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Non-destructive acoustic defect detection in drug tablets

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A B S T R A C T

For physical defect detection in drug tablets, a non-destructive and non-contact technique based on air coupled excitation and interferometric detection is presented. Physical properties and mechanical integrity of drug tablets can often affect their therapeutic and structural functions. The monitoring for defects and the characterization of tablet mechanical properties therefore have been of practical interest for solid oral dosage forms. The presented monitoring approach is based on the analysis of the transient vibrational responses of an acoustically excited tablet in both in temporal and spectral domains. The pulsed acoustic field exciting the tablet is generated by an air-coupled transducer. Using a laser vibrometer, the out-of-plane vibrational transient response of the tablet is detected and acquired in a non-contact manner. The physical state of the tablet is evaluated based on the spectral properties of these transient responses. In the current study, the effectiveness of three types of simple similarity measures is evaluated for their potential uses as defect detection norms, and for their potential use in quantifying the extent of tablet defect is discussed. It is found that these quantities can not only be used for identification of defective tablets, but could also provide a measure for the extent of the damage.

1. Introduction

The physical (mechanical) properties and mechanical integrity of a drug tablet may affect its therapeutic and structural functions. The mechanical state of the tablet could be altered by imperfections and irregularities in the core and the coat of the tablet, as well as its chemical and biological properties. Surface defects can directly affect the effectiveness of tablet coatings that serve many purposes, such as controlling release of active ingredients in the body to avoid irritation of esophagus and stomach, enhancing the drug stability and extending shelf life by protecting the ingredients from degradation. Such imperfections and irregularities are in general related to (i) excipient (and/or active ingredient) and coating starting materials, (ii) tabletting (manufacturing) processes (e.g., compaction, pressing and coating), and (iii) tablet handling systems for transport and processing. Consequently, defects may also be considered as early indications of manufacturing process faults in the starting materials and/or the manufacturing steps. As a result, monitoring tablets for defects is essential to the pharmaceutical industry for quality assurance purposes and federal agencies for regulatory requirements. In the pharmaceutical industry, the development and adoption of non-destructive and non-contact defect detection techniques of tablets may help to achieve improved productivity because, through effective monitoring, production interruptions and material losses can be minimized in a manufacturing process flow. The U.S. Food and Drug Administration (FDA) has recently expressed great interest in manufacturing quality and initiated a program entitled Process Analytical Technology (PAT) to address various aspects of manufacturing problems in the pharmaceutical industry and to forward the idea of improving the quality of the pharmaceutical products by a deeper understanding of the processes involved in design and manufacturing. According to the FDA, the PAT initiative is described as *a system for designing, analyzing, and controlling manufacturing through timely measurements* (*i.e., during processing*) *of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality* (Hussain et al., 2004). One major objective of the PAT framework is to be instrumental in the design and development of process and endpoint monitoring and control tools. Such procedures would be consistent with the basic tenet of 'quality-by-design' and could reduce risks of quality and regulatory concerns while improving efficiency (Cetinkaya et al., 2006).

Although there have been considerable research activities for the determination of mechanical properties of tablets (Fell and Newton, 1970; Rigdway and Aulton, 1970; Stanley et al., 1981; Ketolainen et al., 1995; Kirsch and Drennen, 1999; Roberts and Rowe, 1999; Donoso et al., 2003; Podczeck et al., 2006; Akseli and Cetinkaya, 2008), relatively limited attention has been paid

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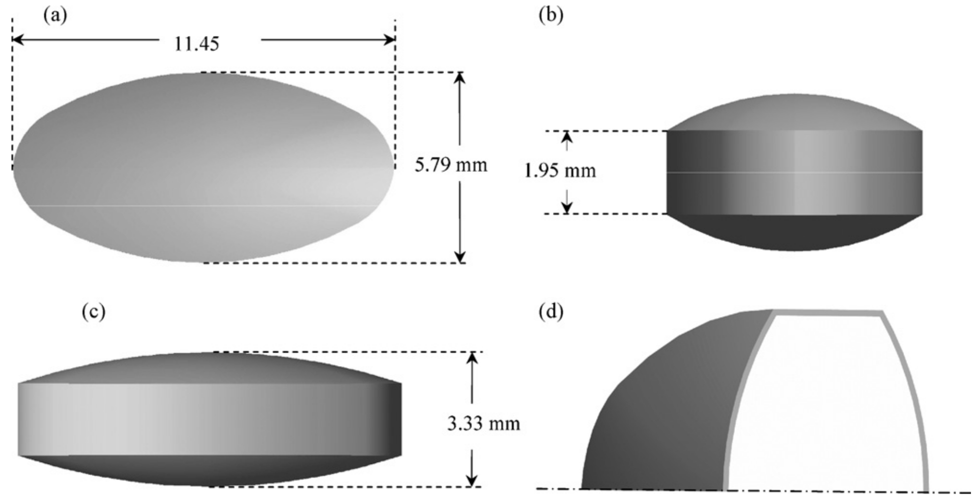

Fig. 1. The dimensions of a coated tablet with its top (a), front (b) and side (c) views. The coating thickness is 102.3 μm (d).

