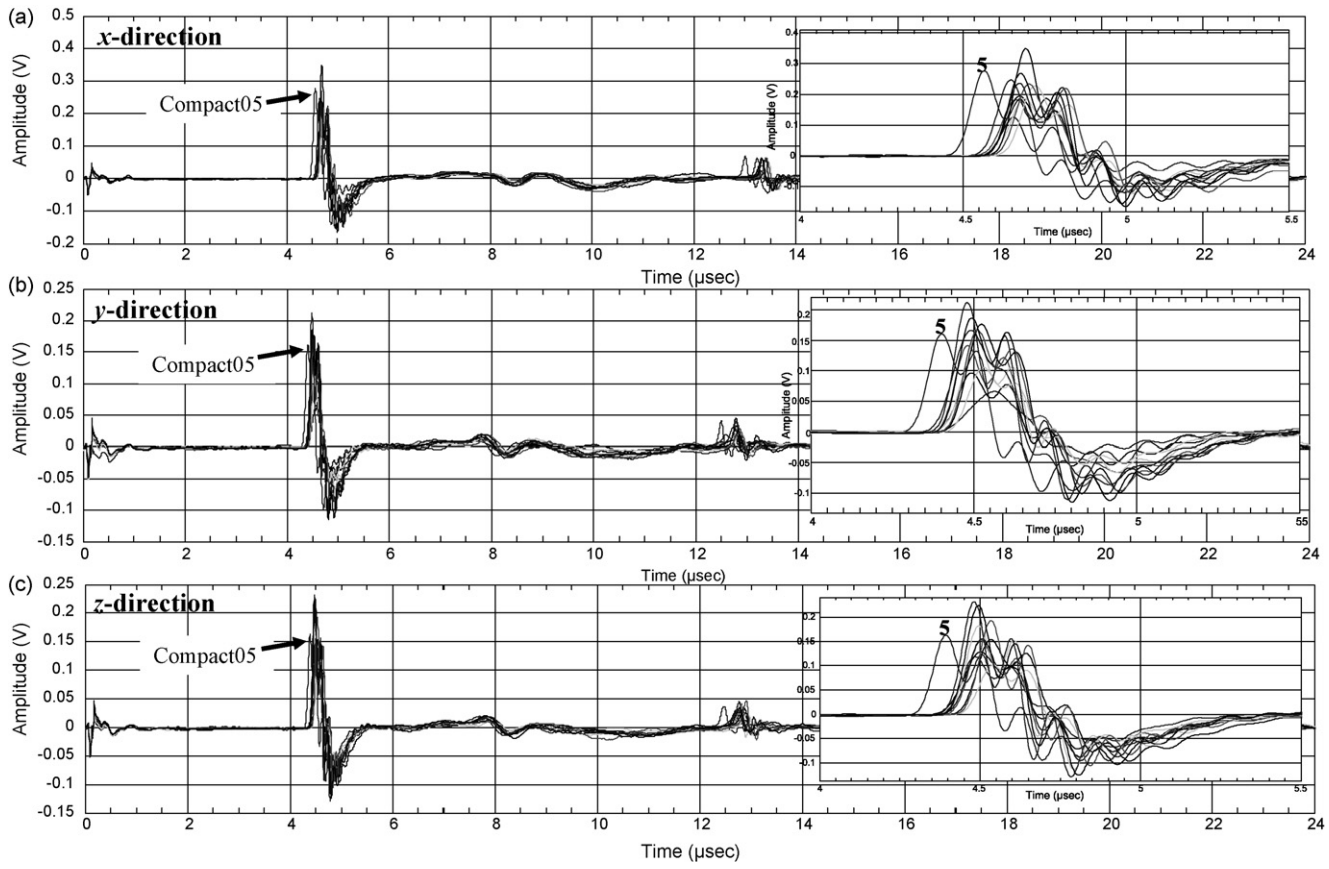

Fig. 7. (a–c) Comparison of the acquired acoustic waveforms for the 11 aspartame compacts in the axial (x) and radial (y and z) directions, respectively. (a–c) Insets depict the compact05 with high solid fraction.

compressed compacts have a discernable non-uniform relative density distribution in their bulk structure (Train, 1957; Eiliazadeh et al., 2003; Wu et al., 2005) which yields testing direction dependent Young's modulus values.

