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Ultrasound transmission measurements for tensile strength evaluation of tablets

Simo-Pekka Simonaho[a,b,*], T. Aleksi Takala[a], Marko Kuosmanen[a], Jarkko Ketolainen[a]

[a] School of Pharmacy, University of Eastern Finland, P.O. Box 1627, FI-70211, Kuopio, Finland
[b] Department of Applied Physics, University of Eastern Finland, P.O. Box 1627, FI-70211, Kuopio, Finland

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ABSTRACT

Ultrasound transmission measurements were performed to evaluate the tensile strength of tablets. Tablets consisting of one ingredient were compressed from dibasic calcium phosphate dehydrate, two grades of microcrystalline cellulose and two grades of lactose monohydrate powders. From each powder, tablets with five different tensile strengths were directly compressed. Ultrasound transmission measurements were conducted on every tablet at frequencies of 2.25 MHz, 5 MHz and 10 MHz and the speed of sound was calculated from the acquired waveforms. The tensile strength of the tablets was determined using a diametrical mechanical testing machine and compared to the calculated speed of sound values. It was found that the speed of sound increased with the tensile strength for the tested excipients. There was a good correlation between the speed of sound and tensile strength. Moreover, based on the statistical tests, the groups with different tensile strengths can be differentiated from each other by measuring the speed of sound. Thus, the ultrasound transmission measurement technique is a potentially useful method for non-destructive and fast evaluation of the tensile strength of tablets.

1. Introduction

Tablets are the most common solid dosage form with many benefits. They are easy to manufacture and are the most convenient way to administer drugs orally. Although tablet manufacturing is an old technique, there are still many critical phases during the manufacturing process that have major effects on the tablets therapeutic response. For example, a tablet has to be resistant to breakage during packing and coating. Breakage during dissolution might cause unwanted therapeutic responses. One measure of tablet strength is its tensile strength. Traditionally tensile strength has been determined using a mechanical tester that presses the tablet until it breaks and the force needed for breakage is recorded. This destructive method is widely used although it is known to provide only an approximation of crushing strength (Morisseau and Rhodes, 1997; Kirch and Drennen, 1999). Thus, an alternative method for determination of tablets tensile strength is needed especially in real time process control purposes.

Alternative techniques have been suggested for the evaluation of tensile strength of tablets, e.g. near infrared (NIR) and Raman spectroscopy (Morisseau and Rhodes, 1997; Kirch and Drennen, 1999; Otsuka and Yamane, 2006; Blanco and Alcalá, 2006; Short et al., 2009; Picker-Feyer and Schmidt, 2004; Virtanen et al., 2008). Since NIR spectroscopy is based on multivariate analysis, each model needs to be calibrated. These calibration procedures are often time consuming and have their own limitations (Blanco and Alcalá, 2006). In addition, according to Kirch, variations in sample positioning affect the spectral baseline and several measurements are needed to minimize this baseline shifting (Kirch and Drennen, 1999). Raman spectroscopy has also been applied to measure the crushing force of tablets (Picker-Feyer and Schmidt, 2004; Virtanen et al., 2008). The surface roughness of tablets is related to the crushing force of tablets (i.e., the smoother the tablet, the higher the crushing force) and the Raman method is based solely on that factor (Virtanen et al., 2008). Since Raman method is sensitive to surface texture, it can be used only when the surfaces of the tablets are unaltered (Virtanen et al., 2008). In Raman measurements, different laser irradiance patterns can influence the measurement accuracy (Johansson et al., 2005). The surface color of tablets has been reported to correlate with the crushing force of both colored and white tablets (Siddiqui and Nazzal, 2007).

Ultrasound is a mechanical wave that propagates in a medium at a certain speed. The speed of sound is sensitive to the mechanical properties of medium. Recently, ultrasound based measurement systems have been introduced in pharmaceutical tablet research. Ultrasound can be used to determine the porosity and elastic properties of pharmaceutical tablets and to detect defects and anisotropy of compacted forms (Hakulinen et al., 2008; Akseli and Cetinkaya, 2008; Akseli et al., 2008, 2009; Leskinen et al., 2010). Hakulinen et al., 2008 measured the speed of sound of tablets with

* Corresponding author at: Department of Applied Physics, University of Eastern Finland, P.O. Box 1627, FI-70211, Kuopio, Finland. Tel.: +358 40 355 20 50; fax: +358 17 162 585.
E-mail address: simo-pekka.simonaho@uef.fi (S.-P. Simonaho).

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varying porosities and noted that the speed of sound decreased with increasing porosity. According to the studies by Akseli et al. (2008, 2009) the mechanical properties of compacts and tablets could be determined accurately using ultrasound. Thus, based on these previous studies, ultrasound seems to be a very promising measurement method for non-destructive determination of tensile strength of pharmaceutical tablets.

In this study, an ultrasound transmission measurement method was used to evaluate the tensile strength of tablets. For this purpose, five sample sets of cylindrical tablets with varying porosities and particle size distributions were compressed and the speed of sound was measured using three different ultrasound frequencies. After the ultrasound measurement, the tensile strength of tablets was determined using a destructive mechanical tester and compared to the speed of sound values.

