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In-line ultrasound measurement system for detecting tablet integrity

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ABSTRACT

An ultrasound measurement system for tablet defect detection is introduced. The measurement system was implemented in an eccentric single station tabletting apparatus, where ultrasound transducers were placed inside the upper and lower punches. These instrumented punches were then used to measure the speed of sound and ultrasound attenuation values in both intact and defective tablets made from dibasic calcium phosphate, microcrystalline cellulose and lactose monohydrate. Ultrasound attenuation was found to be a very sensitive method to discriminate defective tablets from intact ones. In addition, it was found that the determined ultrasound attenuation was different between all three materials used in this study, which indicates that different materials could be distinguished from one another by this detection method.

1. Introduction

A tablet is the most common solid dosage form for orally administered of drug. Tablets are popular for many reasons; for example they are easy to handle and administer, and their cost per dose is relatively low. Also, by using industrial tabletting machines, it becomes possible to quickly manufacture large amounts of tablets.

Capping and lamination are common problems in manufacturing a pharmaceutical tablet. During compression, particles go through various deformation phases, namely fragmentation and both elastic and plastic deformations. If the amount of elastic deformation is high, elastic recovery might break existing permanent interparticle bonds and cause the tablet to cap or laminate. Capping generally refers to the lid of a biconvex tablet that is separated from the compacted tablet (Eriksson and Alderborn, 1995). In lamination, small cracks generate layers within a tablet, parallel to the punch face.

Recently, many studies have been carried out to find measurement systems for defect detection in tablets. The purpose behind such studies is to better understand the processes of tabletting for online control, which is emphasized in the FDA's PAT guidance monograph (US Food and Drug Administration, 2004). This goal can be achieved by using real time measurement systems in these processes. As capping and lamination change the mechanical properties of the tablet, acoustic measurement systems, which are sensitive to mechanical changes, have been studied extensively. One of the first monitoring systems for defect tablet detection was a measurement system based on acoustic emission (AE) (Waring et al., 1987; Serris et al., 2002; Joe Au et al., 2004). Mechanisms of deformation generate AE signals that can be detected, and these acoustic responses may give information on the compression process during tablet formation. In these measurement systems, AE sensors were attached to the side of the upper punch and the system was tested in a single tablet production machine. From the acquired data, probability distribution was calculated and used to classify capped and non-capped tablets. As classification is based on probability, the system correctly classified 95% of the capped tablets (Joe Au et al., 2004).

Ultrasound is a mechanical wave that includes certain wavelengths, propagating in a medium. It is widely used for non-destructive testing in many different areas. Recently, ultrasound based measurement systems have also been introduced in pharmaceutical research. Since ultrasound is a mechanical wave, the speed of sound is sensitive to mechanical properties and thus it has been used to determine the porosity and elastic modulus of tablets and coating thickness (Hakulinen et al., 2008; Akseli and Cetinkaya, 2008; Akseli et al., 2009a,b; Ketolainen et al., 1995). Varghese and Cetinkaya (2007) used photo-acoustic measurements to detect defects in tablets and the system was capable of detecting holes sizes of 500 μm and visible cracks. In photo-acoustic measurements, laser light generates ultrasound pulses inside the sample. The displacement of the sample caused by ultrasound is

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measured and analyzed to obtain structural information on the sample. A similar system was introduced by Akseli et al. (2008), which differed from the previous example in that an air coupled ultrasound transducer was used for generating the ultrasound instead of a laser. Using an air coupled ultrasound measuring device allowed for the detection of various defects that were distinguished from defect-free samples (Akseli et al., 2008). However, these systems are challenging to use as an in-line monitoring system in a tabletting environment because the apparatus uses interferometers, which are sensitive to vibrations.

Acoustic-resonance spectroscopy (ARS) has also been used to monitor tablets. In ARS, the acoustic signal is guided to the surface of a tablet, where the acoustic wave interacts with the tablet, and this interaction can be differentiated between tablets of similar size and shape (Medendorp and Lodder, 2006; Medendorp et al., 2007). ARS might be possible to use as an online measurement technique but it is slow because one measurement takes seconds in time (Medendorp et al., 2007).

In this paper, an in-line ultrasound measurement system is introduced for the detection of tablet defects. The measurement system is based on an ultrasound transducer that is implemented inside the flat-faced tabletting machine punches. One transducer emits a short ultrasound pulse that propagates through the tablet while the other transducer receives the transmitted pulse. This system was implemented in an eccentric single station tabletting machine. Its performance was tested by using both intact and defective tablets that were made with three different excipients. The speed of sound and ultrasound attenuation was determined from the transmitted ultrasound signal.

2. Materials and methods

2.1. Sample preparation

Three common pharmaceutical excipient powders were individually examined as tabletting ingredients; dibasic calcium phosphate dihydrate (DCP), microcrystalline cellulose (MCC) and lactose monohydrate (LM). The DCP was Emcompress® Premium produced by JRS Pharma (Budenheim, Germany), the MCC was Avicel® PH101 produced by FMC Biopolymers (Cork, Ireland) and the LM was Pharmatose® 90M produced by DMV-Fronterra Excipients (Veghel, The Netherlands). The mean densities of the DCP, MCC and LM were 2.389, 1.668 and 1.538 g/cm^3, respectively. The mean density values of powders were measured by five parallel determinations with a Multi-pycnometer (Quanta Chrome, NY, USA) using helium as the measuring gas. The powders were used as received without sieving or any other pre-processing. All powders were stored in dry containers at 24% relative humidity for tablet compaction. Tablets were directly compressed with a compaction simulator (PCS-1, Puuman Oy, Kuopio, Finland) using flat-faced punches of 13 mm in diameter. Prior to the compaction, the powder mass (800 mg for DCP and 600 mg for each, MCC and LM, respectively) was weighed with an analytical balance (A200S, Sartorius, Goettingen, Germany) and manually poured into the die for each tablet. Minimal lubrication was used by contaminating the die with a brush and fine magnesium stearate powder. The employed compaction profile was a single sided triangle for the upper punch while the lower punch was kept stationary. Different filling depths and compaction amplitudes were applied to achieve tablet heights of 3.2, 3.1 and 3.3 mm for MCC, DCP and LM tablets, respectively. After compaction, the tablets were stored with anhydrous silica, the dimensions were measured with a micrometer (Digitrix, NSK, Japan) and tablet weights were determined with the analytical balance within 24 h after compaction. Additionally, sample tablet sets with an artificial lateral defect were prepared by using parchment paper with a 46 μm of thickness. Paper patches (10 mm × 20 mm) were folded in half from the middle to obtain 10 mm × 10 mm patches with a thickness of 92 μm. One patch of paper was laid horizontally in the vertical centre level of the powder bed of the die before compaction. The paper patch was enclosed inside the excipient during compaction and the resulting sample was considered to have a significant lateral defection. The total number of samples was $N = 55$. The number of intact DCP, MCC and LM tablets prepared was 10, 6 and 10, respectively. The number of defected DCP, MCC and LM tablets prepared was 11, 8 and 10, respectively.