The average Young's modulus values of the MCC compacts extracted in the axial (x) direction were consistent with values between 3.70 GPa and 3.95 GPa reported by Roberts et al. (1994) and Hancock et al. (2000). It was observed that the axial longitudinal phase velocity c_L^x values determined for the MCC compacts (1679.96–1733.06 m/s) were substantially different than those determined in the radial (2409.61–2556.49 m/s for c_L^y and 2395.37–2524.65 m/s for c_L^z) directions (Table 2). Processing of the TOF values revealed that the average Young's modulus values extracted for the MCC compacts were comparable in the radial (y, z) directions; however axial direction displayed lower average Young's modulus values than the radial directions (Fig. 8). The longitudinal phase velocity c_L value variations in the axial and radial directions resulted in 104.6–122.5% differences in the average Young's modulus values for the MCC compacts (Table 2). For the lactose compacts, the longitudinal phase velocity c_L values acquired in the y- (2005.75–2086.72 m/s) and z-direction (2049.94–2102.54 m/s) were comparable to each other, however, for the same compacts the longitudinal phase velocity c_L values acquired in the x-direction were slightly higher (2190.93–2258.29 m/s). These variations in the c_L values resulted in 12.1–19.7% difference in the average Young's modulus values (Table 2). For the MCC and lactose compacts the coefficients of variation of the average Young's modulus values, extracted in the same testing directions, are obtained as 2.7%, 1.5% for the x-direction, 4.2%, 2.3% for the y-direction and 3.6%, 1.7% for the z-direction, respectively (Table 2). The results for MCC and lactose compacts (Fig. 8) indicate that lactose compacts into specimens of relatively more homogenous structure compared to MCC. It has earlier been suggested (Karehill and Nyström, 1990) that both MCC and lactose materials cohere by forming a similar type of interparticulate attraction forces. Therefore, the differences in distribution of interparticulate attractions could be related to the way the materials behave when subjected to compression (Karehill and Nyström, 1990). Typically lactose is considered to undergo a volume reduction by particle fragmentation and plastic deformation while MCC undergoes predominantly plastic deformation (Karehill

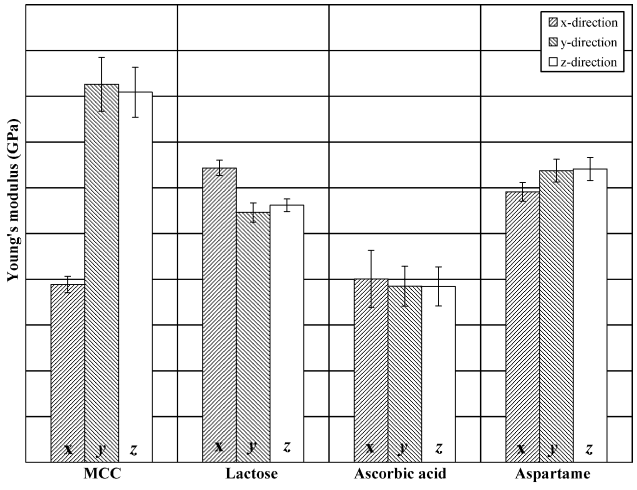

Fig. 8. Average Young's modulus values extracted in the three directions (x, y, z) from contact ultrasonic measurements for different compacts with error bars showing the standard deviation.

and Nyström, 1990). This may imply that lactose could produce a more homogenous bonding system than MCC (Newton et al., 1992).

Ascorbic acid compacts showed relatively lower average Young's modulus values in the axial and radial testing directions than the other materials (Table 3). Other researchers (Kassem and El-Bayoumi, 1983; Kawashima et al., 2003; Mullarney and Hancock, 2004) have described this material as being unsuitable for direct tableting due to its poorly compactable properties and having low hardness and high friability. In contrast, aspartame compacts demonstrated a relatively high average Young's modulus values in both axial and radial testing directions (Table 3). Despite its relatively high average Young's modulus values in all testing directions, aspartame has been described as having high brittleness and poor flowability (Mullarney et al., 2003), which could adversely affect tablet homogeneity and contribute to lamination during roll and tablet pressing in high proportions (Mullarney et al., 2003). For ascorbic acid and aspartame compacts the coefficients of variation of the average Young's modulus values, extracted the same testing directions, are 10.8%, 2.3% for the *x*-direction, 6.9%, 2.2% for the *y*-direction and 7.1%, 2.1% for the *z*-direction, respectively (Table 3).

For the compacts examined for this investigation, the degree of Young's modulus anisotropy (ε) defined as $\varepsilon = E_{axial}/E_{radial}$. The ratio ε is unity for a homogeneous tablet and decreases as the material inhomogeneity increases. The values of ε in the ascending order are as follows: MCC (0.47), lactose (0.85), aspartame (0.92), and ascorbic acid (0.96). These data suggest that the average Young's modulus of a compact may be related to and typically trends with compact anisotropy. For instance, the MCC compacts have the highest average Young's modulus values (radial directions) (Fig. 8) and they have the highest degree of Young's modulus anisotropy. These results could also indicate that MCC deforms elastically to a larger extent during compression compared to other compacts. Therefore, this could cause an increased elastic expansion of the compact during the decompression–ejection phase of the compact (Newton et al., 1992). This is a relevant observation since MCC powder commonly used as a filler-binder in both wet-granulation and direct compression processes (Bolhuis and Armstrong, 2006) and typically creates highly robust tablets. However, as reported in Mullarney and Hancock (2006), MCC has a high tensile strength (6.4 MPa); therefore its high tensile strength might be acting to compensate its intrinsic Young's modulus anisotropy, thus enables robust compact formation and reduces tendency for capping by maintaining strong interparticulate bonds.

