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Abstract

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Recent advances in technology, design, instrumentation, and software have led to the emergence of newer techniques for non-invasive characterization of physical-mechanical properties of tablets. These techniques include near infrared spectroscopy, Raman spectroscopy, X-ray microtomography, nuclear magnetic resonance (NMR) imaging, terahertz pulsed imaging, laser-induced breakdown spectroscopy, and various acoustic- and thermal-based techniques. Such state-of-the-art techniques are currently applied at various stages of development and manufacturing of tablets at industrial scale. Each technique has specific advantages or challenges with respect to operational efficiency and cost, compared to traditional analytical methods. Currently, most of these techniques are used as secondary analytical tools to support the traditional methods in characterizing or monitoring tablet quality attributes. Therefore, further development in the instrumentation and software, and studies on the applications are necessary for their adoption in routine analysis and monitoring of tablet physical-mechanical properties.

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Emerging technologies for the non-invasive characterization of physical-mechanical properties of tablets

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Abstract

The density, porosity, breaking force, viscoelastic properties, and the presence or absence of any structural defects or irregularities are important physical-mechanical quality attributes of popular solid dosage forms like tablets. The irregularities associated with these attributes may influence the drug product functionality. Thus, an accurate and efficient characterization of these properties is critical for successful development and manufacturing of a robust tablets. These properties are mainly analyzed and monitored with traditional pharmacopeial and non-pharmacopeial methods. Such methods are associated with several challenges such as lack of spatial resolution, efficiency, or sample-sparing attributes.

Recent advances in technology, design, instrumentation, and software have led to the emergence of newer techniques for non-invasive characterization of physical-mechanical properties of tablets. These techniques include near infrared spectroscopy, Raman spectroscopy, X-ray microtomography, nuclear magnetic resonance (NMR) imaging, terahertz pulsed imaging, laser-induced breakdown spectroscopy, and various acoustic- and thermal-based techniques. Such state-of-the-art techniques are currently applied at various stages of development and manufacturing of tablets at industrial scale. Each technique has specific advantages or challenges with respect to operational efficiency and cost, compared to traditional analytical methods. Currently, most of these techniques are used as secondary analytical tools to support the traditional methods in characterizing or monitoring tablet quality attributes. Therefore, further development in the instrumentation and software, and studies on the applications are necessary for their adoption in routine analysis and monitoring of tablet physical-mechanical properties.

Key words

Tablet physical-mechanical properties; density; porosity; Tablet breaking force; Pharmacopeial methods; Emerging technologies

1. Introduction

Pharmaceutical tablets are composed of one or more active pharmaceutical ingredients (API) and non-active ingredients. They are the most common form of oral drug administration. Tablet manufacturing is a complex process consisting of several unit operations. A key expectation of tablets with acceptable quality and functionality is the retention of its strength during handling, and maintaining dosage-form integrity until administration. Moreover, it must undergo disintegration, dissolution, and release of the drug efficiently upon administration. The delivery of drugs from a tablet is greatly influenced by its composition and physical-mechanical properties such as geometric dimensions, density, breaking force etc. (Stephens et al., 2013b). Ideally, tablets should also be free from any structural defects or irregularities. Consequently, it is imperative to measure tablet physical-mechanical properties with highly accurate and precise techniques, which allows a timely characterization and monitoring of tablet properties such as porosity, elasticity, and breaking force. The tablet formulation composition and the manufacturing process are often known to cause structural defects such as capping, chipping, cracking, sticking, and lamination. These defects and are considered among important developmental challenges in the industry (Cetinkaya et al., 2010). Structural and functional failures in tablets often result in delayed regulatory approval, delayed time to market or in case of post-approval failures, product recalls from the market. Eventually these failures add economic burdens on the overall cost of the final product.

Pharmacopeias typically provide guidelines and standards to evaluate tablet properties such as homogeneity, friability, content uniformity, breaking force, disintegration, and dissolution. **According to the ‘Q6A specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances’ The USFDA requires the use of these pharmacopeial guideline and standards for drug products.** A majority of pharmacopeial techniques is semi-destructive to the samples. Often these tests lack specificity and spatial resolution. Furthermore, specific tests may vary significantly across different pharmacopeias due to applied testing parameters (Donauer and Löbenberg, 2007). **Moreover, according to the Q6A specifications, the USFDA encourages the use of any new analytical technologies when they are considered to offer additional assurance of quality, or are otherwise justified.** The past few decades have witnessed the development of several efficient, sensitive, practical, material-sparing, and non-invasive techniques for the evaluation of

tablet properties (Fevotte et al., 2014). These techniques include, near infrared spectroscopy, Raman spectroscopy, x-ray microtomography, nuclear magnetic resonance imaging, terahertz pulsed imaging, laser-induced breakdown spectroscopy, acoustic and thermal techniques.