2.2. Ultrasound measurements with contact transducers

The ultrasound (US) transmission signals from tablets were measured with three different pairs of commercial US contact transducers, with an effective element diameter of 6 mm. The sample was axially compressed between the US transducers and the loading force was manually driven by a bolt (Fig. 1). The axial force was monitored by a miniature load cell (LPM560, Cooper Instruments, Warrenton, VA, USA). Transducers of the nominal frequencies of 2.25 MHz (Olympus model V133), 5 MHz (Olympus model C110 sending and V110 receiving) and 10 MHz (Olympus model V112) were used. Through transmission (TT) geometry for US beam along the tablet axis was used, and an US pulser-receiver (model 5077PR, Olympus-NDT Inc., Waltham, MA, USA) was used as a signal source that transmitted signals which were measured by a LeCroy Wavesurfer 42Xs-A digital oscilloscope (LeCroy Corp., NY, USA). To obtain the constant state for acoustic dry coupling, a uniaxial loading of 12 N was used. Any special acoustic couplants or other materials that might contaminate the samples during the measurements were not used. The US pulser voltage of 200 V (excluding 100 V during 5 MHz measurements) with the repeat rate of 1 kHz and receiver gain of −10 dB was used. An average of 512 consecutive measurements, without any filtering, was used during the measurements. The sampling frequency was 50 MHz during the

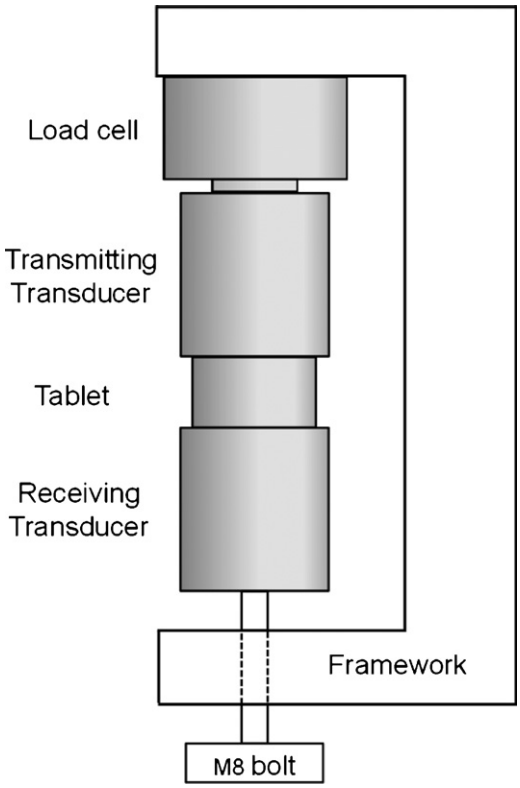

Fig. 1. Component configuration used for US transmission measurements with contact transducers.

Fig. 2. Measurement setup used in US transmission measurements with instrumented punches.

2.25 MHz measurements and 250 MHz during the 5 and 10 MHz measurements.

2.3. Ultrasound measurements with the instrumented tablet press punches

An eccentric single station Korsch EK-0 tabletting machine (Korsch AG, Berlin, Germany) was instrumented with a pair of non-focused 10 MHz miniature US transducers (model XMS-310, Olympus-NDT Inc., Waltham, MA, USA). Additionally, standard strain gages and linear displacement sensors (LP30FQJ, Midori Precisions Co., Ltd., Tokyo, Japan) were implemented into the upper and lower punches for accurate force and position measurements. The US transmission signals of tablets were measured during a static compression of 210 N. The tabletting die was removed from the apparatus in order to measure tablets having diameter of 13 mm (Fig. 2). The loading was established by manipulating the flywheel of the tabletting machine manually and monitored continuously. The diameter of flat-faced punches was 10 mm. TT geometry for the US beam along the tablet axis was used. Any special acoustic couplants or other materials that could contaminate the samples during the measurements were not used. The same US pulser-receiver, with a voltage of 200 V and receiver gain of +30 dB, was used throughout the study. No filtering was used during the measurements. The repeat rate of the pulser was 200 Hz. The averaging of 512 consecutive measurements was used during the measurements. Measurements were made with a LeCroy Wavesurfer 42Xs-A digital oscilloscope at a sampling frequency of 50 MHz.

2.4. Analyses of the measurements

The offline analyses were made by using the Matlab R2008a software (Mathworks Inc., Natick, MA, USA). Time of flight (TOF) (Ragozzino, 1981) was obtained from the measured waveforms by calculating the Hilbert Transform envelope of the recorded signals. The TOF was calculated from the maximum value of the signal using the Hilbert transformation. The speed of sound (SOS) was calculated by dividing the measured tablet thickness by the TOF. The frequency spectrum of the US transmission A was determined by using the Fast Fourier Transform (FFT) algorithm. Only the first pulse of the measured US signal was used.

The US attenuation of tablets was also analyzed. To be sure that the attenuation measurements were done in the far field, the near field distance N was estimated by using (Eq. (1)), as given by the manufacturer of the US transducers:

$$N = \frac{D^2 f}{4c}, \tag{1}$$

where D is the diameter of the US transducer element, f is the frequency and c is the speed of sound in the medium. The value of N was estimated to be 3.9 mm using values $D = 3$ mm, $f = 10$ MHz and an approximation for speed of sound in stainless steel, $c = 5800$ m/s. The punch shaft works as a delay line for the US wave. The length of the shaft is 20 mm, thus the sample is situated in the far field. Finally, the US attenuation coefficient $\alpha_i(f)$ of the samples i was calculated using (Eq. (2)):

$$\alpha_i(f) = \frac{8.686}{x_i} \ln \frac{A_{\text{ref}}(f)}{A_i(f)}, \tag{2}$$

where x_i is the sample thickness and $A_i(f)$ the transmission amplitude of the frequency band f, through the sample i. $A_{\text{ref}}(f)$ is the transmission amplitude of f through the 9.929 mm thick, cylindrical stainless steel reference. $A_{\text{ref}}(f)$ and $A_i(f)$ were calculated from the signal using the FFT algorithm. The average attenuation, α_f, of the frequency band, f, was calculated for the intact and defected tablets using (Eq. (3)):

$$\alpha_f = \frac{1}{n} \sum_{i=1}^{n} \alpha_i(f_i), \tag{3}$$

where $f_i = \{f + 0.1\ k_i\}$, k_i, $\{-3, -2, -1, \ldots, 3\}$ and $n = 7$.