2. Materials and methods

2.1. Sample preparation

Five commonly used pharmaceutical excipient powders were chosen as the test materials: dibasic calcium phosphate dihydrate Emcompress® (DCP) Premium JRS Pharma Budenheim Germany; microcrystalline cellulose Avicel® PH200 (MCC1) FMC Biopolymers Cork Ireland; microcrystalline cellulose Avicel® PH101 (MCC2) FMC Biopolymers Cork Ireland; lactose monohydrate Pharmatose® 90 M (LM1) DMV-Frontera Excipients Veghel the Netherlands; lactose monohydrate Pharmatose® 200 M (LM2) DMV-Frontera Excipients Veghel the Netherlands. The density values of used powders were measured with a helium pycnometer MVP-1 (Quantachrome, Syosset, NY, USA) resulting 2.380 g/cm^3 for DCP, 1.5381 g/cm^3 for MCC1, 1.5307 g/cm^3 for MCC2, 1.5285 g/cm^3 for LM1 and 1.5263 g/cm^3 for LM2, respectively. All powders were used as received. The tablets consisting only one excipient powder were directly compressed with a compaction simulator (PCS-1 Puuman Oy, Kuopio) using a 10 mm flat-faced punch and die set. Before compaction, 350 mg of powder was weighed on an analytical balance (A200S, Sartorius, Goettingen, Germany) and manually filled into the die. A single sided triangle wave compaction profile was used for the upper punch, while the lower punch was kept stationary. The compaction speed was 100 mm/s and the amplitude was adjusted to produce the desired tablet porosity by taking into account the material densities, powder masses, and diameters of the tablets. Five groups with different target porosities (i.e., 13%, 15%, 17%, 19%, and 21%) with eight parallel samples were compressed from each powder. Thus, the total number of tablets was 40 for each excipient. In addition, each tablet was weighed and its dimensions were measured with a micrometer (Digitrix, NSK, Japan) 20 h after compaction. Porosity of tablet was calculated using equation (Sun, 2005)

$$\text{Porosity} = 1 - \frac{\rho_t}{\rho_m} \quad (1)$$

where ρ_t is the density of tablet calculated from the measured dimensions and weights and ρ_m is the measured density of powder. The dimensions and weights of the tablets together with the calculated porosities are listed in Table 2.

2.2. Ultrasound measurement

Ultrasound transmission measurements were made using three pair of contact ultrasound transducers with frequencies of 2.25 MHz (Panametrics V133-RM), 5 MHz (Panametrics C110-RM transmitting and V110-RM receiving) and 10 MHz (Panametrics V112-RM). In the measurements, the tablet was placed between a pair of transducers with diameters of 6 mm, one transmitting the ultrasound pulse (T in Fig. 1) that propagated through the tablet, the other receiving the transmitted ultrasound pulse (R in Fig. 1). The measurement set-up consisted of an ultrasound pulser/receiver unit (Olympus 5077PR, Olympus NDT Inc., Waltham, MA, USA), a pair of ultrasound transducers and a digitizing oscilloscope (LeCroy Wavesurfer 42Xs-A, LeCroy Corp., NY, USA). The contact between transducers and tablet was ensured by applying a constant force on the transmitting transducer. This applied force was adjusted to the value of 12 N and was monitored by a miniature load cell (LPM560, Cooper Instruments, Warrenton, VA, USA). From the acquired data, the speed of sound (SOS) was calculated for every tablet. SOS was calculated using the time of flight (TOF) and the thickness of the tablet. TOF was determined from the transmitted ultrasound signal using Hilbert transform in order to obtain the maximum of the signal. Matlab R2008a software (Mathworks Inc., Natick, MA, USA) was used in signal analysis. Prior to ultrasound measurements, reference measurements using a stainless steel sample were made to test the accuracy of the measurement system.

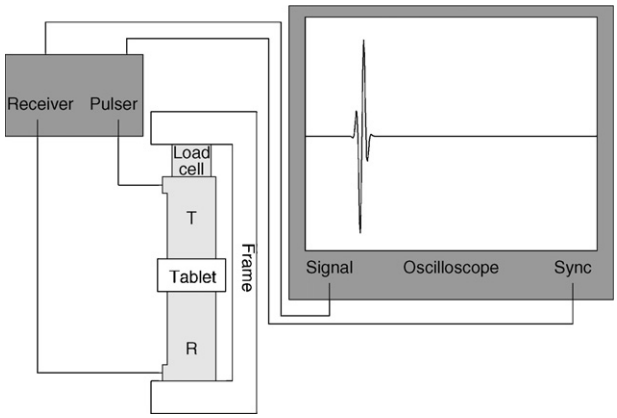

Fig. 1. Measurement set up for ultrasound transmission measurements.

2.3. Tensile strength measurement

A mechanical strength testing machine (CT5, Engineering systems (Nottm), Nottingham, England) was used to determine the crushing force of tablets. The tensile strength of tablets σ_t was calculated using equation (Fell and Newton, 1970)

$$\sigma_t = \frac{2F}{\pi D h} \quad (2)$$

where F is the determined crushing force and D and h are the diameter and the height of the tablet, respectively.