While a comprehensive analysis of all the techniques is beyond the purview of this article, the present review sheds light on the commonly existing methods and elaborates on the emergence of non-invasive analytical tools used for the characterization of physical-mechanical properties pharmaceutical tablets. The following sections, in no specific order, describe the most explored, and some newer technologies. The discussion of individual technology is mainly focused on the operation principle, applications, advantages, and limitations of the technique.

2. Current pharmacopeial/non-pharmacopeial methods

Pharmacopeial conventions establish standards that must be followed by all marketed drug products to ensure their quality, strength, identity, and permissible impurity limits. The United States Pharmacopeia (USP) provides guidelines and standards to assess several properties of pharmaceutical tablets, such as homogeneity, friability, content uniformity, breaking force, disintegration, and dissolution (Zeitler and Gladden, 2009).

The measured porosity is described as the proportion of empty space, or pores, in a compressed tablet, and reflects the solid fraction of a tablet (Wikberg and Alderborn, 1990; Yuasa et al., 1996). The porosity of a compact is determined by two methods described in the USP (Porosimetry by Mercury Intrusion, and by Nitrogen Adsorption-Desorption). In order to obtain meaningful results, it is imperative to standardize the displacement medium, since the porosity measurements can vary significantly with the medium. The friability test, as described in the USP determines the ability of pharmaceutical tablets to tolerate stresses during manufacturing, packaging, and transportation. The test involves subjecting the tablets to a uniform tumbling motion in a drum (friabilator) for a specified period/number of rotations, and measuring the percent weight loss. The externally applied force, which results in the breaking of a tablet in a specific plane is commonly used to analyze the mechanical integrity of tablets (Brook and Marshall, 1968). The USP Chapter on tablet breaking force provides guidelines to analyze the breaking force of tablets. Diametrical hardness testing of tablets is routinely carried out during manufacturing as a part of in-process quality monitoring and control (Fell and Newton, 1970). The evaluation is typically conducted by placing a tablet perpendicular to its banded side (round tablets) or along the longest length (oval tablets) on a platform. The tablet is

then crushed with a flat-faced cylindrical probe moving at a constant, set speed. (Brook and Marshall, 1968). Several variants of tablet hardness testers ranging from manual to automatic are currently being utilized (Bavitz et al., 1973; Fairchild and Michel, 1961; Goodhart et al., 1973; McCallum et al., 1955).

In addition to the traditional quality control tests for tablets, coated tablets are evaluated for the characteristics of the coating films. These evaluations include, (i) adhesion test using a tensile strength tester that determines the force required to remove the coating film from the tablet surface, (ii) evaluation of coating film strength by determining the difference in the breaking force of the coated tablet relative to the uncoated tablet, (iii) effects of temperature and humidity on the film integrity, and (iv) qualitative and quantitative determination of surface roughness, hardness, color homogeneity, etc. of the film, which could be inspected visually or by specific instruments (Zeitler and Gladden, 2009). In addition, coated tablets are tested for film resilience empirically by rubbing the tablets on a white paper sheet, and visual observation of film integrity as well as any transfer of film color on the paper.

Along with the pharmacopeial tests, several non-pharmacopeial techniques are also routinely employed as a secondary supportive measures of the physical-mechanical properties of tablets. The most common among these include the Hiestand Tableting Indices (Hiestand et al., 1971; Hiestand, 1996; Hiestand and Smith, 1984). For materials previously characterized for their physical-mechanical properties, these indices indicate their relative tableting and consolidation behavior. The degree of particle bonding within a tablet that remains after decompression, measured as a ratio of tablet tensile strength and breaking force is known as the *bonding index*. The brittleness of the material, obtained by comparing the tablet tensile strength and the indentation hardness, is indicated by the *brittle fracture index*. The brittle fracture index assists in predicting the probability of capping and lamination. The viscoelastic properties of tableting materials is obtained from the ratio of dynamic indentation harness and the quasi-static tablet breaking force, and known as the *viscoelastic index*.