The statistical tests were made with SPSS 14.0.1 software (Lead Technologies, Inc., Chicago, IL, USA). Normality of distributions was tested by the Shapiro–Wilk test. The statistical significance was tested by the Kolmogorov–Smirnov Z-test and t-test of independent samples for normally distributed parameters and others, respectively. All the prepared samples ($N = 55$) were tested.

3. Results and discussion

3.1. Contact transducer measurements

A short US pulse, transmitted through the tablet, was then measured with three different contact transducers. In the 2.25 MHz US signal, transmitted through a DCP sample, the first pulse is seen at 2 μs and three consecutive harmonic pulses can subsequently be seen at 4.5, 7.0 and 9.5 μs (solid line in Fig. 3a). The first pulse is directly transmitted through the tablet and has the highest amplitude, while the second, the third and the fourth pulses are propagated and reflected back and forth through the tablet, and thus attenuating as a function of the medium's density and propagation distance. Due to the relatively low attenuation of the 2.25 MHz wave, a high number of the reflected pulses are propagated throughout the sample. The transmission spectrum from the first pulse contains information in the frequency range of 0–2.5 MHz with intensity maximum at 0.3 MHz (Fig. 3b). With the 5 MHz transducers, only two clear harmonic pulses are visible (dashed line in Fig. 3a). The attenuation is higher when compared with the 2.25 MHz signal and the spectrum contains information in the frequency range of 0–5 MHz (solid line in Fig. 3b). The transmission spectrum from the first pulse contains information on the frequency range from 0 to 5 MHz with an intensity maximum at 1 MHz. With 10 MHz transducers, only the two first pulses; i.e., the direct and the first harmonic, are seen clearly (dotted line in Fig. 3a). The second harmonic still exists at 6.5 μs, although the shape of this

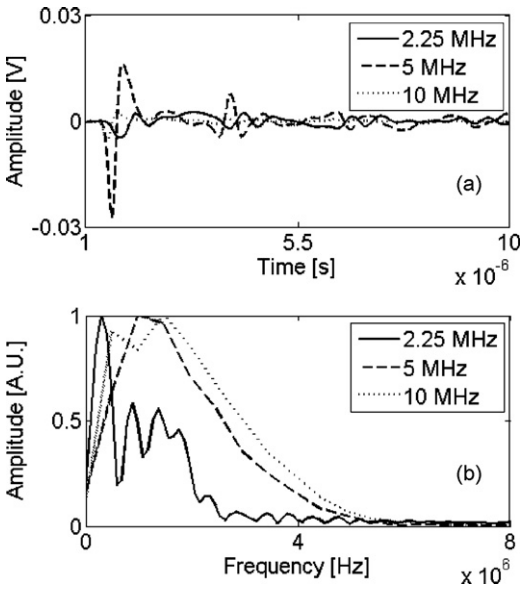

Fig. 3. Transmitted US signal (a) and its spectrum (b), as measured with three different frequency contact transducers from the first pulse transmitted through a DCP sample.

waveform is non-specific, and the attenuation is higher compared to the lower frequency measurements. The transmission spectrum from the first pulse contains information in the frequency range of 0–5 MHz with and intensity maximum at 1.5 MHz (Fig. 3b). Similar to the 5 MHz measurements (dashed line in Fig. 3b), most of the signal exists in a low frequency range between 0 and 1.5 MHz, and thus outside of the transducers' characteristic frequency range (6.7–13.3 MHz). It should be noted that the nominal frequency of the contact transducers differs from the frequencies measured in the tablet study. However, competent US signals were measured at all the transducers of different frequencies and, therefore, it can be stated that every one of these frequencies may be used for couplant-free US measurement, although the widest spectrum was obtained with the 10 MHz transducer (dotted line in Fig. 3b). The mean values of SOS for the DCP measured with 2.25, 5 and 10 MHz contact transducers were 2900, 2753 and 2703 m/s, respectively (Table 1). The deviation decreased as a function of frequency. For MCC, corresponding values were 1823, 1691, 1676 m/s, and for PHA, 884, 952 and 852 m/s, respectively. In the MCC measurements, the deviation was very low, whereas, the deviation was quite high during the LM measurements. The difference of the compaction parameter means between groups was less than two standard deviations (Table 2).

3.2. Transducer instrumented punch measurements

In Fig. 4a, the US transmission signal through a 9.929 mm thick stainless steel cylinder is shown with clear first and second pulses. Instead of the nominal frequency of the XMS-310 transducer; i.e., 10 MHz, the peak of the spectrum was shifted to lower frequency range. The peak of the TT spectrum was at 4 MHz and the full width at half maximum defined spectral width of 2.7–5.8 MHz (Fig. 4b).

The SOS values of intact DCP tablets were between 2395 and 2723 m/s, and defected tablets between 1642 and 2604 m/s (Table 2). The SOS values of intact MCC tablets were between 1716 and 1758 m/s, and defected tablets between 1599 and 1737 m/s (Table 2). A similar response was seen with LM, with SOS values between 723 and 758 m/s with intact tablets and between 692 and 894 m/s with defected tablets. Interestingly, the highest individual values of the SOS for LM were measured during the test of defected tablets. The statistical significance of the difference between groups

Table 1
Speed of sound (c) measured with contact transducers of different frequencies.

	$c_{2.25MHz}$ [m/s]	c_{5MHz} [m/s]	c_{10MHz} [m/s]
DCP			
1	2876	2794	2731
2	2866	2736	2684
3	2865	2783	2647
4	2983	2733	2728
5	2990	2818	2744
6	2954	2778	2725
7	2859	2682	2696
8	2685	2611	2598
9	2936	2820	2775
10	2987	2775	2703
$\mu \pm \sigma$	2900 ± 93	2753 ± 65	2703 ± 51
MCC			
1	1765	1663	1672
2	1853	1705	1671
3	1817	1679	1666
4	1857	1719	1717
5	1801	1692	1656
6	1845	1687	1674
$\mu \pm \sigma$	1823 ± 36	1691 ± 20	1676 ± 21
LM			
1	721	673	676
2	998	853	937
3	942	878	986
4	943	886	977
5	931	985	724
6	946	1005	981
7	995	1021	994
8	772	1075	740
9	816	1104	773
10	772	1043	734
$\mu \pm \sigma$	884 ± 102	952 ± 130	852 ± 132

for each excipients' SOS was calculated with the t-test of independent samples. There was no statistical difference between the intact and defected tablet groups in SOS at the 99% confidence level ($P_{DCP} = 0.012$, $P_{MCC} = 0.042$ and $P_{LM} = 0.728$). Therefore, SOS cannot