3. Results

First the ultrasound transmission measurement system was tested using a cylindrical stainless steel sample with a thickness of 9.917 mm as the reference sample. The transmitted waveforms at frequencies of 2.25 MHz, 5 MHz and 10 MHz are shown in Fig. 2. The first and second pulses are seen after 2 μs and 5.5 μs, respectively, for all three frequencies. As seen in Fig. 2, there are small differences between arrival times of the transmitted pulses at different frequencies but their effect on the SOS is negligible. The highest signal amplitude is obtained at 5 MHz and lowest at 10 MHz. The reference measurements were made before and after each sample set measurement so a total of ten reference measurements was performed for each frequency. SOS was calculated from the acquired waveforms. The mean values and the standard deviations of SOS were 5637 ± 83 m/s, 5741 ± 23 m/s, and 5716 ± 18 m/s at frequencies 2.25 MHz, 5 MHz, and 10 MHz, respectively. In the literature, SOS of stainless steel is reported as 5740 m/s (Ultrasonics

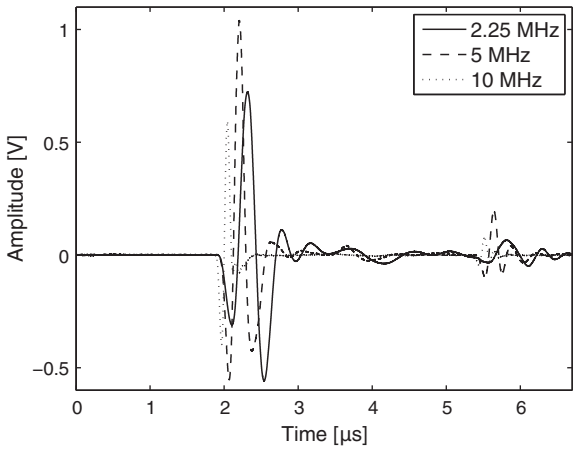

Fig. 2. Transmitted ultrasound pulse through cylindrical steel sample at frequency of 2.25 MHz, 5 MHz and 10 MHz shown as solid, dashed and dotted line, respectively.

Transducers Technical Notes, 2010) i.e., the measurement results are in good agreement with this literature value.

In Fig. 3, the transmitted waveforms through the tablets made from LM1 at frequency of 2.25 MHz, 5 MHz and 10 MHz are shown in (a), (b) and (c), respectively. It is clearly seen that the smaller the porosity, the shorter the TOF of transmitted pulse i.e. SOS increases with decreasing porosity. In addition, at frequency of 10 MHz the amplitude of transmitted pulse is much lower than with frequencies of 2.25 MHz and 5 MHz. This indicates that the tablet attenuates high frequencies. However, SOS can be calculated at frequency of 10 MHz because transmitted pulses are detectable. In Table 2, the calculated SOS for LM1 tablets measured at frequencies of 2.25 MHz, 5 MHz and 10 MHz are shown. The acquired waveforms from the tablets compressed from LM2 are shown in Fig. 4. It is notable that the overall signal levels are higher in LM2 than LM1tablets for all frequencies. The highest signal amplitude is at 5 MHz and the lowest at 10 MHz. The calculated SOS values for LM2 tablets are listed in Table 2. A similar variation of SOS values between different frequencies as noticed with LM1 tablets is also observed for the LM2 tablets. In addition, SOS for LM2 is approximately 200 m/s higher than LM1 at all three frequencies as can be seen in Table 2.

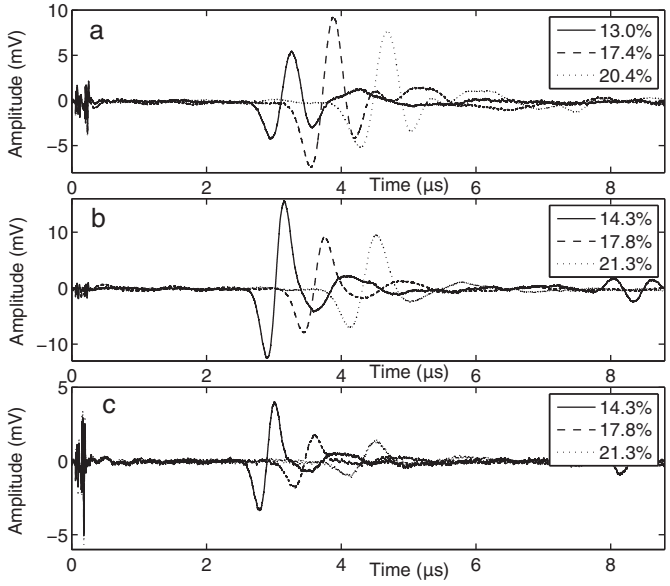

Fig. 4. Transmitted waveforms through LM2 tablets with different porosities. Different measurement frequencies 2.25 MHz, 5 MHz and 10 MHz are shown in (a), (b) and (c).

Fig. 5 shows the transmitted waveforms for tablets compressed from MCC1. Here also SOS increases with decreasing porosity. All of the acquired waveforms have low signal amplitude and thus they are quite noisy, especially at frequency of 10 MHz. In spite of the high noise level in the acquired waveforms, SOS can be calculated reliably as indicated by the low standard deviations. SOS for MCC1 is higher than for LM1 and LM2 as observed in Table 2. The measured waveforms from MCC2 tablets are shown in Fig. 6. In this case, the signal amplitudes are higher than in MCC1 tablets for all three frequencies, but the noise level is still high at 10 MHz. Table 2 reveals that SOS for MCC2 is approximately 100 m/s lower than that of MCC1 at frequency of 5 MHz. At frequencies of 2.25 MHz and 10 MHz, SOS is only 20 m/s (same magnitude as the standard deviation) lower than SOS for MCC1 except for sample set 5 at 2.25 MHz.

