Wireless transmission of ultrasonic waveforms for monitoring drug tablet properties and defects

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Abstract

The geometric and mechanical properties of pharmaceutical materials are crucial to their structural, functional and therapeutic effectiveness. The implementation of automated and convenient quality monitoring procedures is an attempt to balance control of quality against the level of testing; within acceptable levels of probability and costs. The capability of rapid/extentive inspections with minimal time and manufacturing interruption make non-contact quality monitoring systems a desirable approach to optimize this balance. In the current study, a wireless transceiver proof of concept system developed for the real-time quality monitoring of tablets during compaction is presented and demonstrated. The effectiveness of ultrasonic wave transmission through the punch–tablet interface is the boundary condition that dictates the viability of the acoustic in-die compaction monitoring approach. These measurements in the current experimental set-up can be used in determining various mechanical and geometric properties of a compact, such as the tablet thickness, mass density, elasticity and/or integrity of the tablet core, and bonding quality between layers depending on the given parameters, as it is compacted. In the current study, it is demonstrated that the reflection of an ultrasonic pulse generated by a transducer embedded in an upper punch from the lower punch–tablet interface can be acquired by the same transducer in the upper punch and the analog waveform can be transmitted to a computer by means of wireless communications for further signal processing and property extraction. The evolution of apparent Young’s moduli of a powder bed during a full-compaction cycle is derived from the ultrasonic time of flight of an acoustic waveform acquired during compaction-in-die.

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1. Introduction

The drug tablet and its oral administration remains the most commonly utilized mode of drug delivery in medicine today. In drug delivery devices, such as tablets, maintaining a desired systemic drug concentration profile within the circulatory system is a key performance metric. It is well known that the mechanical properties, such as Young’s modulus and porosity, play important roles in achieving and detecting these desired performances in structural and bioavailability (Augsburger and Hoag, 2008).

When considering the millisecond (ms) time-scale dwell time of a typical commercial compaction press (from ~5 ms to 80+ ms) (Levin, 2002) and the micro-seconds of pulse duration and time-of-flight (ToF) of an acoustics pulse in typical tablets, the finding reported in (Akseli et al., 2008) and later (Leskinen et al., 2010) indicates that the ultrasonic approach has potential to be employed for real-time in-die online monitoring of the geometric and mechanical properties of drug tablets. Dwell-time is a key parameter defining the end-mechanical properties of the compacted tablet, such as hardness and porosity. For pharmaceutical applications, a wide-spectrum of techniques for investigating tablet and tabletting powder properties with ultrasonic methods are used: the effects of porosity and particle size distribution of compacted tablets on their acoustic properties (Hakulinen et al., 2008), acoustic emission during compaction (Serris et al., 2002), the potential in identifying counterfeit tablets (Medendorp and Lodder, 2006), elasticity, integrity and defect states of tablets (Akseli et al., 2008b, 2009; Ketolainen et al., 1995; Varghese and Cetinkaya, 2007), and mechanical characterization of multi-layer tablets (Akseli et al., 2010) have been reported.

The objective of the current study is to demonstrate the feasibility and effectiveness of a proof of concept wireless in-die real-time online tablet quality monitoring system for tablets by integrating the traditional die-punch set with an ultrasonic pulse-echo measurement system. The critical element of such a monitoring system is its ability to capture reflection waveforms from
interfaces as pulses propagate from the embedded transducer into the die-punch materials and components of the tablet, and transmit the analog waveform to a computer via a wireless telecommunication system. From the frequency-dependent attenuation coefficient of a transmitted waveform, grain size distribution (Smith et al., 2011) can also be approximated if a transducer with a sufficiently large bandwidth is employed. In the case of quality monitoring of tablets, in addition to detecting the waves reflected from the coat-core interface and to extract the ToF data and amplitude reduction indicators from this acquired waveform, the key challenge is to transmit the waveform obtained in a rapidly moving die-punch component of the compaction press to a computer for further inspection analysis without interfering with the normal operation of the compaction press and support machinery. Also, it is noteworthy that the amplitudes of the acquired waves are extremely low due to the high acoustic impedance mismatches between tablet and die/punch materials, but are capable of being distinguished from the noise level of the signal (Liu et al., 2011).