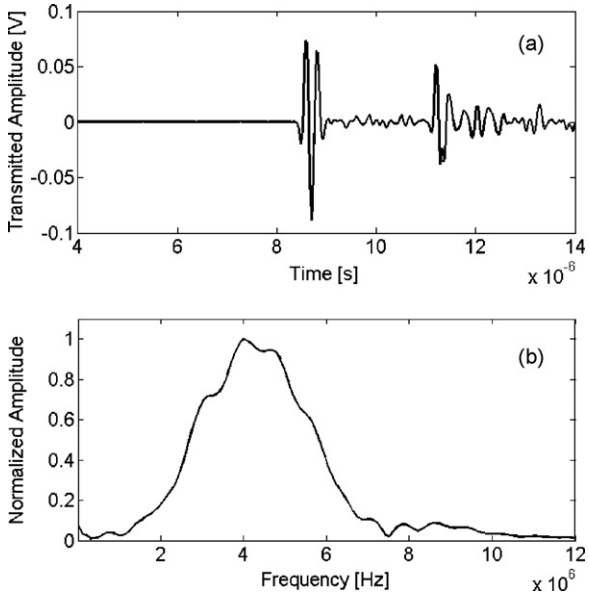

Fig. 4. US transmission signal (a) through a 9.929 mm thick stainless steel cylinder using transducer instrumented tablet punches. A clear first and second pulse can be seen at 8.7 and 11.3 μs, respectively. (b) Normalized transmission spectrum of the first temporal pulse at 8.7 μs.

Table 2
The speed of sound ($c_{punches}$) of tablets measured with transducers attached to punches. The mean of speed of sound (c), compression force (F), tablet mass (m), height (h), and calculated porosity (p%), is shown with their calculated deviations (σ).

#	$c_{punches}$ [m/s]		
	DCP	MCC	LM
1	2723	1721	739
2	2628	1720	723
3	2424	1745	730
4	2504	1758	742
5	2395	1716	758
6	2451	1729	755
7	2432	–	730
8	2424	–	748
9	2465	–	739
10	2467	–	740
$c \pm \sigma_c$	2491 ± 104	1731 ± 17	740 ± 11
$F \pm \sigma_F$	28186 ± 1599	30221 ± 761	21978 ± 1849
$m \pm \sigma_m$	800.0 ± 13.7	596.3 ± 4.7	594.9 ± 3.1
$h \pm \sigma_h$	3.124 ± 0.034	3.244 ± 0.014	3.336 ± 0.028
$p\% \pm \sigma_{p\%}$	19.871 ± 0.538	17.084 ± 0.361	13.515 ± 0.821
P1	2338	1737	700
P2	2277	1702	721
P3	1799	1723	894
P4	2335	1723	847
P5	1716	1666	692
P6	2604	1688	740
P7	2368	1696	723
P8	2409	1599	733
P9	2301	–	712
P10	2334	–	719
P11	1642	–	–
$c \pm \sigma_c$	2193 ± 318	1692 ± 44	748 ± 67
$F \pm \sigma_F$	29621 ± 291	30327 ± 1502	20961 ± 1284
$m \pm \sigma_m$	806.9 ± 3.1	602.0 ± 9.1	600.6 ± 8.5
$h \pm \sigma_h$	3.169 ± 0.010	3.299 ± 0.037	3.418 ± 0.025
$p\% \pm \sigma_{p\%}$	20.365 ± 0.149	17.692 ± 0.556	14.817 ± 0.668

be used as a reliable method to distinguish between intact and defected.

It can be seen in Tables 1 and 2, that when SOS values are similar in magnitude when measured with contact transducers and punches. There are differences that cannot be explained only by sample preparation data; e.g., the sample thickness, as shown in Table 2. However, there are considerable differences in measurement conditions; e.g., contact pressure. For example, the normal compressions of 12 and 210 N were used during the contact and punch measurements, respectively. Thus, the US transducers implemented inside the punches can be used for SOS measurements. Moreover, as the force between punch and surface of tablet was higher than in the contact transducer measurements, the SOS values are more coherent in punch measurements than in contact transducer measurements.

The US pulse through a defected tablet is attenuated, roughly by one third in amplitude when compared to the intact sample, as seen in Fig. 5a and b. The spectra of the first temporal pulse, measured from an intact and defected DCP samples, are shown in Fig. 5c and d, respectively. Such spectra have similar properties when compared with the reference spectrum (Fig. 4), as the maximum amplitude exists at approximately 4 MHz and the frequency range is 1–7 MHz. From this observation different frequencies were found to attenuate differently when comparing intact and defected samples. In other words, the maximum amplitude occurred at 3.8 MHz for the intact sample and at 3.0 MHz with the defected sample. The same phenomenon occurred with MCC tablets, where the frequency range was 1–6 MHz and the attenuation behavior was similar between the intact and the defected samples (Fig. 6). Moreover, the spectral shape was similar to a Gaussian curve (Fig. 6). The results with the LM tablets differed from those from DCP and MCC. The TT ultrasound signal was weak for both intact and defected samples, due to the material characteristics of LM; e.g., proneness to fragmentation, density, and porosity. The LM tablets completely attenuated the 2.5 MHz and higher frequencies (Fig. 7), while MCC and DCP tablets transmitted frequencies up to 6 and 7 MHz, respectively. The signal amplitude was lower in LM measurements with the same pulser settings used with DCP and MCC,