Most of the pharmacopeial and non-pharmacopeial techniques described above are semi-destructive or invasive to the samples. Moreover, some of these tests lack specificity and spatial resolution. Furthermore, specific tests vary considerably across different pharmacopeias (Donauer and Löbenberg, 2007). Nevertheless, these techniques are useful, have been used for

many years, and have significantly contributed to the development of pharmaceutical tablet products.

3. Emerging technologies

3.1. Near infrared spectroscopy

Near infrared spectroscopy (NIRS) is among the most commonly used analytical tools in pharmaceutical development. Since the early 1990s, several studies and review articles have shed light on various applications of NIRS (Aldridge et al., 1994; Morisseau and Rhodes, 1995, 1997). NIR is defined as the section of the electromagnetic spectrum between 780 and 2526 nm. In this spectral area, the fundamental vibrations of specific functional groups (e.g. $-\text{CH}$, $-\text{NH}$, $-\text{OH}$, SH , etc.) on the molecules interact with radiation to produce specific spectral bands. These NIR bands are also highly sensitive and responds to the physical and chemical characteristics of the analyte. These properties make NIRS a useful tool for the analytical investigation of samples with high absorption and/or scattering properties e.g. solids. Typically, NIR analyzers are generally consist of a radiation source, a radiation processing unit, a sample presentation unit, and signal acquisition/processing unit (Figure 1).

Figure1: Basic configuration of a NIR spectrometer.

The NIR spectra, however, are broad and consist of overlapping and fused peaks. Thus, in order to extract meaningful information, NIR spectra require systematic data processing with the use of Chemometrics (Dave et al., 2015; Dave et al., 2017). Moreover, development of robust multivariate calibration models using large datasets, and validation of the developed models is required to reliably use NIRS for the qualitative and quantitative examination of materials. NIRS, along with Chemometrics-assisted model development, have resulted in its extensive applications in research, production, product quality assessment, and control of pharmaceutical products (Dave et al., 2015; Uppaluri et al., 2014). A wide variety of NIRS measurement technologies that differ in spectral coverage and resolution, are currently available. Short and specific wavelengths are covered by light emitting diode (LED)-based instruments; whereas, higher resolution and wider spectral coverage is obtained via acoustic-optic tunable filter (AOTF) - and interferometer-based instruments. The required sensitivity, speed, reliability, and specific application determines the selection of an appropriate technology (Reich, 2005).

A relatively recent advancement over conventional single-point NIRS, is NIRS imaging. Spatial distribution of heterogeneous samples can be determined by the combination of traditional NIRS with modern imaging technologies. With NIRS imaging, a 3-D data set can be created where, the spatial information and the spectral information of the analyzed sample are represented on the three axes. The NIRS imaging data appears in the form of a chemical map of the sample surface that could be used in detecting physical as well as functional properties of the sample, e.g. drug concentration, or the existence of any impurities or moisture (Reich, 2005). NIR imaging outweighs the conventional NIRS in various aspects. The spectral imaging data provide spectra of heterogeneous samples which compensates the need for calibration in quantitative analysis. This property of NIRS imaging is both, time-saving and cost-effective, considering the size of the data set. In addition to the determination of physical and chemical homogeneity of a sample, NIR imaging also allows data collection from multiple samples in parallel.

Over the past few decades, NIRS has found a vast number of applications in the analysis of physical, chemical and functional properties of pharmaceutical tablets. Among the earliest prominent studies reporting the utility of NIRS to tablets was that by Drennen et al., who demonstrated the feasibility of using NIRS for nondestructive analysis of degradation products in intact tablets (Drennen and Lodder, 1990). Dempster et al. explored the ability of NIRS in

differentiating tablets of different strengths, as well as a placebo used in clinical trials (Dempster et al., 1993). Ebube et al. used NIRS as a nondestructive technique to distinguish between the grades of microcrystalline cellulose powder form with and without a lubricant, analyze the lubricant ratios in the tablets, and predict tablet breaking force at different compression forces (Ebube et al., 1999). Zannikos et al. successfully predicted the rate of carbamazepine dissolution in tablets using NIRS (Zannikos et al., 1991).