In the current study, it is demonstrated that the reflection of an ultrasonic pulse generated by a transducer, embedded in the upper punch of a standard type B punch and die tooling set, propagating through the upper punch-tablet interface and reflected from the lower punch-tablet interface can be acquired during compaction. The transmission of analog waveforms to a computer by means of wireless communication system for conversion from an analog to digital signal and then further signal processing is demonstrated. The evolution of apparent Young’s modulus of elasticity of tablet materials during a full-compaction cycle is presented.

The characterization of geometric and mechanical properties of tablets as well as integrity in real-time is of interest to a wide spectrum of stakeholders, from the pharmaceutical manufacturing industry to regulatory agencies, as these parameters are directly related to tablet “hardness”, porosity (solid fraction), and the overall quality of the end-product. In addition to the obvious contribution in pharmaceutical manufacturing, the described real-time in-die approach supports the main objectives of the quality-by-design (QbD) and process analytical technology (PAT) initiatives of the U.S. Food and Drug Administration (FDA).

2. Experimental set-up and materials

2.1. Materials

In the current study, a set of nine sample cylindrical compacts was compacted with an industry standard excipient powder: destabil calcium carbonate 95S ultra 250 (Particle Dynamics, St. Louis, Missouri). Also mixed with the excipient base powder is a die wall lubricant, Magnesium Stearate (Mallinckrodt, St. Louis, Missouri) at 1% concentration by weight. The average particle size of the calcium carbonate (DCC) powder is approximately 95 µm with roughly spherical particles. The compact size is controlled by a measured average pre-compaction powder mass of 600 mg (with a standard deviation of 22 mg) utilizing a digital mass balance (Mettler and Toledo, Inc., Columbus, Ohio), the diameter of the compact remains constant during compaction within the die at 12.68 mm, while the final out-of-die tablet thickness, H, in die powder bed height, h, and expected differentials in the tablet mechanical properties are a function of the compressive force used during compaction. In Table 1 the final tablet masses, dimensions, and mass densities (ρ) are reported; measurements are taken by the digital mass balance for the mass, and digital calipers (Mitutoyo, Model CD-6, Aurora, Illinois) for the dimensions.

2.2. Experimental set-up

The objective of the current work is to demonstrate that ultrasonic waveforms acquired for real-time compaction monitoring can be transmitted to a base station connected to a computer with signal processing software in a non-contact manner. In a typical application, the ultrasonic piezo-electric transducer can sequentially emit an acoustic field by converting an electric signal (square pulse) originating in the pulser/receiver into a strain field (elastic wave), followed by the conversion of the returning strain field (reflected wave) into an electric signal delivered back to the pulser/receiver unit. The pulser/receiver amplifies and transmits the acquired electric field (analog signal) to the digitizing oscilloscope, which then stores the waveform in the computer for further signal processing. Each step in the process is traditionally accomplished with wired connections utilizing standard 50 Ω impedance radio frequency (RF) cables. In the current study the electric signal received from the transducer is transmitted from the pulser/receiver to the digitizing oscilloscope via a wireless transmission method.