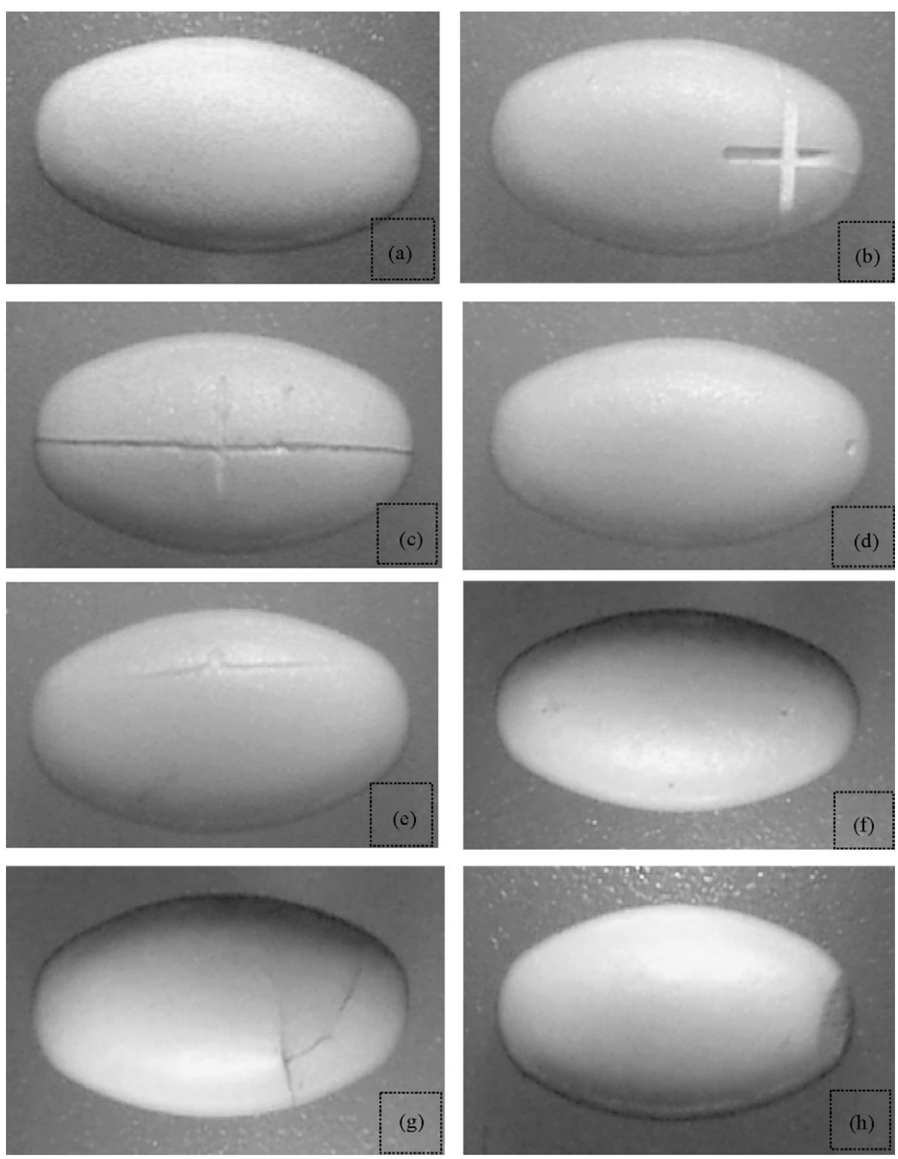

Fig. 2. Microscope images of eight different groups of tablets at 10× with their critical dimensions: nominal (non-defective) (a), cross (trench width: 396 μm, depth: 396 μm) (b), cross-crack (trench width: 127 μm, depth: 203 μm) (c), hole (trench width: 396 μm, depth: 198 μm) (d), hole-crack (trench width: 396 μm, depth: 198 μm) (e), hole (trench width: 58 μm, depth: 98 μm) (f), hair line crack (defect extent: 60–100 μm) (g), chipping (defect extent > 400 μm) (h).

to address the quality issues associated with structural integrity (e.g., surface defects, core cracks, and delamination) and geometric attributes (e.g., size and shape). The utilization of a contact approach based on acoustic-resonance spectrometry (ARS) to rapidly differentiate tablets of similar size and shape has been investigated (Medendorp and Lodder, 2006). It was argued that ARS can potentially serve as an online pharmaceutical sensor to classify tablets based on size and shape. An automated machine vision system based on a nonparametric clustering-based segmentation method has been described for detecting irregularities and deviations in size and shape, and surface defects of color tablets (Derganc et al., 2003). However, this image processing method is limited to spatial color non-uniformity and could fail to detect any alterations causing no color variations such as mechanical properties of core–coat interfaces and tablet cores due to the internal defects and delamination. In an effort to detect structural defects in tablets in a non-contact/non-destructive manner, a novel method has been introduced (Varghese et al., 2006; Varghese and Cetinkaya, 2007) using acoustic waves in air to excite and interferometrically detect the vibrational modes of the tablets by utilizing (i) a plate thermoelastically vibrated by a pulsed-laser, and (ii) a shock-wave front generated from the expansion of a pulsed laser-induced plasma core. It was concluded that these acoustic techniques can potentially be employed to differentiate defective tablets from the non-defective ones.

In the reported study, a non-destructive air-coupled acoustic technique is presented for defect detection in drug tablets. The resonance frequencies of a tablet are extracted from the acquired transient displacement waveforms using the Fast Fourier Transform (FFT) routine. Since the resonance frequencies of the tablet are functions of the mechanical properties and geometric attributes (shape, dimensions and defects), as well as residual stress state of the tablet structure, the analysis of multi-mode excitation data can be utilized in testing for its mechanical properties and geometric attributes. In order to form a baseline, well-defined defects on a set of tablets are created artificially to mimic some damage and imperfection types that could occur in tablet manufacturing and handling. Some damage types and damage extents inflicted in the test tablets are extreme. In the proposed acoustic technique, the transient vibrational response (out-of-plane surface displacement) of a tablet excited by a pulsed acoustic field is acquired. The acoustic field is generated by an air-coupled transducer driven by a pulser/receiver unit. The transient responses of the tablets are then analyzed numerically both in temporal and

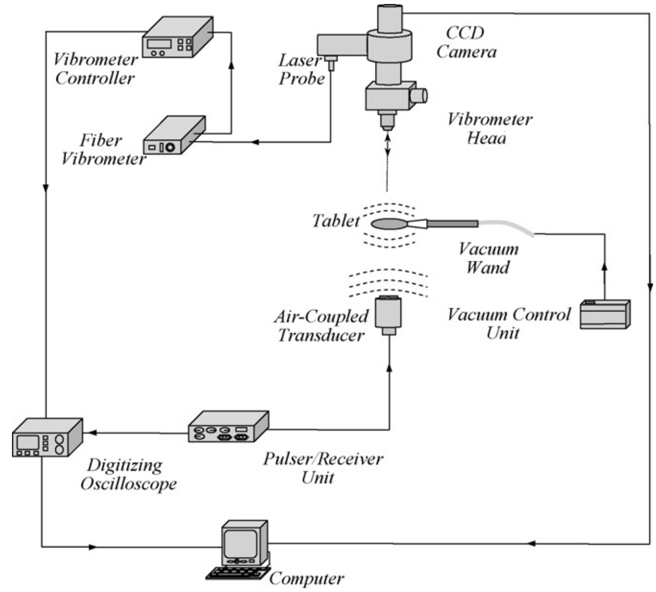

Fig. 4. The instrumentation diagram of the acoustic excitation and interferometric detection set-up and the tablet mounting apparatus for acquiring transient responses of tablets.

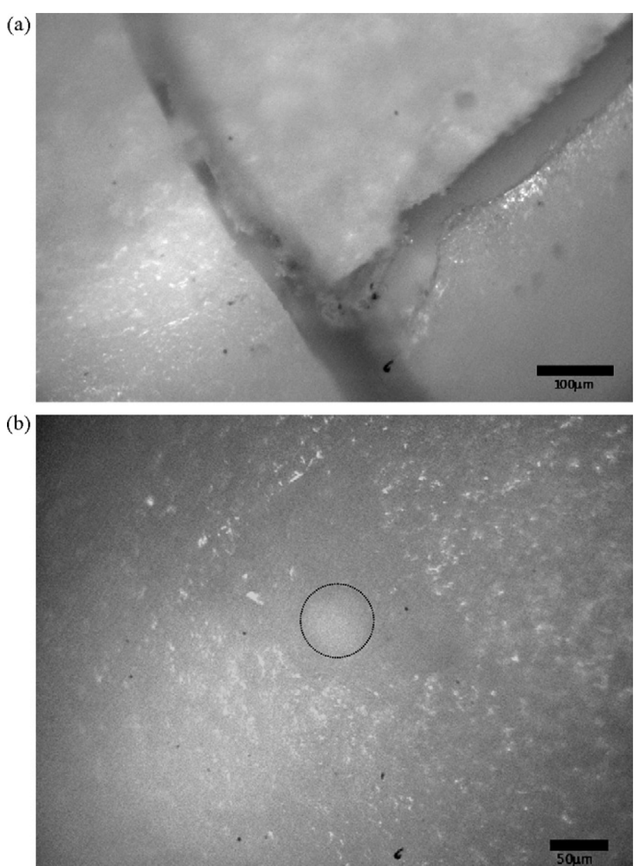

Fig. 3. Microscope images of the hair line crack with a defect extent of 60–100 μm (a) at 50× and hole defect with a hole diameter of 58 μm (b) at 100×. Dashed circle marks the boundaries of the hole.