Kirsch et al., in a sequence of investigations demonstrated the usefulness of NIRS as a non-destructive method to determine several tablet physical and functional properties (Kirsch and Drennen, 1995, 1999). In the first study, the authors determined the coating thickness, time to 50% dissolution ($t_{50\%}$), and tablet breaking force of theophylline tablets film-coated with ethyl cellulose (Kirsch and Drennen, 1995). In the latter study, the authors compared PCA, PCR and spectral best fit method for their reliability and efficiency in predicting breaking force of cimetidine tablets of various potencies (Kirsch and Drennen, 1999). Chen et al. used artificial neural networks (ANN)- based NIRS modeling to predict the theophylline composition and breaking force of tablets prepared at various potencies, manufactured over a range of compression forces (Chen et al., 2001). Donoso et al. modeled the porosity and breaking force of theophylline tablets using NIRS along with common Chemometric techniques (Donoso et al., 2003).

Tanabe et al. applied chemoinformetric NIRS to study the theoretical basis of tablet breaking force variation at different compression forces. A calibrated model was created to predict the tablet breaking force and porosity. The developed model was validated to obtain information regarding the contributions of physical and chemical factors influencing tablet breaking force (Tanabe et al., 2007). Otsuka et al. developed Chemometric models to predict the influence of lubricant concentration and blending on tablet breaking force using NIR based spectral analysis of raw blended powders (Otsuka and Yamane, 2009). In another study, the authors developed NIRS-based Chemometric models to successfully predict the influence of storage conditions on the phase transition of theophylline anhydrate tablets, and resulting changes in the tablet properties such as breaking force and dissolution (Otsuka et al., 2015).

Dave et al. explored the feasibility of NIRS to analyze the effects of sintering temperature and triethyl citrate (plasticizer) levels on the breaking force of Eudragit[®] polymers-based tablets prepared via dry granulation (Dave et al., 2015). Igne et al. compared the usefulness of

traditional single-point NIRS and spatially resolved spectroscopy (SRS) for assessing the homogeneity of tablet composition, and detection of tablet defects (Igne et al., 2015). In addition to traditional single-point NIRS, several published reports mention NIR chemical imaging as a highly useful, non-invasive technique for the analysis of tablet physical-mechanical properties. Ellison et al., showed the effectiveness of NIR chemical imaging in the qualitative and quantitative determination of intra-tablet density variation as a function of lubricant (Magnesium stearate) concentration and resulting changes in the die wall friction during compaction of tablets (Ellison et al., 2008).

The wide variety of studies mentioned above reflect the usefulness of NIRS as a non-destructive analytical tool to analyze tablet properties. Among the main advantage of NIRS over conventional analytical techniques include, simplicity of use, speed, ease of sample preparation, portability, and flexibility between *in-line*, *at-line*, or *off-line* uses. NIRS is among the most rapid analytical techniques; scanning tablets on a typical NIR instrument takes a few seconds to a few minutes. Most samples can be presented for analysis in ‘*as is*’ physical form; practically eliminating the elaborate sample preparation required by other techniques. Most NIR instruments can be simply operated with minimal training and supervision. Most new NIR instruments are highly portable, saving time, labor, and multiple material transfer steps.

Along with these advantages, NIRS is also associated with several challenges such as low sensitivity, higher signal-to-noise ratio, and cumbersome post-scanning data processing and interpretation of information. NIR absorption bands are 10-100 times lower in strength compared to their corresponding IR signals. NIR signals exhibit broad, overlapped, ill-defined bands, and are a function of physical/chemical properties of the matrix rather than individual component. The relationship between signal occurrence and sample property is not well understood, and relies heavily on probability rather than a direct cause-effect relationship. Moreover, all possible variables have to be taken into account in order to develop a robust calibration model of a system. Any changes in the system, or occurrence of an unknown variable can be deleterious to the reliability of the model. Additionally, the development of a prediction model with NIRS relies on a reference analytical method, thus it cannot be more accurate than the reference method.