Compacts at a high SF (0.857–0.859) were also differentiated from the compacts at a SF of 0.85. It seems reasonable that compacts at a SF of 0.85 are containing relatively more microscopic voids or flaws than those with high SF, which weaken the system and thus decreasing the stiffness of the compacts. MCC compact08, lactose compact07, ascorbic acid compact03 and compact10 and aspartame compact05 were compressed to relatively high SF (0.857–0.859, that is, <15% porosity); therefore their average Young's modulus values were different than those at a SF of 0.85 (Tables 2 and 3). From the acquired acoustic waveforms, it was observed that in the *x*- and *y*-direction MCC compact08, in the *y*- and *z*-direction lactose compact07, ascorbic acid compact03 and compact10 and in both axial and radial directions aspartame compact05 at high SF (0.857–0.859) were differentiated among other compacts in their groups. This is a particularly notable result since the solid fraction levels of these compacts were 1.1% higher than other compacts. In other words, decrease in porosity with increasing compaction force for these compacts results in increase in their longitudinal phase velocity c_L values, and consequently increase in their average Young's modulus values (Tables 2 and 3).

4. Conclusions and remarks

A non-destructive contact ultrasonic method is implemented for determining the mechanical anisotropy in pharmaceutical compacts made by uni-axial compression. Measurable degrees of average Young's modulus anisotropy are detected in powder compacts. Analysis revealed that powder compacts with higher average Young's modulus (e.g., E_{MCC} in radial directions and $E_{lactose}$ in axial direction) also have higher average Young's modulus anisotropy (MCC > lactose > aspartame > ascorbic acid) suggesting that they are more likely to have non-uniform stress and density distribution induced during uni-axial compression. From the analysis of the acoustic waveforms, powder compacts at higher solid faction appear to be clearly discernible from the other compacts in their groups. The measurement of the average Young's modulus anisotropy in pharmaceutical excipient compacts may be an indicator of tablet hardness and may help to describe the disintegration profiles of uni-axially compressed compacts. The described non-destructive contact ultrasonic method has the potential to identify quality and dissolution rate problems related to the anisotropic behaviour of the pharmaceutical excipient materials early on the formulation process and, consequently, reduce associated cost and material waste. However, it is noteworthy that a separate experimental study for each material is required for forming an accurate correlation between the material Young's modulus and its dissolution properties.

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References

Achenbach, J.D., 1984. Wave propagation in elastic solids. In: Lauwerier, H.A., Koiter, W.T. (Eds.), Applied Mathematics and Mechanics. Elsevier Science Publishers, B.V., New York, pp. 26–30.
Alderborn, G., Nyström, C., 1984. Radial and axial tensile strength and strength variability of paracetamol tablets. Acta Pharmaceutica Suecica 2, 1–8.
Ando, T., Yuasa, H., Kanaya, Y., Asahina, K., 1983. Studies on anisotropy of compressed powder. III. Effects of different granulation methods on anisotropy, pore size and crushing strength of tablets. Chem. Pharm. Bull. 31, 2045–2054.
Aulton, M.E., Travers, D.N., White, P.J., 1973. Strain recovery of compacts on extended storage. J. Pharm. Pharmacol. 25, 79P–86P.
Bolhuis, G.K., Armstrong, N.A., 2006. Excipients for direct compaction—an update. Pharm. Dev. Technol. 11, 111–124.
Edge, S., Steele, D.F., Tobyn, M.J., Staniforth, J.N., Chen, A., 2001. Directional bonding in compacted microcrystalline cellulose. Drug Dev. Ind. Pharm. 27, 613–621.
Eichhorn, S.J., Young, R.J., 2001. The Young's modulus of a microcrystalline cellulose. Cellulose 8, 197–207.
Eiliazadeh, B., Briscoe, B.J., Yong, S., Pitt, K.G., 2003. Investigating density distributions for tablets of different geometry during the compaction of pharmaceuticals. Particulate Sci. Technol. 21, 303–316.
Galen, S., Zavaliangos, A., 2005. Strength anisotropy in cold compacted ductile and brittle powders. Acta Materialia 53, 4801–4815.
Hancock, B.C., Clas, S.D., Christensen, K., 2000. Micro-scale measurement of the mechanical properties of compressed pharmaceutical powders.1. The elasticity and fracture behaviour of microcrystalline cellulose. Int. J. Pharm. 209, 27–35.
Hancock, B.C., Colvin, J.T., Mullarney, P.M., Zinchuk, A.V., 2003. The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets. Pharm. Technol. 27, 64–80.
Hussain, A.S., Watts, C., Afnan, A.M., Wu, H., 2004. Foreword. J. Process Anal. Technol. 1, 3.
Indiran, S.P., Russell, I., Syce, J.A., Neau, S.H., 1998. Sustained release theophylline tablets by direct compression. Part 1. Formulation and in vitro testing. Int. J. Pharm. 164, 1–10.