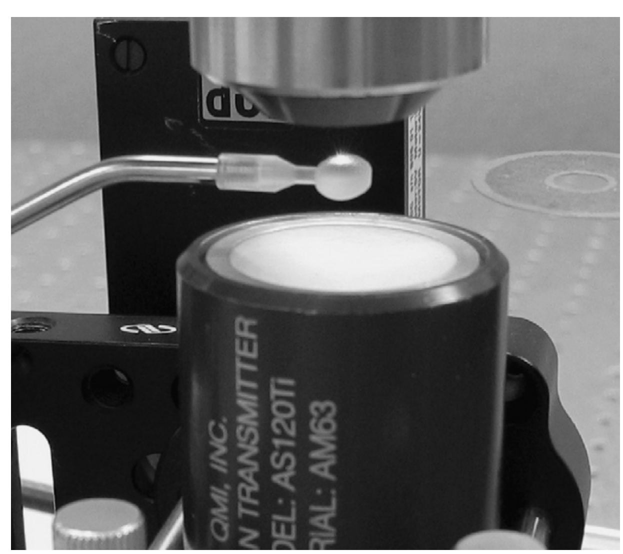

Fig. 5. A close-up image of the experimental set-up with a 120 kHz transducer and a vacuum wand sucking the tablet in place. The vibrometer laser beam is visible on top of the tablet.

spectral domains with respect to the response of a reference non-defective tablet under the same excitation conditions to determine the values of the proposed defect measures (norms). Three types of potential defect measures (norms) are adopted and their effectiveness and sensitivities in detecting these pre-determined defects are evaluated: (i) the frequency domain quadratic norm, (ii) the coefficient at zeroth time shift, and (iii) the similarity norm. The frequency domain quadratic norm is based on frequency domain transient responses of the tablets while the coefficient at zeroth time shift and the similarity norm are both based on the analysis of the time domain transient responses. It is observed that the measures calculated from the transient responses of defective tablets are substantially different from that of non-defective tablets which enable the proposed technique to potentially differentiate defective tablets from the nominal tablets and provide insight on the type and extent of tablet damage. In the reported experiments, a non-defective tablet is defined as a tablet that contains no known material property deviations and geometric irregularities.

2. Materials and methods

2.1. Materials

In general, the structural defects and imperfections in tablets can be linked to starting materials deficiencies and manufacturing processing faults (Cetinkaya et al., 2006). Sample tablets (referred to as P-tablets) with the average mass of 200 mg and with the characteristic dimensions of 5.79 mm width, 11.45 mm length, 3.33 mm thickness and a coating thickness of 102.3 μm are employed in the experiments (Fig. 1). In an effort to mimic some surface defects, seven types of defects on the defect-free tablets (Fig. 2a) are created artificially on the sets of four tablets: the defect types include a cross (a cross shape occurring on one side of the tablet surface) (Fig. 2b), a cross-crack (a cross shape combined with a surface crack that damages the tablet coating) (Fig. 2c), a hole (a shallow circular hole with a diameter of 396 μm primarily affecting the coating layer) (Fig. 2d), a hole-crack (a shallow circular hole combined with a surface crack) (Fig. 2e), a second type of hole (a shallow circular hole with a diameter of 58 μm primarily affecting the coating layer) (Fig. 2f), a hair line crack (a hair line surface crack that damages the tablet coating) (Fig. 2g), chipping defect (Fig. 2h). All defects except hair line crack and chipping defect are created by computer numerical control (CNC) machining. Hair line surface cracks (Fig. 3a) are created by tensile strength tester (EJA Vantage-1 tensile tester) and chipping defects are created using extra fine sandpaper with an average particle diameter of 35 μm. The surface cracks in the tablets of the cross-crack and hole-crack defect types are formed naturally in a few days following the CNC machining due to the compaction-related residual stresses present in the tablet core and coating layer. For the cross type defect, the diameter of the machine tool tip (the width of the resulting trench) was 396 μm and the drill depth was 396 μm (Fig. 2b). The dimensions for the cross-crack defect are 127 and 203 μm (Fig. 2c); for the hole type defect are 396 and 198 μm (Fig. 2d); for the hole-crack defect are 396 and 198 μm (Fig. 2e); and for the second hole type defect are 58 and 98 μm (Fig. 3b), respectively.

2.2. Experimental set-up and procedure for acquiring transient responses of tablets

The experimental set-up utilized for the current study consists of three major components: (i) air-coupled acoustic excitation source (a pulser/receiver unit and an air-coupled transducer),

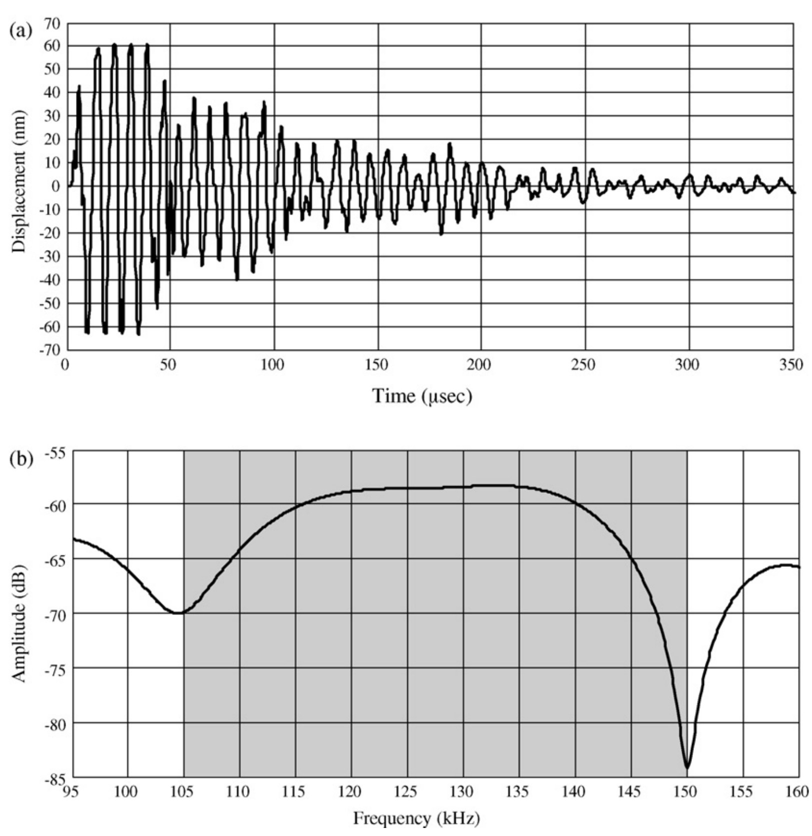

Fig. 6. Transient displacement (a) and frequency response (b) of a point on the surface of the 120 kHz transducer under a square pulse excitation with a pulse width of 8.33 μs, an amplitude of 100 V, and a bandwidth of 105–150 kHz (shaded area).