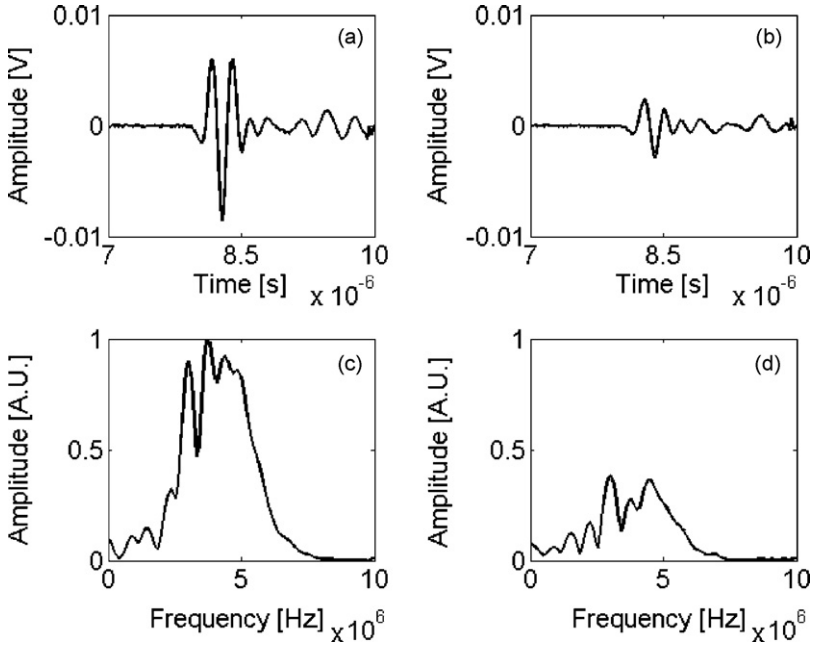

Fig. 5. Transmitted US signals and spectra through DCP samples with transducer instrumented tablet punches. The US signal (a) and the spectrum (c) for the intact tablet and US signals (b) and spectrum (d) for defected tablet.

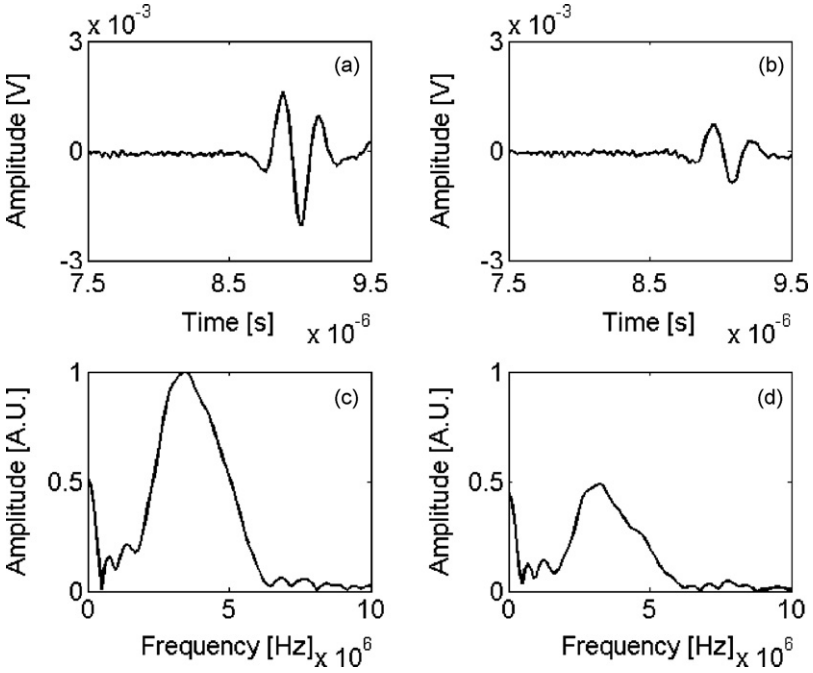

Fig. 6. Transmitted US signals and spectra through MCC samples by using transducer instrumented tablet punches. The US signal (a) and the spectrum (c) for intact tablet and US signal (b) and spectrum (d) for defected tablet.

because the frequency spectrum of LM was outside of the characteristic spectrum of the transducer implemented to the punches (Fig. 4b).

To discriminate the defected tablets from intact ones, the US attenuations of different frequency bands were calculated from the measured data. The US analysis for discriminating the intact and defected tablets can be done in the frequency ranges of 2–6 MHz (Figs. 4–6), except with the LM (Fig. 7). The TT ultrasound spectrum for LM includes only frequencies between 0 and 2 MHz.

A higher attenuation level was found with the defected DCP tablets. The difference between the intact and defected tablets group was statistically significant ($P < 0.01$) at all frequencies except the frequency of 1.8 MHz (Table 3). The linear attenuation coefficient was determined by using a linear fit to the attenuation values within the linear frequency range. For DCP (Fig. 8), the linear attenuation coefficient in the range of 3.0–5.4 MHz was 0.85 and 1.41 dB/mm/MHz for the intact and defected tablets, respectively. The attenuation differences between the intact and defected

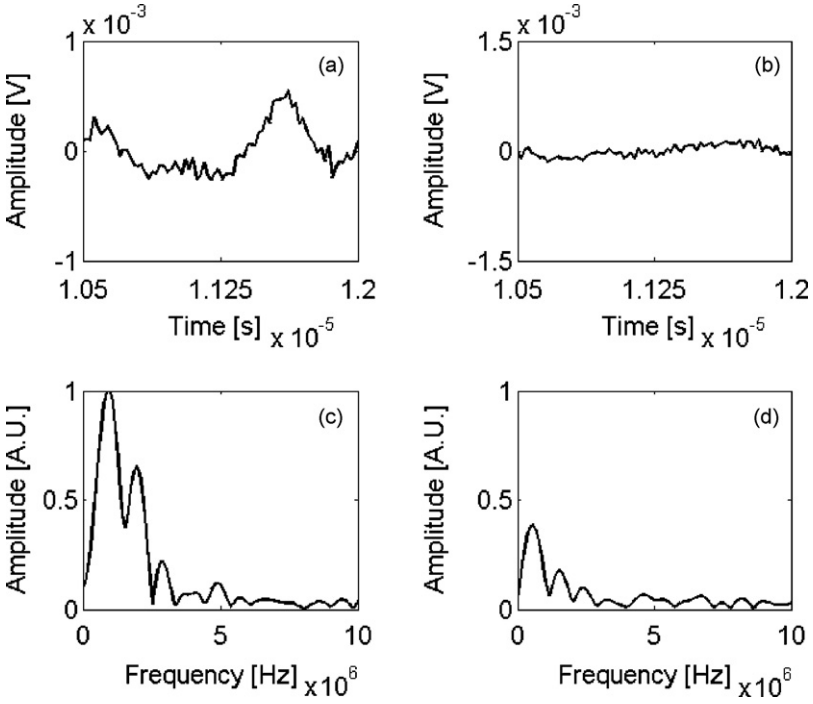

Fig. 7. Transmitted US signals and spectra through LM samples by using transducer instrumented tablet punches. The US signal (a) and the spectrum (c) for intact tablet and US signal (b) and spectrum (d) for defected tablet.

Table 3
Attenuation values (α) of different frequency bands (f) for DCP tablets measured with transducer instrumented punches; mean (μ), standard deviation (σ) of attenuation (α_f) and the difference between intact and defected means ($\Delta\mu = \mu_{defected} - \mu_{intact}$). Significance is shown as P-values.