Jarosz, P.J., Parrott, E.L., 1982. Factors influencing axial and radial tensile strengths of tablets. J. Pharm. Sci. 71, 607–614.
Karehill, P.G., Nyström, C., 1990. Studies on direct compression of tablets. XXI. Investigation of bonding mechanisms of some directly compressed materials by strength characterization in media with different dielectric constants (relative permittivity). Int. J. Pharm. 61, 251–260.
Kassem, M.A.A., El-Bayoumi, T., 1983. Manufacture and physical characteristics of directly compressed tablets of different types of L-ascorbic acid. J. Drug Res. 14, 141–149.
Kawashima, Y., Imai, M., Takeuchi, H., Yamamoto, H., Kamiya, K., Hino, T., 2003. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. Powder Technol. 130, 283–289.
Kuppuswamy, R., Anderson, S.R., Augsburger, L.L., Hoag, S.W., 2001. Estimation of capping incidence by indentation fracture tests. AAPS PharmSci. 3, 1–12.
Li, F., Puri, V.M., 1996. Measurement of anisotropic behavior of dry cohesive and cohesionless powders using a cubical triaxial tester. Powder Technol. 89, 197–207.
Malamataris, S., Hatjichristos, T., Rees, J.E., 1996. Apparent compressive elastic modulus and strengths isotropy of compacts formed from binary powder mixes. Int. J. Pharm. 141, 101–108.
Mizumoto, T., Masuda, Y., Yamamoto, T., Yonemochi, E., Terada, K., 2005. Formulation design of a novel fast-disintegrating tablet. Int. J. Pharm. 306, 83–90.
Moe, D.V., Rippie, E.G., 1997. Non-destructive viscoelastic analysis of anisotropy in compressed tablets. J. Pharm. Sci. 86, 26–32.
Mullarney, M.P., Hancock, B.C., Carlson, G.T., Ladipo, D.D., Langdon, B.A., 2003. The powder flow and compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets. Int. J. Pharm. 257, 227–236.
Mullarney, M.P., Hancock, B.C., 2004. Improving the prediction of exceptionally poor tableting performance: an investigation into Hiestand's 'special case'. J. Pharm. Sci. 93, 2017–2021.
Mullarney, M.P., Hancock, B.C., 2006. Mechanical property anisotropy of pharmaceutical excipient compacts. Int. J. Pharm. 314, 9–14.
Newton, J.M., Alderborn, G., Nyström, C., 1992. A method of evaluating the mechanical characteristics of powders from the determination of the strength of compacts. Powder Technol. 72, 97–99.
Nyström, C., Malmquist, K., Mazur, J., 1978. Measurement of axial and radial tensile strength of tablets and their relation to capping. Acta Pharmaceutica Suecica 15, 226–232.
Podczeck, F., Drake, K.R., Newton, J.M., Haririan, I., 2006. The strength of bi-layered tablet. Eur. J. Pharm. Sci. 29, 361–366.
Roberts, R.J., Rowe, R.C., York, P., 1994. The Poisson's ratio of microcrystalline cellulose. Int. J. Pharm. 105, 177–180.
Saravanan, M., Nataraj, K.S., Ganesh, K.S., 2002. The effect of tablet formulation and hardness on in vitro release of cephalexin from eudragit L100 based extended release tablets. Biol. Pharm. Bull. 25, 541–545.
Train, D., 1957. Transmission of forces through a powder mass during the process of pelleting. Trans. Inst. Chem. Eng. 35, 258–266.
Wu, C.Y., Ruddy, O., Bentham, A.C., Hancock, B.C., Best, S.M., Elliott, J.A., 2005. Modelling the mechanical behaviour of pharmaceutical powders during compaction. Powder Technol. 152, 107–117.
Wu, Y.S., van Vliet, L.J., Frijlink, H.W., Stokroos, I., van der Voort Maarschalk, K., 2008. Pore direction in relation to anisotropy of mechanical strength in a cubic starch compact. AAPS PharmSciTech. 9, 528–535.