(ii) non-contact interferometric out-of-plane displacement measurement system (a vibrometer), and (iii) tablet transport and handling system. The set-up incorporates a square pulser/receiver (Panametrics 5077PR), an air-coupled transducer (QMI AS120Ti), a vibrometer controller (Polytec OFV3001), a laser Doppler vibrometer (Polytec OFV511), a digitizing oscilloscope (Tektronix TDS3052), and a vacuum handling apparatus consisting of a vacuum wand and a vacuum pump with a suction pressure of −30 kPa (FVW-110 Duovac). The experimental set-up utilized for non-contact defect detection in tablets and tablet mounting apparatus with a vacuum wand is depicted in Figs. 4 and 5. The pulser/receiver unit employed in this study delivers a square electrical pulse with amplitude of up to 400 V to the air-coupled transducer and provides a synchronizing trigger to the digital oscilloscope. In the current study, the pulser/receiver voltage was set to 100 V. In the test set-up, the air-coupled transducer (a central frequency of 120 kHz) is placed under the sample P-tablet at the focal distance of the transducer (specified as 2.35 mm) (Fig. 5). The tablet is placed such a way that the central point of its bottom coincides with the focal point of the transducer for maximum tablet-acoustic field interactions and, therefore, maximum tablet vibrations. The tablet is excited by an acoustic field generated by the air-coupled transducer in a frequency range sufficiently high to excite several vibrational modes (harmonics) of the tablet. The bandwidth of the air-coupled transducer employed for the set of experiments reported in this study is measured as 105–150 kHz (Fig. 6). In data acquisition, the laser vibrometer embedded into the optical microscope is directly focused at a point on the tablet surface through the objective lens of the microscope. The tablet is placed under the objective at a distance of approximately 6.5 mm and its transient responses

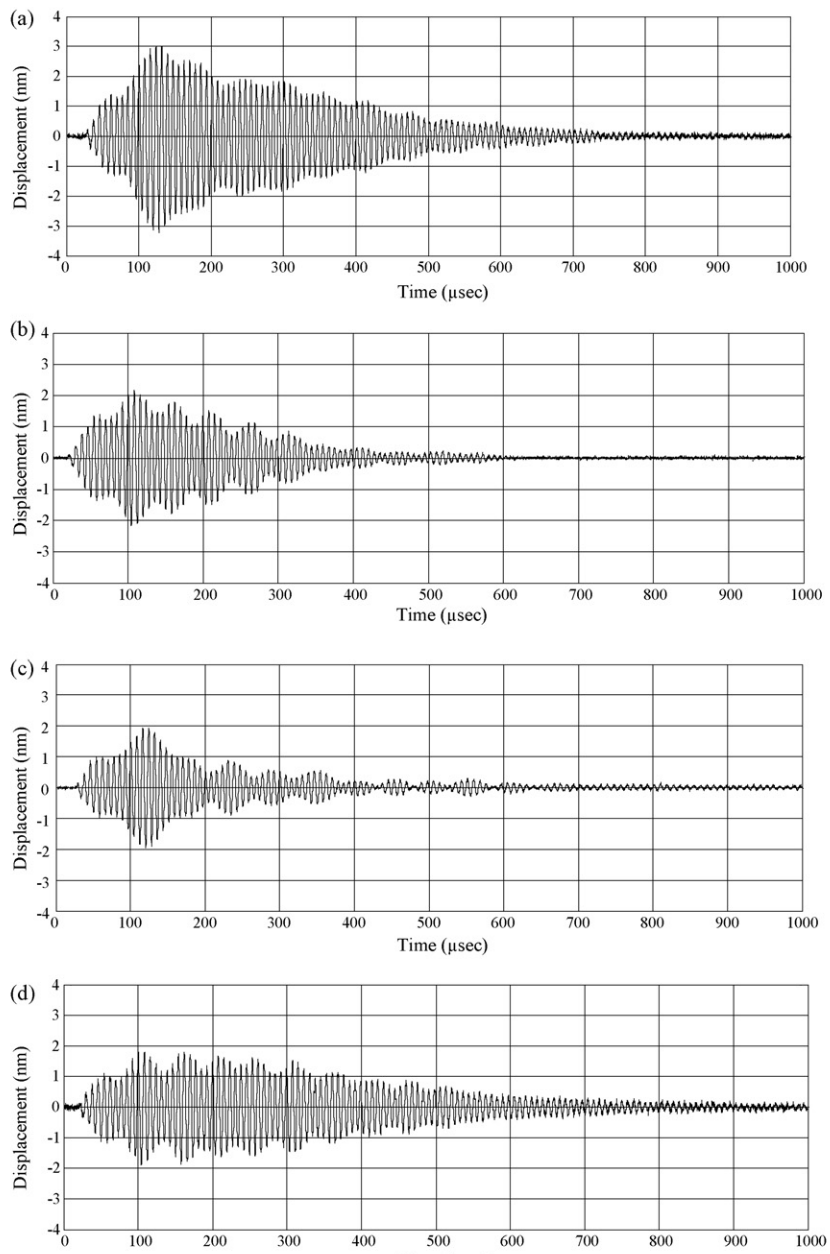

Fig. 7. Waveforms for the tablets with no defect (a), cross (b), cross-crack (c), hole (396 μm) (d), hole-crack (e), hole (58 μm) (f), hair line crack (g), and chipping (h). Each waveform includes the waveform of one tablet from each group.