The experimental set-up consists of a pulser/receiver unit (5077PR, Panametrics, Waltham, MA), a commercial ultrasonic piezoelectric transducer (V129, Panametrics) with the central frequency of 10 MHz, a digitizing oscilloscope (TDS, 3052, Tektronix) with a frequency band of 500 MHz, a wireless transmission station-receiver station pair with antennas, a tablet compaction apparatus utilized to house the instrumented and customized type B tooling, a hydraulic compaction press (Type C Carver Laboratory Press, Fred S Carver Inc., Wabash, Indiana), a LVDT digital displacement gauge (Fowler Digital Guage, Fred M Fowler Company Inc., Newton Massachusetts) to measure the position of the compacting upper punch, and a personal computer for storing and signal-processing waveforms. Based on the designs described in (Balais, 2005; Proakis, 2002; Lathi, 1983), the circuit block and instrumentation diagrams of the signal acquisition experimental set-up with a wireless electromagnetic waveform transmission system are included in Fig. 1a and b, respectively. The transmission station-receiver station pair and accompanying antennas are specifically designed and developed as a proof-of-concept system. Further development work (especially for size-optimization and autonomous power supply) is required for its integration into a commercial compaction press for practical quality monitoring applications. In the current set-up, the pulser/receiver unit generates and delivers a series of electrical
square pulses with the prescribed values of pulse duration, voltage amplitude and pulse repetition frequency (PRF) into a piezoelectric transducer with matched electrical impedance. As a result, the ultrasonic transducer generates acoustic wave pulses in a bandwidth around its resonance frequency as it is excited by each electrical pulse.

In the reported experiments, the data sampling frequency of the oscilloscope was set to 1 GHz with an oversampling (averaging) of 512 waveforms to take advantage of deconstructive interference of normal noise experienced during testing applications. A wireless waveform transmission system for pulse-echo measurements was developed to obtain the ToF of the longitudinal (pressure)

Fig. 1. Instrumentation diagram of the experimental set-up (a), the block diagram of the transmitter and receiver components (b) and the photographs of the experimental set-up, instrumented upper punch, and Hapster apparatus (c).
pulse transmitted into the closest perpendicular surface of the tablet (upper punch–tablet) and reflected from the interface of the farthest perpendicular tablet surface (lower punch–tablet) back to the originating transducer. Using signal processing techniques, the waveforms acquired by the wireless transmission system and pulser/receiver unit are analyzed to extract temporal and amplitude information and eventually to determine the ToF in the compact.

As previously mentioned, the electrical pulse captured by the pulser/receiver unit (from the transducer) is relayed to the input of a transmitter station. The transmitter station circuit consists of a voltage controlled oscillator (VCO) (POS-200, Mini-Circuits) as a frequency modulator, a frequency multiplier (AMK-2-13, Mini-Circuits) for multiplying the frequency by a factor of 2, an RF power amplifier (BGA, 2002, NXP Semiconductors N.V.), a buffer amplifier (Op-Amp, THS4271, Texas Instruments, Inc.) and two power supply units ((1760 A, BK Precision) and (XANTREX, XT 250-0.25)), voltages range from 4 to 12 V. The buffer and power amplifiers are used to amplify the voltage and power levels, respectively. The current transmitter operates in a wide spectrum bandwidth from a few MHz to 400 MHz. A 35-cm long transmitting dipole antenna with an ideal bandwidth of over 120 MHz is capable of transmitting the ultrasonic waveform to a receiving dipole antenna, with a similar length and bandwidth, connected to the receiving station several meters away (see Fig. 1a and b).

The pulsed electromagnetic wave packet from the transmitting antenna propagates in free space and is recovered by the receiving antenna. The energy of the electromagnetic waves approximately decay by the travel distance cubed, $d^3$, as they propagate through the air. The modulated electrical pulses from the receiving antenna are relayed through an RF power amplifier to increase the power level. A local oscillator (POS-200, Mini-Circuits) is utilized to generate a clocking frequency while a frequency mixer (SBX-3, Mini-Circuits) is used to convert the signal from high frequency to low frequency, and a low pass filter (PLP 10.7, Mini-Circuits) operating from DC to 11 MHz is utilized to filter (analog) the noise floor from the signal, and then the buffer amplifier amplifies the voltage level of the remaining signal, and finally a demodulator (CD74HCT4046AM, Texas Instruments, Inc.) detects/rectifies the original signal. The recovered, amplified, filtered, and demodulated signal from the receiver circuit is then transmitted to the digitizing oscilloscope to be saved as a digitized waveform for further analysis and signal processing to extract the ToF. From the measured ToF other properties can be extracted such as geometric properties (thickness, layer thickness in case of multi-layer tablets), physical properties (e.g. Young’s modulus, Poisson’s ratio, porosity ratio (solid fraction), mass density, and attenuation coefficient) and various indicators for defect state of the compact (attenuation, dispersion, nonlinearity, etc.).