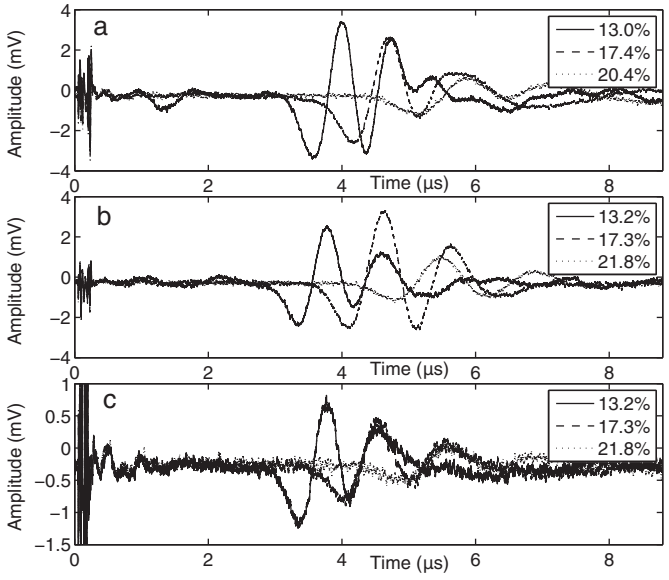

Fig. 3. Transmitted waveforms through LM1 tablets with different porosities. Different measurement frequencies 2.25 MHz, 5 MHz and 10 MHz are shown in (a), (b) and (c).

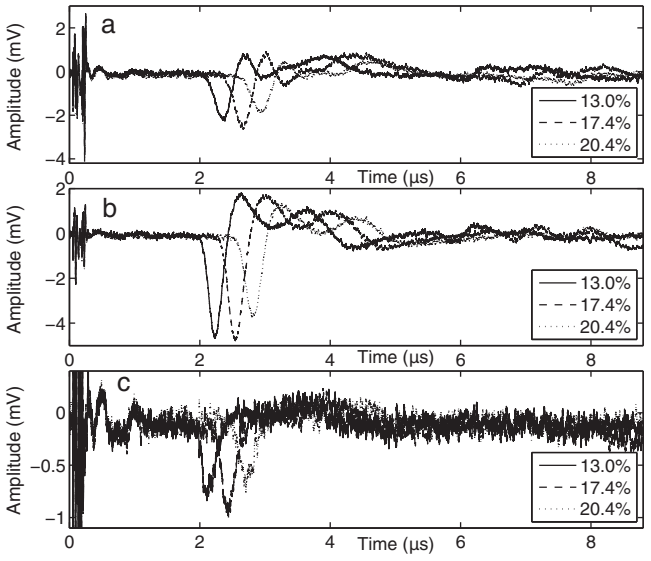

Fig. 5. Transmitted waveforms through MCC1 tablets with different porosities. Different measurement frequencies 2.25 MHz, 5 MHz and 10 MHz are shown in (a), (b) and (c).

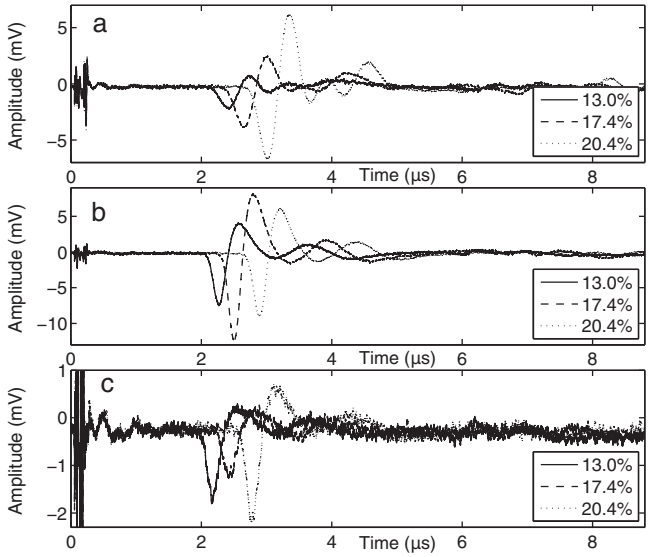

Fig. 6. Transmitted waveforms through MCC2 tablets with different porosities. Different measurement frequencies 2.25 MHz, 5 MHz and 10 MHz are shown in (a), (b) and (c).

In Fig. 7 the transmitted waveforms for tablets compressed from DCP are shown. At all frequencies, multiple reflections are clearly seen which indicates that ultrasound attenuation is lower in DCP tablets than in LM and MCC tablets. The calculated SOS values for DCP are listed in Table 2. At 5 MHz, SOS is higher than determined at frequencies of 2.25 MHz and 10 MHz. In addition, SOS is the highest of all for DCP tablets.

From Table 2 it is seen that SOS is not a function of frequency for tablets compressed from LM1, LM2, MCC1, MCC2 and DCP. Moreover, every excipient has different SOS. DCP has the highest value and LM1 the lowest value. At frequency of 5 MHz SOS values are slightly higher than frequencies of 2.25 MHz and 10 MHz.