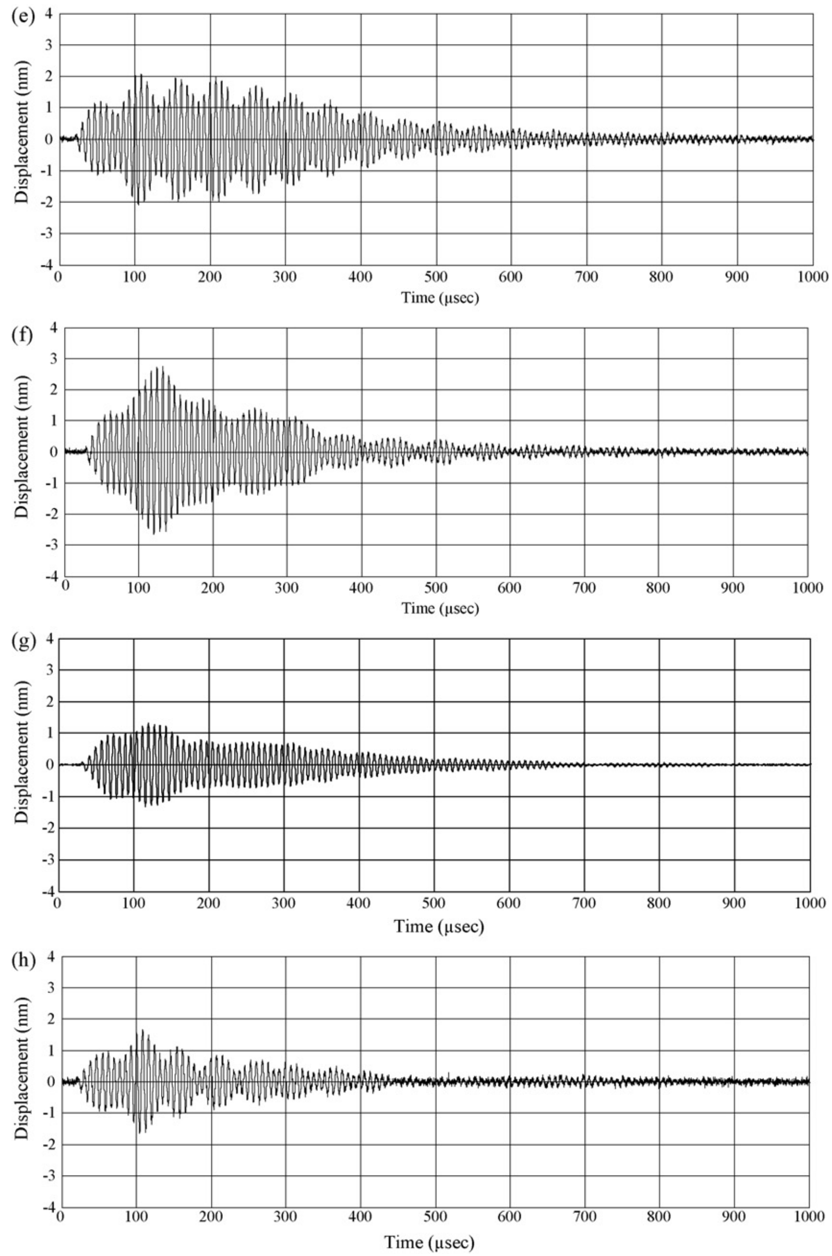

Fig. 7. (*Continued*).

(out-of-plane displacements) are acquired at a set of measurement points by the vibrometer in non-contact manner over a bandwidth of 50 kHz to 30 MHz, including a displacement decoder with (specified) sub-nanometer resolution in the range of ±75 nm. The diameter of the probe laser beam is specified down to the submicron range. The tablet transient responses (Fig. 7) are digitized through the oscilloscope and uploaded to a computer for signal processing.

2.3. Signal processing of tablet transient responses

The transient vibration waveforms obtained from experiments are numerically processed both in temporal and spectral domains to evaluate the values of the similarity measures (norms) that can be representative of the types and extents of defects in a tablet. This procedure comprises of a number of stages and the flow chart of the process is depicted in Fig. 8. First, the acquired waveforms are pre-processed for arrival times and other biases. Following the signal pre-conditioning, amplitude normalization is performed in time domain to set the maximum amplitude of each waveform to unity. This step is necessary to ensure that different waveforms are compared consistently to extract meaningful features. In the second stage, the normalized tablet transient response is transformed to the spectral domain using the Fast Fourier Transform (FFT) routine. The three defect measures representing deviations from the nominal response are evaluated for all the tablets tested. In addition to frequency norms (Fig. 8), other features that can be used for classification in the frequency domain include (i) relative amplitudes of the natural frequency spikes in the frequency response, (ii) modal damping coefficients of the natural frequencies and (iii) phase information. Finally, the results of all three evaluated features are compiled, a confidence analysis is performed at 95% ($\alpha = 0.05$) confidence level and it is determined whether the tablet is defective or defect-free (non-defective).

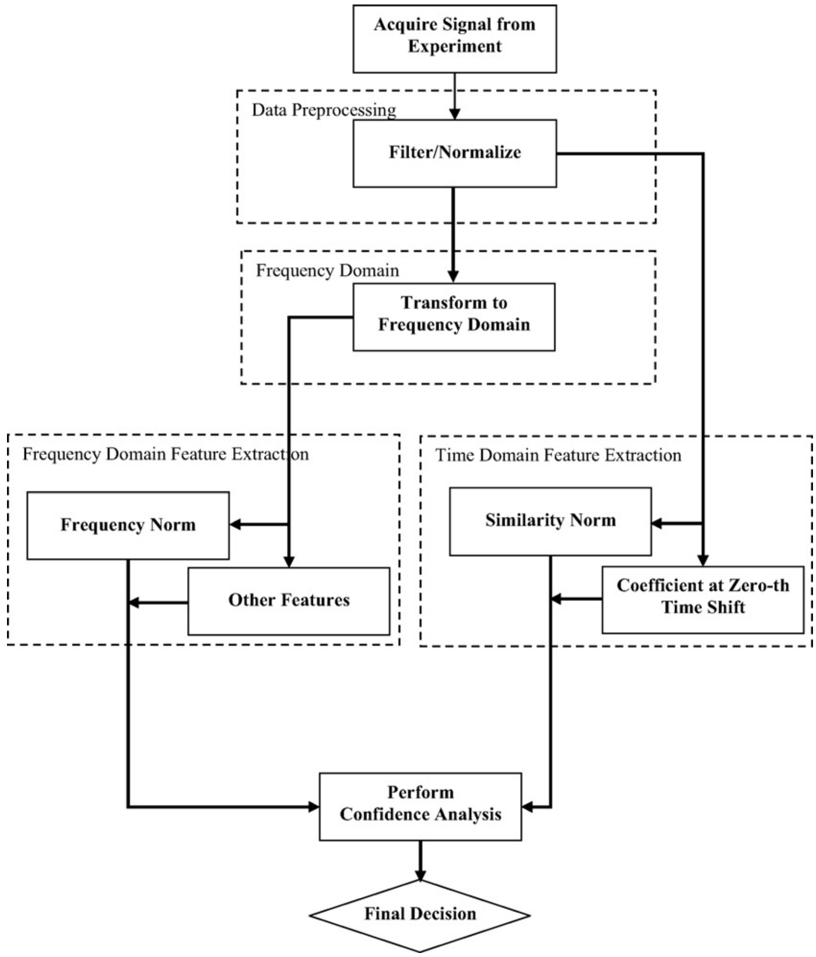

Fig. 8. Flow chart of the signal processing steps for the defect detection scheme.

2.3.1. Frequency domain quadratic norm

Defects and irregularities could alter the mechanical properties and geometric attributes of a tablet. The changes in the mechanical properties and geometry as well as internal (residual) stress state of the tablet affect the frequency response of the tablet. Therefore, it is expected that the frequency response of a defective tablet is different from that of a nominal tablet and can potentially indicate a defect state of the tablet. If sufficiently significant, this difference can be quantified using the frequency domain quadratic norm, defined as follows:

$$\alpha(f_2 - f_1) = \frac{\int_{f_1}^{f_2} (s_2(f) - s_1(f))^2 \, df}{\int_{f_1}^{f_2} (s_1(f))^2 \, df} \quad (1)$$

where s_1 is the normalized frequency (f) response of the reference nominal tablet and s_2 is the normalized frequency response of the tablet being examined under the same excitation conditions, both s_1 and s_2 are in dB scale and the norm bandwidth is from f_1 to f_2. After obtaining the frequency domain responses by the FFT routine to the transient response of a tablet, a dimensionless frequency domain quadratic norm is calculated.