3. Experimental procedures

3.1. Pre-compaction

Prior to the compaction process the punch and die set is cleaned using isopropyl alcohol and a cotton swab. Die lubrication is accomplished through the 1% magnesium stearate mixed in the excipient powder blend. Each compact begins with a controlled amount of powder (600 mg) that is poured vertically from a height of 200 mm into the die cavity employing a clear polymer (nylon) funnel. The height of the powder bed, $h$, is initially 9 mm, and the mass density, $\rho$, of the blend is approximately 528 kg/m$^3$.

Prior to compaction, the instrument must be calibrated: (i) an acoustic pulse response (waveform) of only the punch tip in contact with air (the upper punch removed from the die) is acquired (Fig. 2), followed by (ii) the upper punch in contact with the powder bed (approximately no acoustic transmission), and finally (iii) a pre-compaction force of 400 N is applied to the powder bed and another waveform is acquired as a compaction starting point. The waveform with no compaction force and no contact with the powder bed will be used as the reference transient response of the upper punch tip-transducer assembly to determine the ToF of back-reflection pulses from the upper punch-compact interface.

3.2. In-die compaction

In waveform acquisitions, the lower punch is kept stationary while the upper punch is lowered by the load frame with the compressive force of $F_c$, and the die height $h$ is recorded. The material properties of the steel that the upper punch tip is made of are as follows: Young’s modulus of $E = 205$ GPa, the mass density of $\rho = 7850$ kg/m$^3$, the acoustic impedance (for pressure waves) of $Z = 42.15$ MRayl, based on ToF measurements. The compaction force levels $\sigma_c$ are incremented by 4.4 kN until the maximum compaction force is achieved, $F_c = 32$ kN ($\sigma_c = 253.4$ MPa). The pulser/receiver parameters are set at the PRF of 100 Hz, the amplitude of pulse voltage at 400 V, the amplification gain of 0 dB, and the transducer frequency bandwidth specified at 10 MHz. The digitizing oscilloscope has an 8-bit amplitude depth with a 1 GHz sampling frequency, and an averaging rate of 512 samples, with a set data buffer size of 10,000 data points. For verification purposes, a set of three tablet samples was compacted utilizing a wired in-die compaction monitoring.

Tablets remain in-die during these measurements and are radially and axially constrained, thus their elastic properties are called apparent, indicating they are different from those obtained when tablets are unconstrained (out-of-die). The ToF data was extracted directly from each individual acquired waveform at a particular value of $F_c$. The ensemble of waveforms acquired during a full compaction cycle is represented via a waterfall format (Fig. 4).
arrival times of the back-reflected pulses in the ensemble become shorter with increasing compaction force and their incrementation as a function of $F_c$ are clearly visible. The significant change in ToF over the compaction cycle indicates a substantial change in material property (i.e. $E$) and powder bed height ($h$). The results for the wired and wireless samples are portrayed along with the wireless results to show correlating values of ToF, and mechanical properties (Figs. 5 and 6).

3.3. Out-of-die post-compaction

Post-compaction ToF measurements for determining the Young’s moduli of unconstrained (out-of-die) compacts are performed, after the tablet is removed from the die, using a pair of 2.25 MHz transducers (AT024, Valpey Fisher Corp., Hopkinton, Massachusetts), a custom-made delay line made of Rexolite ($c = 2362 \text{ m/s}$, $Z = 2.5 \text{ MRayls}$, and $\rho = 1050 \text{ kg/m}^3$), and a computer. The transducers are utilized in a standard A-scan pitch-catch capacity, and are employed using the acoustic tablet tester (ATT) instrument (Pharmacoustics Technologies, Potsdam, New York) in the reported out-of-die measurements. The ATT instrument is a computer-controlled waveform acquisition and analysis system consisting of transducer(s), delay lines(s), and a pulser/receiver/digitizing board as well as a LabView incrementation-based waveform acquisition and analysis software package. The pulser/receiver and digitizing oscilloscope settings for ToF data acquisition are as follows: the sampling rate of 100 MHz, the voltage amplitude of $-50 \text{ V}$, an amplification gain of $-20 \text{ dB}$, a pulse width of 200 ns, and a waveform averaging rate of 100 samples. From the acquired waveforms, the ToF is extracted for each tablet in the sample set for a baseline comparison of the in-die monitoring system, and is recorded in Table 2.