After the ultrasound measurements, the tensile strength of tablets was determined using the mechanical strength testing machine. The results for the tensile strength of tablets are shown in Table 1. As can be seen from Table 1, the tablets made from

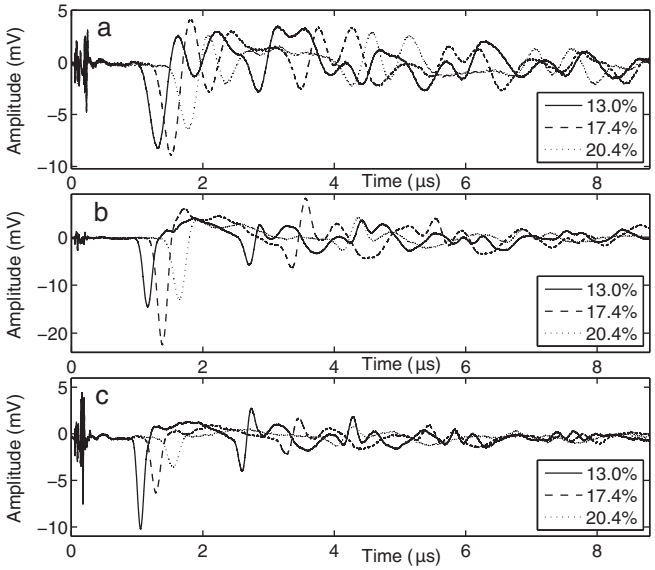

Fig. 7. Transmitted waveforms through DCP tablets with different porosities. Different measurement frequencies 2.25 MHz, 5 MHz and 10 MHz are shown in (a), (b) and (c).

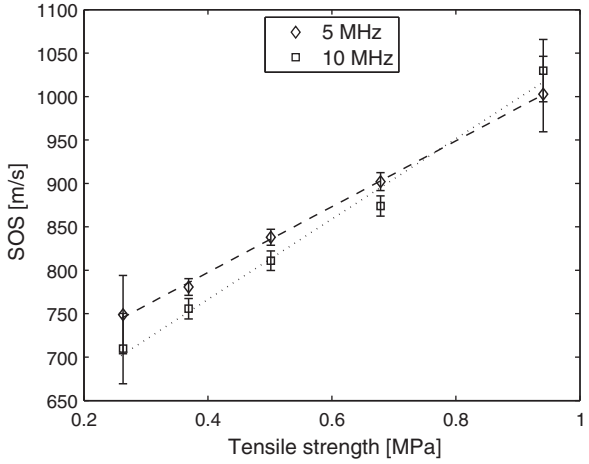

Fig. 8. Speed of sound (SOS) measured at frequencies of 5 MHz and 10 MHz as a function of tensile strength for LM1 tablets shown as diamonds and squares, respectively. Error bars show the standard deviations and lines are linear fits.

MCC2 have the highest tensile strength values from 4.74 MPa to 7.83 MPa while the tablets made from LM1 have the lowest values from 0.26 MPa to 0.94 MPa. The list of tablets arranged in descending order of tensile strength is MCC2, MCC1, DCP, LM2 and LM1. There are large differences in the tensile strength between the used excipients as seen in Table 1.

Next, statistical tests were performed to investigate the relationship between SOS and tensile strength. The measured SOS values were divided into groups and statistical differences between the groups were tested using Mann–Whitney *U* test with SPSS software (Release 14.0.1, LEAD Technologies Inc., Chicago, IL, USA). With respect to the DCP tablets, all groups can be differentiated statistically from each other ($p < 0.05$, Mann–Whitney *U* test) at every frequency. SOS changes roughly 200 m/s between groups. SOS values were also statistically different between groups of MCC1 and MCC2 ($p < 0.05$, Mann–Whitney *U* test) at every frequency. Now the difference in SOS was 70 m/s between adjacent groups for both MCC1 and MCC2 tablets. For the LM1 tablets, SOS was statistically different ($p < 0.05$, Mann–Whitney *U* test) between groups at frequencies of 5 MHz and 10 MHz. However, at frequency of 2.25 MHz, there were no statistical differences between groups 2, 3 and 4, 5 ($p > 0.05$, Mann–Whitney *U* test). This means that SOS values are the same for these groups as can be seen in Table 2 where the mean values of SOS for groups 2 and 3 are 821 m/s and 831 m/s, respec-

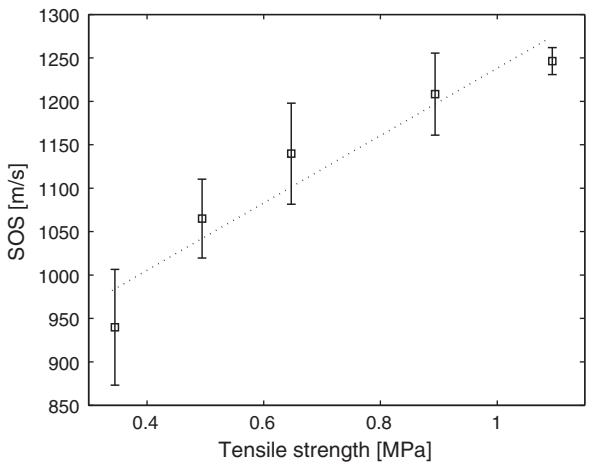

Fig. 9. Speed of sound (SOS) measured at frequency of 10 MHz as a function of tensile strength for LM2 tablets. Error bars show the standard deviations and the dotted line is the linear fit.

Table 1
Calculated porosities, dimensions (weight, height and diameter), crushing forces and tensile strength of tablets and their standard deviations.