2.3.2. Cross-correlation-based defect measure

Cross-correlation is a standard method for estimating the degree to which two data series are correlated and, consequently, similar. In analyzing transient responses, cross-correlation of two responses can be an effective computational measure to determine the degree of similarity between the two responses. The cross-correlation of two vectors, x and y, is defined as

$$C_y(m) = \sum_{i=0}^{n-m-1} x_{i+m} y_i \quad (2)$$

where n is the length of each vector and m is the (time) shift between the two vectors. In the current study, the transient responses of the reference (defective-free) tablet and the sample tablet are represented by x and y, respectively. Since, these coefficients represent the degree of similarity between the two vectors, higher values are expected for two non-defective tablets to signify higher similarity whereas a defective tablet correlated to another defective tablet and/or a non-defective tablet should lead to lower values to signify lower similarity. From these correlation coefficients, the two defect measures can be derived: the coefficient at zeroth time shift and the similarity norm.

2.3.2.1. Coefficient at zeroth time shift. This coefficient is the value of $C_{xy}(m)$ at $m = 0$ (Eq. (2)). The higher the value of this coefficient for the responses of the two tablets, the more similar the transient responses are, and, consequently, the more similar the mechanical defect states of the two tablets are. Similarity here indicates less damage and/or very similar damages between the two tablets compared. In general, the degree of similarity between the transient responses of two nominal tablets is expected to be the highest. If the coefficients are normalized, the value of the coefficient at zeroth time shift is expected to be close to unity for the non-defective tablets. In contrast, the degree of similarity between the transient responses of a nominal tablet and a defective one is expected to be comparatively low (less than one). Moreover, the degree of similarity is expected to diminish as the severity of defect increases.

2.3.2.2. Similarity norm. In the reported study, a similarity norm is calculated based on the all cross-correlation coefficients calculated for two tablets using a dimensionless similarity norm is defined as follows:

$$\beta_{xy} = \frac{C_{xy}^{\mathrm{T}} C_{xy}}{C_{xx}^{\mathrm{T}} C_{xx}} \qquad (3)$$

where C_{xy} is the cross-correlation (between the series x and y) vector, the superscript T denotes the transpose of a vector, and the vector C_{xx} is the auto-correlation of the vector x. The largest possible value of this similarity norm is unity which occurs when two

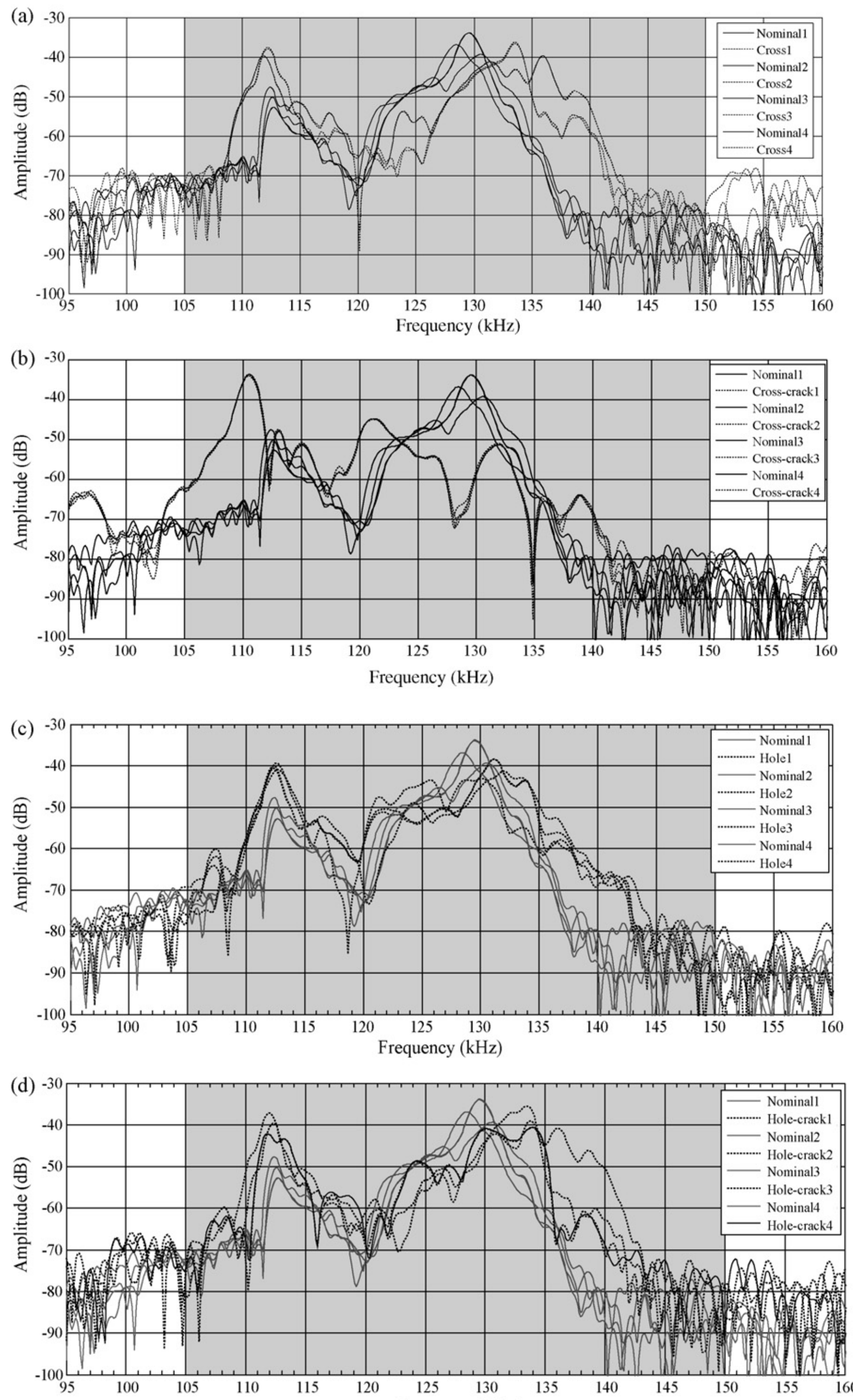

Fig. 9. Comparisons of the frequency domain responses of the tablets from each defective group (dashed lines) with those of the non-defective tablets (solid lines): cross (a), cross-crack (b), hole (396 μm) (c), hole-crack (d), hole (58 μm) (e), hair line crack (f), and chipping (g). Shaded area indicates the bandwidth of the air-coupled transducer.