3.2. Raman spectroscopy

As a result of rapid technological advancements in the area of optics over the past decades, Raman spectroscopy has proven to be a valuable analytical technique in the area of pharmaceutical development (Gala and Chauhan, 2015). Raman spectroscopy involves subjecting the surface of a sample to monochromatic electromagnetic radiation. The interaction between the absorbed radiation and the electrons within the samples result in light scattering. 'Rayleigh scattering' occurs if the wavelength of scattered light is the same as that of irradiated light. A 'Raman scattering' results when the electrons in the ground state are excited by a photon to a virtual energy state. After a certain resonance period, the electrons relax to the vibrationally stable state. The energy difference between the original and excited state causes a wavelength shift in the emitted photons, resulting in the scattering. . In a 'Stokes-Raman shift', the scattered light has a higher wavelength (lower energy) than the irradiated light. On the contrary, if the scattered light has a lower wavelength than the irradiated light, 'anti-Stokes-Raman shift' results.

A typical Raman spectrometer setup includes a light source, focusing optics, a spectrograph (dispersing element), and a detector. The resulting spectra are collected by either a dispersive Raman detector (visible region), or a Fourier Transform Raman detector (NIR region). The collected Raman spectra is separated into constituent wavelength for data analysis. The Raman spectrum is represented as an intensity vs. frequency plot. The plot consists of three parts viz. Rayleigh lines (zero Raman shift), Stokes lines (positive shift), and anti-Stokes lines (negative shift). Each material has a characteristic shift that depends on its chemical composition. The width of the peak determines the sample quality while the intensity denotes the quantity of the sample.

Raman spectroscopy has been extensively employed to monitor several pharmaceutical unit operations involved with tablet manufacture such as powder and granule blending, granulation, drying, tableting, and coating. Additionally, several studies report the application of Raman spectroscopy in assessing the properties of finished tablets. Williams et al. compared Raman spectroscopy with traditional wet chemistry analysis to identify the minimum testing batch size for quality testing of tablets. Reliability parameters such as, the desired statistical significance, error margins, efficiency of analysis and production were used for comparison (Williams and Bonawi-Tan, 2004). Their results demonstrated that the quality of tablet analysis by Raman spectroscopy was as reliable as that of wet chemistry analysis. Romero-Torres et al.

employed Raman spectroscopy with Chemometrics for quantitatively analyzing tablet coating thickness, using coating formulation containing a fluorescent marker (Romero-Torres et al., 2006). Heigl et al. reported the use of Raman spectroscopy in studying the influence of granulation on tablet physical properties. The tablets were subjected to crushing, sieving and re-compaction under different compression forces to simulate dry granulation process. These tablets were then analyzed *via* x-ray scattering to assess their sensitivity to Raman spectroscopy. Furthermore, the generated Raman spectra were Chemometrically treated for quantitative prediction of tablet breaking force. (Heigl et al., 2012). Virtanen et al. demonstrated the use of Raman spectroscopy along with Partial Least Squares-based Chemometric modeling in measuring crushing strength of theophylline anhydrate tablets (Virtanen et al., 2008). The measured and predicted values for tablets breaking force were highly correlated; and these results were supported by electron microscopy and non-contact laser profilometry studies.

Raman spectroscopy is a valuable PAT tool in pharmaceutical development. In addition to being sensitive, accurate, and non-invasive, Raman spectroscopy is relatively easier in operation (requiring minimal training) than traditional analytical methods. It requires minimal sample preparation, and samples within their packaging materials can be analyzed. Other advantages of Raman spectroscopy include good reproducibility of results, small sample size required, and minimal sensitivity towards interference by water. Raman spectroscopy certainly has some limitations. Raman spectroscopy can be cost-prohibitive for routine analysis. Another challenge with Raman measurements is the interference in the spectra by intrinsic or impurities-caused fluorescence. However, shifting the wavelength to NIRS region can overcome this challenge. Finally, thermal decomposition of the sample is known to occur when higher excitation intensities are used (Vankeirsbilck et al., 2002).

3.3. X-ray microtomography

X-ray microtomography is a relatively newer analytical technology used to study the microstructure of a solid material. The analytical technique involves irradiating the sample with x-rays generated from a high-powered source, followed by detection of the transmitted X-rays (Figure 2). The attenuation of the transmitted X-rays depends on the density and atomic number of the sample, as well as the incident X-ray energy, and results in a 2-dimensional (2D) image. Multiple 2D images of the sample are obtained by changing the orientation of the samples. The 2D images, coupled with sophisticated algorithms, generates a complete 3D map of the sample.