DCP	α_f [dB/mm]							
	$\alpha_{1.2MHz}$	$\alpha_{1.8MHz}$	$\alpha_{2.4MHz}$	$\alpha_{3.0MHz}$	$\alpha_{3.6MHz}$	$\alpha_{4.2MHz}$	$\alpha_{4.8MHz}$	$\alpha_{5.4MHz}$
1	2.0	5.2	4.3	4.3	4.2	4.6	4.4	4.2
2	1.8	4.9	4.0	3.9	4.0	4.1	4.0	4.4
3	2.4	2.8	3.2	3.0	4.2	5.4	6.8	8.7
4	1.6	3.9	3.6	3.6	4.4	4.5	4.7	4.9
5	1.3	4.3	4.2	4.1	5.1	5.0	5.3	6.6
6	1.5	4.0	4.0	3.6	4.6	4.6	5.2	6.5
7	1.7	5.1	4.2	4.0	4.4	5.3	6.5	7.3
8	1.7	5.0	4.8	4.9	5.7	5.6	5.5	6.6
9	1.9	3.8	3.7	3.5	4.4	4.2	5.1	6.6
10	1.6	4.5	4.1	4.2	4.5	4.8	4.5	5.0
$\mu \pm \sigma$	1.8 ± 0.3	4.4 ± 0.7	4.0 ± 0.4	3.9 ± 0.5	4.6 ± 0.5	4.8 ± 0.5	5.2 ± 0.5	6.1 ± 1.4
P1	2.4	4.7	5.7	5.5	6.4	6.7	7.1	7.2
P2	1.3	4.7	6.3	5.9	8.8	10.4	10.2	12.6
P3	3.6	5.9	6.7	6.1	6.5	7.2	8.0	9.0
P4	3.4	4.6	5.2	5.5	6.2	6.8	6.8	6.8
P5	3.3	3.3	6.9	6.0	6.4	7.4	8.8	10.9
P6	3.4	6.6	6.2	6.3	7.1	6.9	6.6	7.4
P7	4.0	5.8	6.1	5.9	6.6	7.6	8.1	9.2
P8	3.0	5.4	6.4	6.3	7.5	6.9	6.9	7.3
P9	3.1	5.3	5.5	6.0	6.6	6.7	6.5	7.1
P10	3.8	4.9	4.9	5.0	5.9	8.3	10.7	14.0
P11	3.5	4.6	8.0	9.6	9.4	10.4	12.7	14.5
$\mu \pm \sigma$	3.2 ± 0.7	5.1 ± 0.9	6.2 ± 0.8	6.2 ± 1.2	7.0 ± 1.1	7.7 ± 1.4	8.4 ± 2.0	9.6 ± 2.9
$\Delta\mu$	1.4	0.7	2.2	2.3	2.4	2.9	3.2	3.5
P	<0.001***	0.132[a]	<0.001[a,***]	<0.001***	<0.001***	<0.001***	0.002[a,**]	0.003**

[a] Normal distribution.
** Significant difference for 99% confidence level.
*** Significant difference for 99.9% confidence level.

tablet groups increased as a function of frequency (Fig. 8). Similar to the DCP samples, a higher attenuation level was found with the defected MCC tablets as well. The difference between the intact and defected tablet groups was statistically significant ($P < 0.01$) and ($P < 0.05$) at frequencies between 4.2–5.4 and 3.0–3.6 MHz, respectively (Table 4). For MCC (Fig. 9), the linear attenuation coefficient in the range of 3.0–5.4 MHz was 1.11 and 1.39 dB/mm/MHz for the intact and defected tablets, respectively. As with DCP, The difference between the intact and defected tablets group in attenuation values for MCC also increased as a function of frequency (Fig. 9). In contrast to DCP and MCC, LM was a completely different material. The US attenuation in LM increased as a function of frequency

Table 4
Attenuation values α_f different frequency bands f for MCC tablets measured with transducer instrumented punches; mean μ, standard deviation σ of attenuation α_f and the difference between intact and defected means $\Delta\mu = \mu_{defected} - \mu_{intact}$. Significance is shown as P-values.

MCC	α_f [dB/mm]							
	$\alpha_{1.2MHz}$	$\alpha_{1.8MHz}$	$\alpha_{2.4MHz}$	$\alpha_{3.0MHz}$	$\alpha_{3.6MHz}$	$\alpha_{4.2MHz}$	$\alpha_{4.8MHz}$	$\alpha_{5.4MHz}$
1	3.9	5.7	5.5	6.0	6.7	7.5	8.1	8.9
2	5.7	7.1	6.4	6.9	7.5	8.3	9.1	9.9
3	6.1	8.1	6.9	7.8	8.3	8.7	8.9	9.2
4	4.3	6.0	5.7	6.6	7.5	8.4	8.7	9.6
5	5.1	7.0	6.2	6.7	7.3	8.1	8.8	9.2
6	5.8	7.1	6.7	7.1	7.8	8.5	9.1	9.9
$\mu \pm \sigma$	5.2 ± 0.9	6.8 ± 0.9	6.2 ± 0.6	6.8 ± 0.6	7.5 ± 0.5	8.2 ± 0.4	8.8 ± 0.4	9.5 ± 0.4
P1	5.1	7.9	7.7	8.0	8.6	9.4	10.3	11.1
P2	5.6	7.1	7.1	7.9	8.8	9.5	9.8	10.2
P3	5.7	7.5	7.3	8.0	8.5	9.1	9.6	10.0
P4	5.3	7.3	7.3	7.7	8.4	9.3	10.0	10.9
P5	4.7	7.3	6.9	7.6	8.4	9.7	10.5	11.3
P6	5.6	7.2	6.7	7.7	8.6	9.6	10.0	10.7
P7	5.0	7.3	6.9	7.7	8.8	9.8	10.4	11.6
P8	4.5	5.5	6.6	7.6	8.3	9.5	10.6	12.8
$\mu \pm \sigma$	5.2 ± 0.5	7.1 ± 0.7	7.1 ± 0.4	7.8 ± 0.2	8.6 ± 0.2	9.5 ± 0.2	10.1 ± 0.3	11.1 ± 0.9
$\Delta\mu$	0.0	0.3	0.9	1.0	1.1	1.3	1.3	1.6
P	0.721[a]	0.499	0.095[a]	0.012*	0.010[a,*]	0.002[a,**]	0.002[a,**]	0.002[a,**]

[a] Normal distribution.
* Significant difference for 95% confidence interval.
** Significant difference for 99% confidence interval.