![Fig. 3.](image)

**Fig. 3.** The ToF measurements from the wireless (dotted black), digitally filtered (dashed blue), and STFT method based (solid black) waveforms overlayed, demonstrating the effectiveness of the signal processing methods and the ToF determination technique. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

![Fig. 4.](image)

**Fig. 4.** Waterfall representation of 14 signal processed waveforms at consecutive compaction force levels ($F_c$) in a full compaction cycle for the wireless WL1_1 tablet with the change in decreasing ToF clearly demonstrated as compaction progresses.

![Fig. 5.](image)

**Fig. 5.** The ToF vs $F_c$ population mean with one standard deviation depicted for the wireless and wired measurement set-ups.

![Fig. 6.](image)

**Fig. 6.** Young’s moduli ($E$) as a function of compaction force ($F_c$) with one standard deviation depicted for the wireless and wired measurement set-ups.
4. Experimental results and analysis

4.1. Material property determination

From the relationships between elastic wave propagation speed and geometric/mass properties, the material properties can be determined from the extracted knowledge of how an acoustic wave has traveled through a material. The present experiment utilizes ToF, depicted in Fig. 3, to empirically measure the longitudinal phase velocity \( c_l \) in the material and can be calculated through \( c_l = h/\text{ToF} \), where \( h \) is the thickness of the tablet (or the variable powder bed height during the compaction cycle), and ToF is the time of flight of the propagating longitudinal waveform. The modulus of elasticity (effective Young’s modulus \( E \)) is related to the \( c_l \) of a propagating elastic wave through

\[
E = \rho c_l^2 \tag{1}
\]

where \( \rho \) is the apparent mass density, and \( c_l \) is evaluated at a prescribed stress state (for in-die measurements) or in an equilibrium state (for out-of-die measurements).

4.2. Experimental data and analysis

In the course of the experimental study, a number of waveforms have been acquired utilizing the wireless monitoring system (Figs. 1 and 2). Signal processing is accomplished through a Matlab\textsuperscript{TM} based program developed and utilized for applying band-pass digital filters to filter out high frequency noise allowing the recovery of the signal that resides below the noise floor. The finite impulse response (FIR) Keiser window technique of band-pass filtering with a lowpass frequency of 0.5 MHz, a highpass frequency of 6.5 MHz, a filter order of 2000 and \( \beta = 60 \) is applied to the captured signal to filter the noise and recover the features contained in the original signal. The wired and wireless upper punch reflection waveforms are depicted in Fig. 2, demonstrating the result of effect of wireless transmission to the waveform. Further signal processing is necessary due to the relatively undesirable shape and features of the relayed waveform from the wireless transmission system, and thus a second signal processing step is undertaken utilizing a short term Fourier transform (STFT) method with a Hamming window, of which each signal processing technique is depicted in Fig. 3. The STFT takes a time domain waveform and breaks it into a time–amplitude–frequency surface spectrogram that can then be utilized for time–frequency analysis; specifically to isolate a single frequency resulting in the accurate measurement of ToF. The ToF in the tablet as a function of compaction forces \( F_c \) in compression and release (equilibrium force) phases is obtained (Fig. 5). It is observed that the ToF decreases with an increase in compaction force, followed by an increase during the relaxation phase, but at a lower level than in the compaction phase. For example, from Fig. 5, as the compaction force is increased from \( F_c = 8.8 \text{kN} \) to \( 32 \text{kN} \), the ToF changes from 1.05 \( \mu \text{s} \) to 0.64 \( \mu \text{s} \). The strong hysteresis observed indicates a permanent change (e.g. plastic deformation) in material properties due to compacting mechanisms.