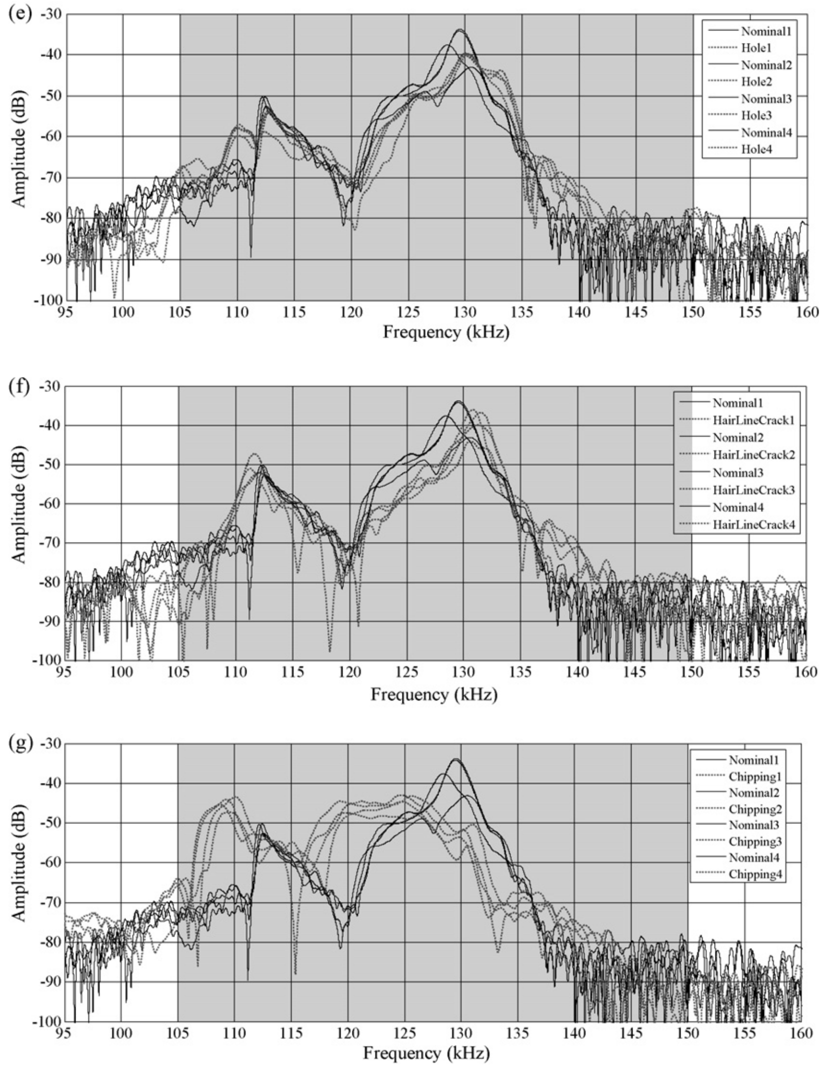

Fig. 9. (*Continued*).

identical vectors are compared because, in this case, C_{xy} becomes identical to C_{xx}. Any deviation in the vector results in a value lower than unity. This norm is basically the summation of the square of all cross-correlation coefficients which, in supplement to the coefficient at zeroth time shift, measures the comprehensive degree of similarity.

3. Results and discussion

The frequency responses of the set of four tablets from each defective group and the nominal (non-defective) group indicate that the responses of the non-defective tablets under the same excitation conditions are rather consistent (Fig. 9). Multiple measurements of each tablet were conducted to establish the reliability and repeatability of the experimental set-up system. The overall trend for each group (defective and nominal) remains consistent as evidenced by the frequency response plots depicted in Fig. 9. However, the frequency responses clearly exhibit discernible trends between the nominal group (solid lines) and each of defective groups (dashed lines).

The evaluated frequency domain quadratic norms of the non-defective tablets are clearly very low or close to zero (Fig. 10a). This result was reasonable as the signal of a non-defective tablet is expected to be very similar to that of another non-defective tablet. In comparison, the frequency domain quadratic norms corresponding to each of the defective groups are much higher which can differentiate the defective groups. It is also observed that the norms corresponding to the chipping and cross-crack defect types are significantly high indicating relatively large damage. The size and extent of these defects can be verified by visual inspection of the tablets tested (Fig. 2). Fig. 10b depicts the average and standard deviations of the frequency domain quadratic norms for each group of tablets.

A comparison of the calculated values of cross-correlation coefficient at zeroth time shift for each tablet group reveals that the values corresponding to the non-defective group are close to unity (signifying high similarity with other non-defective tablets) whereas the values corresponding to each defective group deviate from unity (signifying low similarity with a non-defective tablet) and are sufficiently low to be distinguished (Fig. 11a and b). In addition, the coefficients corresponding to the chipping and cross-crack defect types are very low compared to the coefficients for the other defect types. These results indicate extensive damage and/or defect.

Similar to the measure based on the coefficient at zeroth time shift, the similarity norm represents the likeness of the transient

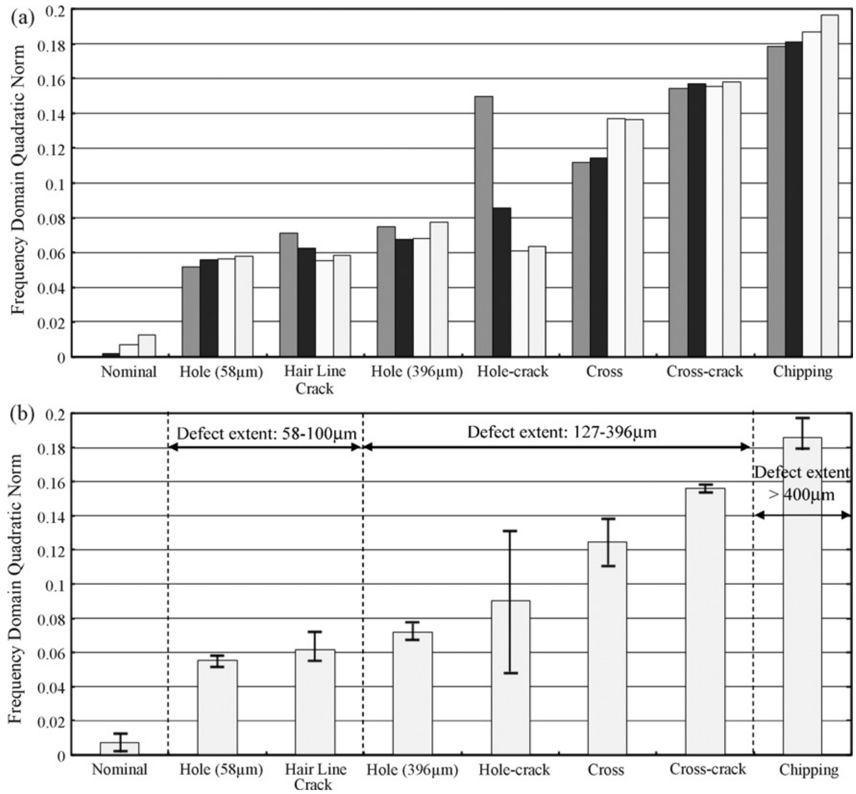

Fig. 10. Comparison of the values of the frequency domain quadratic norms for the four tablets in each group with a non-defective tablet (a), and the averages and standard deviations of the values of these norms (b).