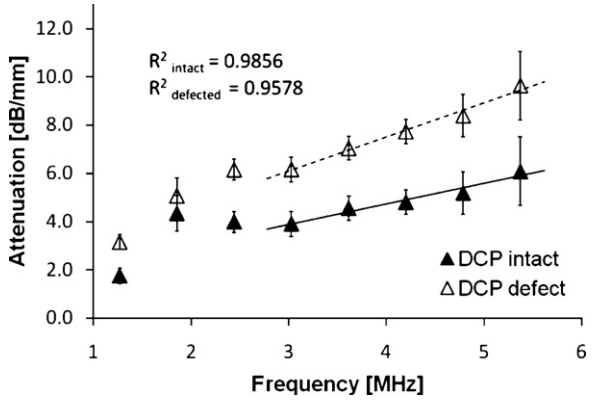

Fig. 8. Mean US attenuation values plotted as a function of frequency of intact and defected DCP tablets measured with transducer instrumented punches. The standard deviation of the mean values is shown with error bars. Linear fits of attenuation are shown for intact and defected DCPs in the frequency range of 1.2–5.4 MHz.

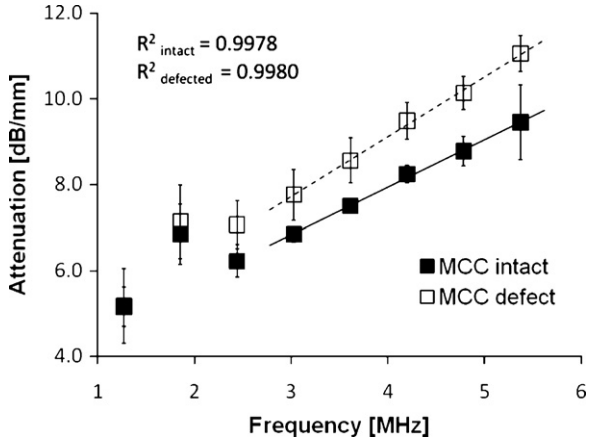

Fig. 9. Mean US attenuation values as a function of frequency of intact and defected MCC tablets measured with transducer instrumented punches. Standard deviation of the mean values is shown as error bars. Linear fits of attenuation are shown for intact and defected MCCs in the frequency range of 1.2–5.4 MHz.

within the 1.2–3.6 MHz range, but slightly decreased at the higher frequencies; 4.2–5.4 MHz (Fig. 10). For LM, the difference between the intact and defected tablet groups was statistically significant ($P < 0.01$) at frequencies between 1.2 and 1.8 MHz. The attenuation above 2.4 MHz was not used in the analysis of LM, as the frequency spectrum of the transmitted signal was between 0.1 and 2.4 MHz (Fig. 7c and d). At 1.2 MHz, the attenuation difference for LM between the intact and the defected tablets was 1.8 dB/mm, and the linear coefficient of attenuation in the range of 1.2–2.4 MHz was 7.47 and 7.04 dB/mm/MHz for the intact and defected tablets, respectively. It can be noticed that the signal in this frequency range was too weak to be used reliably in these analyses, as seen in Fig. 7c and d. Also, the signal level at 3 MHz and higher frequencies is very low, as hardly any of the signal can transmit through the LM sample in either intact or defected tablets.

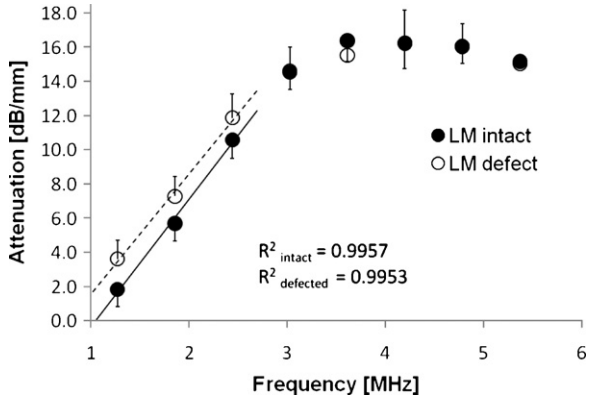

Fig. 10. Mean US attenuation values as a function of frequency of intact and defected LM tablets measured with transducer instrumented punches. Standard deviation of the mean values is shown as error bars. Linear fits of attenuation are shown for intact and defected LMs in the frequency range of 1.2–2.4 MHz.

In order to find the most sensitive frequency bands for the discrimination between intact and defected tablet samples, the difference in response between groups was analyzed. The attenuation values of each individual sample was observed and used for ranking. From the calculated *P*-values (Table 3) it can be seen that there is no statistical difference between intact and defective groups only at 1.8 MHz, and the attenuation for all intact and defective tablets overlaps at frequencies 1.2, 4.8 and 5.4 MHz (Table 3). At the remaining frequencies, namely 2.4, 3.0, 3.6 and 4.2 MHz, the intact tablets have a smaller attenuation than the defective ones, and these frequencies can be used to discriminate between intact and defective DCP tablets. The highest difference between the mean attenuation values within the frequency range of 2.4–4.2 MHz was found at frequency of 4.2 MHz. The differences between mean attenuation values of intact and defected tablets, $\Delta\mu$, are shown in Table 3. The threshold value for discrimination was set to be at the highest attenuation value of intact tablets. At a frequency of 4.2 MHz, the threshold value was 5.6 dB/mm and samples with an attenuation higher than 5.6 dB/mm were considered defective. Using this frequency band, the discrimination of the DCP tablets was effective.

Using calculated *P*-values for MCC tablets (Table 4) frequencies between 1.2 and 2.4 MHz were excluded because there was no statistical significant difference between intact and defected tablets in this range. In addition, frequencies of 3.0 and 3.6 MHz were excluded because attenuation values overlapped significantly between intact and defective tablets in this range. For MCC, the non-overlapping frequencies were 4.2, 4.8 and 5.4 MHz. The difference between mean attenuation values of intact and defective MCC tablets was highest at 5.4 MHz, but the difference between the highest attenuation value of intact tablets (9.9 dB/mm) and lowest value of defected (10.0 dB/mm) was only 0.1 dB/mm. At a frequency of 4.8 MHz, the difference between the highest and lowest values of intact and defective MCC tablets was 0.5 dB/mm. By using this frequency band, the discrimination of between intact and defective MCC tablets was feasible. The detection threshold value was 9.1 dB/mm, i.e., the highest value for intact at 4.8 MHz. Additionally, using a frequency of 4.2 or 5.4 MHz with detection threshold value of 8.7 and 9.9 dB/mm, respectively, similar results were obtained (Table 4).