The average apparent Young’s moduli (in-die) for the experimental compacts are obtained based on the ToFs and coupled with the change in \( F_c \) (Fig. 6). The average apparent Young’s moduli increase during compaction at a rapid rate, followed by a slow decline as equilibrium forces (relaxation) occurs. The aforementioned trend is expected, because the elastic modulus should reflect the state of inter-particle bonding. As the powder is compacted, the increase of inter-particle bonding is very large, resulting in a more solid-like structure (thus higher \( E \)). As the compacted powder is released, the internal residual stresses force the compact to deform into an equilibrium state. Finally, the equilibrium forces are allowed to dominate the deformed state of the compacted tablet, the Young’s modulus will assume increasingly lower values until in-die equilibrium conditions prevail. Note, however, that the compacted tablet is still constrained radially; making the measured Young’s moduli an average apparent Young’s modulus despite the lack of axial constraint \( F_c \approx 0 \) at the end of the release phase.

The out-of-die Young’s moduli in the direction of compaction direction of the experimental compacts are determined using a contact ultrasonic ToF method similar to in-die measurements with the exception of a pitch-catch A-scan setup rather than the pulse-echo A-scan setup utilized during in-die measurements. As previously mentioned, each compacted tablet experiences large residual stresses due to elastic and plastic deformations while being externally constrained; leading to the transition of significant internal geometric constraints opposing the residual stresses. As the compacts are removed from the die, the external geometric constraints are lifted and a new equilibrium is achieved (i.e. considerable relaxation) resulting in the tablets expanding and becoming softer (less rigid and lower hardness). For example, the compact diameter increases from 12.68 mm to 12.80 mm, and the tablet thicknesses range from 2.25 mm to 2.53 mm, as expected. The difference between in-die average apparent Young’s moduli measurements and out-of-die Young’s moduli measurements are predicted to be non-trivial, but within an order of magnitude or less, as shown in Fig. 6 and Table 2. In Table 2, out-of-die values of geometric properties, Young’s moduli and acoustic impedances for tablets allowed to reach an equilibrium over 24 h are reported. It is noted that the values for apparent Young’s moduli in Fig. 6 (in-die) are substantially higher than those reported in Table 2 (out-of-die).

5. Conclusions

A study for demonstrating the feasibility of ultrasonic non-destructive characterization of the geometric/mechanical
properties and integrity of tablets during compaction utilizing a wireless electromagnetic transmission approach was conducted. In the current study, it is demonstrated that the reflection of an ultrasonic pulse generated by a transducer embedded in the upper punch of a type B rotary press punch-die set back reflected from the tablet-lower punch interface can be acquired by the same transducer (pulse-echo). The acquired waveform can then be transmitted wirelessly from the tabletting equipment to a data processing computer allowing the calculation of geometric and mechanical properties during the full compaction cycle; indicating that the implementation of an in-die system to actively monitor in-die mechanical properties is an achievable system. The access to indie monitoring in a wireless fashion supports the application of ultrasonic non-destructive testing while a rotary press and/or an otherwise difficult to instrument tabletting press is the equipment that is to be monitored. The characterization of tablet geometric and mechanical properties in a real time approach is of interest to the pharmaceutical manufacturing industry and to regulatory agencies; as these parameters are directly related to tablet hardness (affecting bonding, mechanical strength, and relating to the Young’s modulus), porosity for its effect on dissolution profiles, and product quality (e.g. mechanical integrity). The preliminary substantiation of real-time in-die wireless compaction monitoring supports the key objectives of quality monitoring and regulatory initiatives such as the quality by design (QbD) and process analytical technology (PAT) of the U.S. Food and Drug Administration (FDA).

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