	Porosity	Weight (mg)	Height (mm)	Diameter (mm)	Crushing force (N)	Tensile strength (MPa)
LM1						
1	21.3 ± 0.2	350.0 ± 0.5	3.646 ± 0.008	10.047 ± 0.001	15.1 ± 1.6	0.26 ± 0.03
2	19.6 ± 0.2	350.3 ± 0.2	3.569 ± 0.010	10.053 ± 0.001	20.8 ± 0.8	0.37 ± 0.02
3	17.8 ± 0.3	350.2 ± 0.3	3.486 ± 0.012	10.058 ± 0.001	27.6 ± 1.3	0.50 ± 0.03
4	15.7 ± 0.3	350.3 ± 0.3	3.397 ± 0.010	10.062 ± 0.001	36.4 ± 1.6	0.68 ± 0.03
5	13.6 ± 0.2	350.2 ± 0.4	3.314 ± 0.007	10.063 ± 0.001	49.3 ± 2.7	0.94 ± 0.05
LM2						
1	21.4 ± 0.3	350.1 ± 0.7	3.669 ± 0.015	10.047 ± 0.002	20.0 ± 1.2	0.35 ± 0.02
2	19.4 ± 0.3	350.7 ± 0.6	3.583 ± 0.014	10.053 ± 0.001	28.0 ± 1.3	0.49 ± 0.02
3	17.7 ± 0.3	350.3 ± 0.8	3.500 ± 0.020	10.056 ± 0.001	35.8 ± 1.6	0.65 ± 0.03
4	15.5 ± 0.3	350.7 ± 0.4	3.414 ± 0.015	10.058 ± 0.001	48.2 ± 2.6	0.89 ± 0.05
5	14.2 ± 0.2	350.5 ± 0.3	3.358 ± 0.009	10.059 ± 0.001	58.1 ± 1.8	1.09 ± 0.04
MCC1						
1	20.5 ± 0.3	351.6 ± 0.6	3.666 ± 0.014	10.031 ± 0.002	273.4 ± 7.6	4.73 ± 0.14
2	18.1 ± 0.2	352.0 ± 0.3	3.570 ± 0.010	10.027 ± 0.001	298.9 ± 5.3	5.32 ± 0.10
3	16.5 ± 0.3	352.2 ± 0.4	3.504 ± 0.016	10.023 ± 0.001	331.3 ± 6.0	6.00 ± 0.12
4	14.1 ± 0.3	351.9 ± 0.7	3.406 ± 0.009	10.019 ± 0.001	361.1 ± 6.5	6.74 ± 0.13
5	11.9 ± 0.2	352.3 ± 0.4	3.329 ± 0.005	10.012 ± 0.002	397.4 ± 7.3	7.60 ± 0.15
MCC2						
1	21.2 ± 0.3	349.6 ± 0.8	3.681 ± 0.006	10.019 ± 0.001	274.4 ± 4.3	4.74 ± 0.08
2	18.6 ± 0.3	350.2 ± 0.3	3.573 ± 0.013	10.014 ± 0.002	311.4 ± 5.3	5.54 ± 0.11
3	16.4 ± 0.1	350.0 ± 0.6	3.480 ± 0.005	10.010 ± 0.001	343.0 ± 3.3	6.27 ± 0.06
4	14.4 ± 0.1	350.6 ± 0.5	3.405 ± 0.005	10.008 ± 0.001	378.7 ± 5.3	7.08 ± 0.10
5	12.5 ± 0.1	350.1 ± 0.6	3.329 ± 0.005	10.005 ± 0.001	409.8 ± 5.4	7.83 ± 0.10
DCP						
1	20.8 ± 0.2	351.1 ± 0.3	2.331 ± 0.009	10.068 ± 0.010	55.8 ± 4.1	1.51 ± 0.12
2	19.0 ± 0.3	350.7 ± 0.3	2.278 ± 0.008	10.065 ± 0.001	74.3 ± 4.1	2.06 ± 0.12
3	17.5 ± 0.4	350.2 ± 1.1	2.232 ± 0.010	10.067 ± 0.001	95.6 ± 7.3	2.71 ± 0.21
4	15.6 ± 0.3	350.5 ± 0.2	2.183 ± 0.006	10.069 ± 0.001	130.1 ± 8.2	3.77 ± 0.25
5	13.1 ± 0.2	350.7 ± 0.2	2.121 ± 0.004	10.071 ± 0.001	172.6 ± 11.7	5.15 ± 0.34

tively. SOS was found to be statistical different between groups ($p < 0.05$, Mann–Whitney U test) only at frequency of 10 MHz for LM2 tablets. At frequency of 2.25 MHz, there were no statistical differences ($p > 0.05$, Mann–Whitney U test) between groups 2, 3 and 3, 4. In addition, no statistical difference ($p > 0.05$, Mann–Whitney U test) was found between groups 4 and 5 at frequency of 5 MHz.

After the statistical tests, SOS values were plotted against the tensile strength of tablets at frequencies where a difference between groups had been found to be statistically significant. Fig. 8 shows SOS as a function of tensile strength at 5 MHz and 10 MHz for LM1 tablets. As can be seen in Fig. 8, there is a linear relationship between the tensile strength of LM1 tablets and their SOS values. Calculation of the correlation coefficient between the tensile strength and SOS yielded values of $r^2 = 0.9990$ and $r^2 = 0.9884$ for 5 MHz and 10 MHz, respectively. In Fig. 9, SOS at 10 MHz is plotted as a function of tensile strength for LM2 together with the standard deviations and linear fit. For LM2 tablets, the relationship between SOS and the tensile strength was nonlinear as seen in Fig. 9. The correlation coefficient between SOS and the tensile strength for LM2 was $r^2 = 0.9177$. In Fig. 10, SOS is plotted as a function of tensile strength for frequencies of 2.25 MHz, 5 MHz and 10 MHz with circles, diamonds and squares, respectively for MCC1 tablets. Linear fits are excellent for all three frequencies and r^2 values were 0.9944, 0.9964 and 0.9985 for 2.25 MHz, 5 MHz and 10 MHz, respectively. An excellent linear relationship between SOS and tensile strength was also observed for MCC2 tablets as shown in Fig. 11. The calculated r^2 values were 0.9998, 0.9978 and 0.9972 for 2.25 MHz, 5 MHz and 10 MHz, respectively. In Fig. 12, SOS for DCP is plotted as a function of tensile strength. For the DCP tablets, the best linear fit was observed at frequency of 10 MHz with an r^2 value of 0.9949. At frequencies of 2.25 MHz and 5 MHz, the respective values of r^2 were 0.9843 and 0.9829.