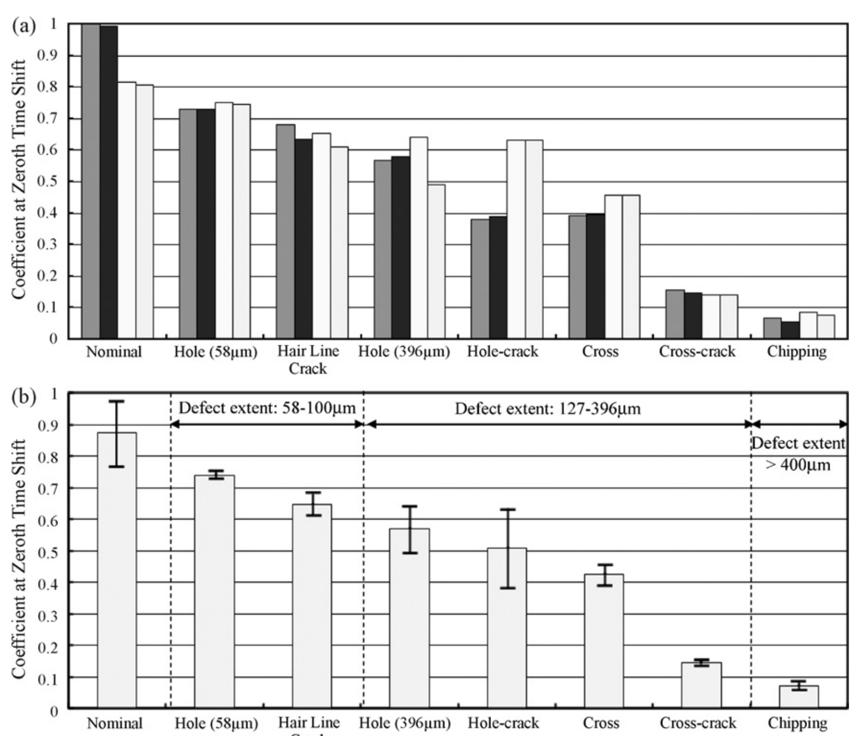

Fig. 11. Comparisons of the values of the coefficient at zeroth time shift of the four tablets in each group with a non-defective tablet (a) and the average and standard deviations of these measures (b).

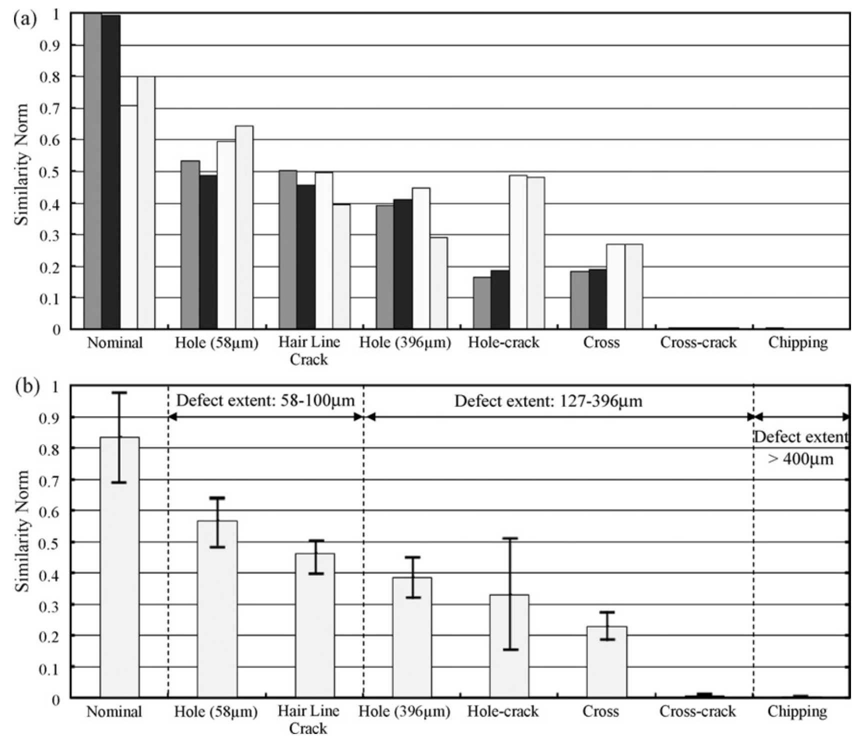

Fig. 12. Comparison of the values of similarity norms of the four tablets in each group with a non-defective tablet (a) and the average and standard deviations of these measures (b).

responses of a sample tablet to that of a reference non-defective tablet. Expectedly, the norms of non-defective tablets are close to unity whereas the values of the norms corresponding to the defective tablet groups are sufficiently low indicating relatively low degree of similarity (Fig. 12a and b). The values of similarity norm for defective and non-defective tablet groups appear to provide a better indicator for the extent of damage than the coefficient at zeroth time shift does as a comparison of Figs. 11b and 12b reveals. For example, the norms corresponding to the chipping and cross-crack defect types are virtually zero, whereas the values of the coefficient at zeroth time shift are approximately 7% and 14%, respectively.

4. Conclusions and remarks

A non-destructive and non-contact air-coupled acoustic technique is introduced and utilized for defect detection in drug tablets. Three measures for defect detection and identification are considered and evaluated for their effectiveness on seven defective tablet groups as well as a non-defective tablet group: (i) the frequency domain quadratic norm, (ii) the coefficient at zeroth time shift and (iii) the similarity norm. The frequency domain quadratic norm represents the measure of the difference between the frequency responses of a sample tablet with respect to a reference non-defective tablet. Therefore, the frequency domain norm of a non-defective sample tablet is expected to be small. This quantity should be sufficiently higher for defective sample tablets. On the other hand, both the coefficient at zeroth time shift and the similarity norm are evaluated by utilizing cross-correlation signal processing technique and are indicative of the likeness of two transient responses. Accordingly, each of these measures evaluated for a non-defective sample tablet is expected to be large to indicate high similarity and should be close to unity with non-dimensionalization. The value of this measure should be sufficiently low for defective tablets due to the reduced similarity. The results of the experiments for the seven defect types for the tablets sets are reported in this study and the following conclusions can be made:

(a) from the analysis of the values of the three measures, the defective tablets appear to be clearly distinguishable from the non-defective ones,
(b) in the case of chipping and cross-crack defect types, the value of each measure is much different from that of the nominal type. This clearly indicates substantial damage and it is consistent with what one would expect because the damage is in fact large as that can be verified by visual inspection,
(c) the evaluated value of each measure for the hair line crack and hole type defects are sufficiently away from that for non-defective tablets. Thus, these measures can be utilized to detect even minor defects, and
(d) although both the coefficient at zeroth time shift and the similarity norms are evaluated from the same set of cross-correlation coefficients, similarity norm appears to provide better indication of damage than the coefficient at zeroth time shift does. In the case of chipping and cross-crack defect, for example, the similarity norms nearly vanish, whereas the values of the coefficient at zeroth time shift are approximately 7% and 14%, respectively.

The frequency spectra for different defect types indicate that the experimental set-up and the data (transient vibration responses) acquisition in the experiments are repeatable and consistent. In the signal processing of these temporal responses, it is established that the transient responses of non-defective tablets can be clearly distinguishable from those of the defective tablets by estimating and comparing various measures. Although only three basic measures are evaluated and discussed in the current work, several other more sophisticated norms such as empirical mode decomposition, *k*-means clustering, principal component analysis, independent component analysis, singular spectrum analysis and wavelet-based techniques (e.g., wavelet grey moment) can be adopted and integrated to increase confidence in making final decisions of the mechanical state of a tablet. Moreover, the results of different measures can be compared and the more effective ones can be chosen for specific defect type detection and monitoring requirements.

In practice, the some surface defects can be considerably smaller that the defects used in the current study. The signal processing techniques employed in this study are relatively basic to demonstrate the potential of the presented defect detection approach. For smaller defects, significantly stronger (high amplitude) air-coupled excitation with broader frequency bands and more sophisticated knowledge-based signal processing techniques than the ones employed in this proof-of-concept investigation will be required.

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