The calculated *P*-values for LM measurements (Table 5) show that only at 1.2 and 1.8 MHz attenuation values were significantly different between intact and defective tablets. However, the attenuation between intact and defective LM tablets overlapped in all frequency bands. According to the results in the Table 5, a frequency of 1.2 MHz gave the smallest number of incorrect discriminations when compared to other frequencies used for LM. Discrimination was accomplished by using a threshold value of 2.7 dB/mm, and three incorrect discriminations were observed; namely samples P2, P4 and P10. With LM samples, a discrimination based on the attenuation of single frequency band was not as successful as with DCP and MCC samples. This was probably a result of the poor signal-to-noise ratio for the LM measurement; i.e., the employed frequency band did not exist within the full width at half maximum spectral range of the equipment used in this study (Fig. 4b).

Table 5
Attenuation values α of different frequency bands f of LM tablets measured with transducer instrumented punches. Mean μ and standard deviation σ of attenuation α_f and the difference between intact and defected means $\Delta\mu = \mu_{\text{defected}} - \mu_{\text{intact}}$. Significance is shown as P-values.

LM	α_f [dB/mm]							
	$\alpha_{1.2\text{MHz}}$	$\alpha_{1.8\text{MHz}}$	$\alpha_{2.4\text{MHz}}$	$\alpha_{3.0\text{MHz}}$	$\alpha_{3.6\text{MHz}}$	$\alpha_{4.2\text{MHz}}$	$\alpha_{4.8\text{MHz}}$	$\alpha_{5.4\text{MHz}}$
1	2.3	5.7	9.9	15.4	17.4	15.4	20.3	18.7
2	1.9	7.8	10.4	14.0	15.1	17.3	15.0	14.7
3	1.3	5.4	10.5	14.6	17.8	17.5	16.8	14.6
4	1.4	4.6	9.6	12.8	14.9	15.3	13.7	15.2
5	1.3	7.4	13.3	17.5	16.1	14.8	14.8	14.1
6	1.7	4.5	10.9	14.3	14.1	16.2	14.8	15.0
7	2.7	5.6	11.0	15.1	16.5	15.9	14.5	15.4
8	2.4	5.3	10.2	13.3	16.0	17.2	16.3	14.1
9	2.2	5.1	9.1	13.1	18.2	16.1	17.0	15.1
10	1.1	5.4	10.9	15.3	17.8	16.6	17.3	14.7
$\mu \pm \sigma$	1.8 ± 0.5	5.7 ± 1.1	10.6 ± 1.1	14.5 ± 1.4	16.4 ± 1.4	16.2 ± 0.9	16.0 ± 1.9	15.2 ± 1.3
P1	3.6	7.4	12.8	14.5	15.9	14.9	15.1	13.5
P2	2.7	7.4	12.0	15.1	15.2	17.7	19.5	15.4
P3	4.8	6.7	11.7	13.9	15.1	16.8	16.4	15.4
P4	2.2	6.5	10.8	13.7	14.4	15.0	16.6	16.0
P5	4.0	6.8	10.7	13.0	14.1	15.1	14.6	14.0
P6	3.3	8.6	13.9	16.0	16.2	14.5	14.8	15.3
P7	3.3	5.8	10.7	13.9	16.3	17.5	14.9	14.3
P8	3.8	6.9	12.0	14.2	14.9	17.1	16.5	16.5
P9	5.6	9.3	11.8	15.7	17.6	16.5	15.1	15.8
P10	2.7	7.2	12.4	16.1	15.4	17.1	17.2	14.1
$\mu \pm \sigma$	3.6 ± 1.0	7.3 ± 1.0	11.9 ± 1.0	14.6 ± 1.1	15.5 ± 1.0	16.2 ± 1.2	16.1 ± 1.5	15.0 ± 1.0
$\Delta\mu$	1.8	1.6	1.3	0.1	−0.9	0.0	0.1	−0.2
P	0.003[a,**]	0.003[a,**]	0.055[a]	0.988[a]	0.400[a]	0.758[a]	0.980	0.806

[a] Normal distribution.
[**] Significant difference for 99% confidence interval.

4. Conclusions

In this study, contact ultrasound transducers were used to measure the speed of sound in three different pharmaceutical tabletting materials at three different frequencies. All the measurements were made without any additional acoustic couplant. The SOS values were found to be independent of the applied frequency. Moreover, it was observed that an increase in frequency did not increase the high frequency content in the transmitted frequency spectrum. Thus, in couplant-free ultrasound measurements, high frequencies are attenuated.

Next SOS measurements were made by using instrumented tablet press punches. Results were the same as those obtained with contact transducers. Thus, the instrumented tablet press punches can be used for ultrasound measurements, despite the fact that their centre frequency shifted from 10 to 4.5 MHz. One should note that the force between the punch and the surface of tablet was higher than in contact transducer measurements, so SOS values are more coherent in punch measurements than in contact transducer measurements. This observation verifies that ultrasound measurements can be made without additional couplants when the force between transducer and tablet is sufficient. Next, the SOS values from defective tablets were measured by using "instrumented" punches, and comparing SOS values between the intact and defective tablets show that they are different. However, based on the statistical analyses, the SOS values cannot reliably discriminate defective from intact tablets.

To detect defects in tablets, the frequency spectrum of the transmitted ultrasound signals was measured and analyzed. The US attenuation was calculated as a function of frequency for each tablet and used to discriminate them as either intact or defected. Ultrasound attenuation was found to be a very selective and sensitive analysis method that discriminated between intact and defective tablets. With LM, only two samples were discriminated incorrect, but a possible reason for this may be related to the poor signal-to-noise ratio for this sample. In addition, the ultrasound attenuation was found to have different behaviors that were apparently dependent on the physical properties of the material being measured. In DCP, for example, attenuation was nearly constant and had the lowest value (ca. 4 dB/mm). Attenuation values for MCC and LM increase as a function of frequency, but this increase was much higher in LM than MCC samples. Moreover, LM had higher attenuation values than MCC. This indicates that different materials may be identified by using measured ultrasound attenuation. However, this possibility warrants further investigation.

The ultrasound measuring system introduced in this study has great potential as a monitoring tool during tablet compaction. As transducers are located inside the press punches, and measurements are made within a few microseconds, this system can be used in the real time defect detection of pharmaceutical tablets. In addition, the signal analysis needed for discrimination is based on relatively simple Fast Fourier Transform calculations. These calculations can be made in real time, using real time data acquisition hardware. Thus, this application fulfills all the required characteristics as a PAT device for in-line ultrasound detection during the compaction of pharmaceutical tablets.

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