Table 2
Speed of sound c measured at frequencies of 2.25 MHz, 5 MHz and 10 MHz.

	$c_{2.25}$ (m/s)	c_5 (m/s)	c_{10} (m/s)
LM1			
1	741 ± 43	749 ± 45	710 ± 40
2	821 ± 45	781 ± 10	756 ± 12
3	831 ± 32	838 ± 9	811 ± 11
4	958 ± 43	902 ± 10	874 ± 12
5	985 ± 58	1003 ± 43	1030 ± 36
LM2			
1	934 ± 42	905 ± 21	940 ± 67
2	976 ± 108	1047 ± 56	1065 ± 45
3	1164 ± 74	1158 ± 57	1140 ± 58
4	1229 ± 72	1239 ± 60	1208 ± 47
5	1298 ± 72	1289 ± 34	1246 ± 16
MCC1			
1	1515 ± 21	1594 ± 20	1496 ± 20
2	1590 ± 20	1689 ± 18	1557 ± 33
3	1673 ± 12	1777 ± 25	1642 ± 30
4	1730 ± 27	1861 ± 7	1708 ± 31
5	1829 ± 12	1969 ± 14	1805 ± 20
MCC2			
1	1491 ± 9	1513 ± 8	1483 ± 16
2	1571 ± 18	1605 ± 15	1570 ± 12
3	1643 ± 17	1688 ± 9	1640 ± 15
4	1722 ± 22	1768 ± 11	1703 ± 21
5	1792 ± 25	1839 ± 10	1784 ± 14
DCP			
1	1935 ± 38	1937 ± 118	1866 ± 42
2	2129 ± 31	2236 ± 55	2062 ± 28
3	2329 ± 56	2445 ± 43	2249 ± 46
4	2638 ± 81	2731 ± 43	2494 ± 40
5	2892 ± 77	3104 ± 50	2839 ± 48

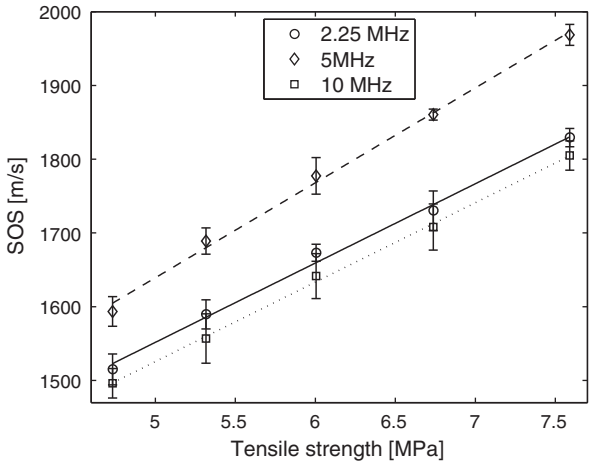

Fig. 10. Speed of sound (SOS) measured at frequencies of 2.25 MHz, 5 MHz and 10 MHz as a function of tensile strength for MCC1 tablets shown as circles, diamonds and squares, respectively. Error bars show the standard deviations and lines are linear fits.

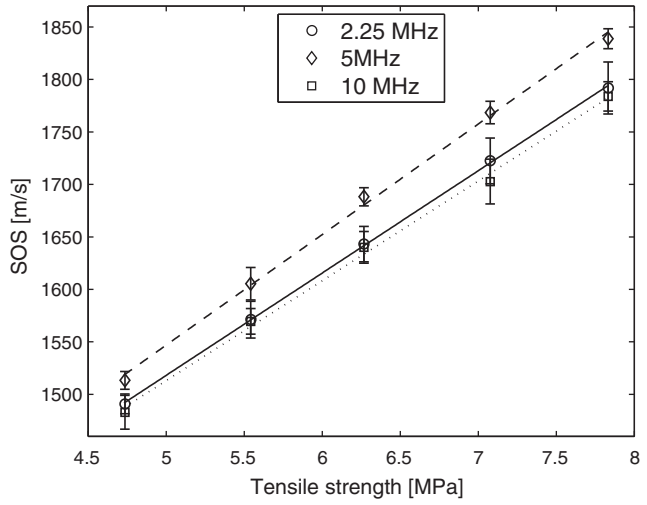

Fig. 11. Speed of sound (SOS) measured at frequencies of 2.25 MHz, 5 MHz and 10 MHz as a function of tensile strength for MCC2 tablets shown as circles, diamonds and squares, respectively. Error bars show the standard deviations and lines are linear fits.

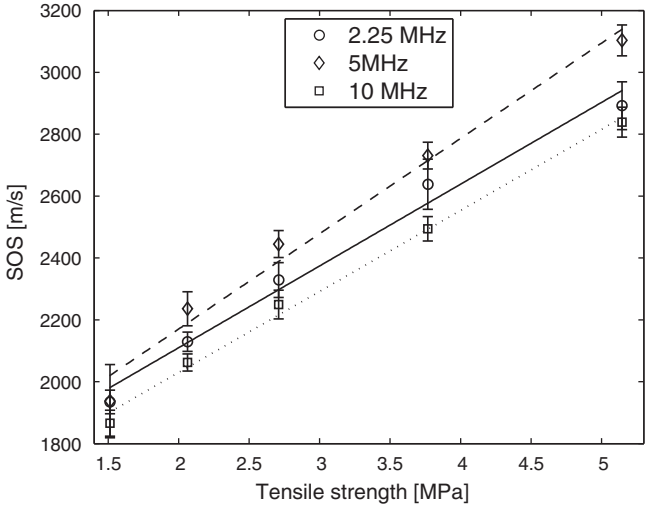

Fig. 12. Speed of sound (SOS) measured at frequencies of 2.25 MHz, 5 MHz and 10 MHz as a function of tensile strength for DCP tablets shown as circles, diamonds and squares, respectively. Error bars show the standard deviations and lines are linear fits.

4. Discussion

The ultrasound transmission measurements indicated that SOS was sensitive for tablets tensile strength. Based on the statistical analysis, SOS values can be used in the evaluation of the tensile strength of the tablets. For DCP, MCC1 and MCC2, the results are equal for used frequencies while the results for LM1 and LM2 were dependent on frequency. At frequency of 2.25 MHz, SOS is not statistically different between groups for LM1 tablets and thus at this frequency SOS is not a reliable measure for tensile strength. The tensile strength of LM2 tablets can be evaluated with SOS measured at frequency of 10 MHz because only at 10 MHz, the SOS values were statistically different between the groups. In addition, SOS was found to increase linearly with the tensile strength for DCP, MCC1, MCC2 and LM1 tablets as can be seen in Figs. 8 and 10–12. This is not the case for LM2 as seen in Fig. 9 where SOS is increasing with the tensile strength but the increase is nonlinear. It seems that SOS value approaches a certain value after tensile strength value of 0.65 MPa. This is also observed in Table 2 by comparison between SOS values for groups 4 and 5 for LM2 at frequency of 10 MHz. This nonlinear relationship between SOS and tensile strength is observed for LM1 at frequency of 2.25 MHz and frequencies of 2.25 MHz and 5 MHz for LM2. The difference in SOS between these two groups is only about 38 m/s while that of tensile strength is 0.20 MPa.

The particle size distribution has an effect on SOS values for lactose. Tablets compressed from LM2 (particles mainly below 100 μm) have higher SOS values than tablets compressed from LM1 (particles mainly above 100 μm). In contrast, LM2 have higher tensile strength values than LM1 which might explain for the higher SOS. For microcrystalline cellulose, the SOS values differ between MCC1 (the nominal particle size 180 μm) and MCC2 (the nominal particle size 50 μm) only at frequency of 5 MHz. At this frequency, MCC1 has higher SOS values than MCC2. The tensile strength of MCC1 and MCC2 tablets is also virtually the same as seen in Table 1. Thus, the particle size has a very minor effect on the SOS for microcrystalline cellulose. In addition, it seems that the particle size affects on the SOS when it also exerts an effect on the tensile strength of tablets.

In general, a high SOS value does not imply that the tablet necessarily possess high tensile strength. This can be seen when comparing DCP and MCC2 tablets. MCC2 tablets have the highest tensile strengths of the investigated tablets whereas DCP tablets have the highest SOS values. However, SOS values can be used for evaluation of tensile strength within a certain material. It was also found that excipients had different SOS values as can be seen from Table 2. The highest SOS values were obtained with DCP and the lowest with LM1. On the other hand, it is known that these used excipients have different compression behaviors. DCP forms tablets mainly by fragmentation while MCC is a plastic material (Alderborn and Nyström, 1996). A comparison of SOS for DCP, MCC1 and MCC2 tablets reveals that SOS for DCP is approximately 500 m/s higher. In other words, tablets that are deformed via fragmentation seem to have higher SOS than tablets that are consolidated by plastic deformation. In addition, LM1 and LM2 tablets have the lowest SOS values and lactose is known to be a hybrid material that deforms via both plastic deformation and fragmentation. Based on these compression behaviors and measured SOS values, the tablet formation mechanism might be related to SOS of tablets.

5. Conclusions

Tablets with only one ingredient were compressed and ultrasound transmission measurement technique was used to determine their SOS values. These values were compared to the tensile strength of tablets determined by crushing force. It was found that

SOS is sensitive to changes in the tensile strength and it increased with tensile strength for all studied excipients. Thus, ultrasound can be used to evaluate tensile strength of tablets non-destructively. However, a high SOS does not imply a high tensile strength in general. In addition, every excipient seems to have a typical SOS value. This might be related to the fact that these excipients have different compression behavior. Microcrystalline cellulose is a typical plastically deforming material whereas dicalcium phosphate is a fragmenting material and lactose is a hybrid material since it undergoes fragmentation and plastic deformation. Thus, SOS might also provide some information about the deformation behavior of material but this need to be studied in more detail in the future.

Developed ultrasound measurement system can be used to monitor changes in the tensile strength of tablets. The speed of sound is related to the mechanical properties of the structure of tablet and thus changes in the structure will affect on the speed of sound. This is also valid for commercial tablets because possible variations in the formulation will change the structure of tablet. However, it should be noted that based on the presented results changes in the tensile strength not absolute values can be evaluated using ultrasound. Since ultrasound measurements are relatively straightforward and no sample preparation is needed, the developed ultrasound measurement system is a potential tool for non-destructive evaluation of tablet tensile strength.

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