The X-ray attenuation coefficient, as well as the distance between the X-ray source and the sample controls the intensity of X-rays that reach the detector (Cao et al., 2003). The information on the thickness, density and attenuation properties of the tested material are obtained from the fluctuations in the generated signal intensity in the form of a grayscale in the images. The image contrast correlates to the solid-fraction and dimensions of the sample (Hancock and Mullarney, 2005).

Figure 2: A schematic representation of x-ray microtomography for the analysis of pharmaceutical tablets

X-ray microtomography have been explored to study a wide range properties related to pharmaceutical tablets. These include, but not limited to, qualitative and quantitative measurements of tablet density and thickness, determination of tablet shape and size, studying the microstructure of fast-dissolving tablets, monitoring tablet coating process, detecting internal and/or external tablet defects, and uniformity of API distribution in the tablets (Cao et al., 2003; Fu et al., 2006; Hancock and Mullarney, 2005; Liu et al., 2013; Miguélez-Morán et al., 2009; Sinka et al., 2004; Yin et al., 2013). Additionally, this technique has been used to detect counterfeit tablets, and the presence of foreign materials added intentionally or unintentionally during tablet manufacturing (Hancock and Mullarney, 2005). A study published by Wu et al. aimed to determine the fundamental causes of tablets defects such as capping, and explore possible solutions to prevent the capping phenomena. The authors successfully used X-ray microtomography to identify the failure patterns in the tablets. The obtained results were compared with numerical analysis like finite element methods (FEM) and showed consistency between the methods (Wu et al., 2008). Sinka et al. utilized X-ray computed tomography to

quantitatively evaluated the variations in density in tablets by generating a density map (Sinka et al., 2004). The authors modified the standard technique with the use of specialized extensions such as collimators, and applied mathematical algorithms to the calibration curves to reduce scatter and ‘beam hardening’ (instrumental effects).

Busignies et al. demonstrated the use of X-ray microfocus computed tomography in determining compact homogeneity of the binary mixtures of pharmaceutical excipients with a goal to predict tablet mechanical properties (Busignies et al., 2006). The authors correlated measured properties such as Young’s modulus, Brinell hardness, and tensile strength with the compact mass distribution heterogeneity observed in the images. X-ray microtomography successfully explained the non-linear variations observed in the mechanical properties of studied binary mixtures. Fu et al. used X-ray microtomography along with imaging and simulation tools to investigate particle packing during powder compaction (Fu et al., 2006). Their results demonstrated the utility of X-ray microtomography in reproducing the three-dimensional structure of particle packing systems.

X-ray microtomography is characterized by high penetration power and acceptable image resolution (~5-20 mm) (Hancock and Mullarney, 2005). The modified technique, synchrotron radiation X-ray microtomography (SR- μ CT) is known to provide higher order of photon transfer in relatively parallel beam morphology compared to traditional X-ray computed microtomography. Moreover, with the use of a high specification detector, data with high intensity and strong alignment can be obtained rapidly (Liu et al., 2013). Despite these broad applications, X-ray microtomography as an analytical technique has some limitations. The technique requires the samples to be analyzed to be small in size, but strong enough to withstand handling. Similar to other techniques, correlating image pixel values to the solid-fraction of the sample requires the development of a calibration model. Additionally, caution needs to be exercised during the analysis of multicomponent systems since, the linear attenuation of the material analyzed by X-ray microtomography depends not only on the material density but also on the atomic number of the components. Moreover, certain artifacts in X-ray micro-CT images, such as the ring artifact or beam hardening may influence the reliability of the generated results (Miguélez-Morán et al., 2009).

3.4. Nuclear magnetic resonance imaging

Nuclear magnetic resonance (NMR) imaging is a non-destructive investigational technique that allows capturing cross-sectional images across a sample surface. Radio-frequency (RF) irradiation (B_1) of nuclei with a magnetic moment (μ), situated in an external magnetic field (B_0), results in nuclear precessions and recorded as NMR signals. (Djemai and Sinka, 2006). The unexcited protons normally remain in the ground energy level (relaxed state) with an orientation parallel to the externally imposed field. An application of external RF radiation with energy equivalent to the energy difference between the levels induces the repetitive flipping or “resonance” of the protons between the two energy levels. The resulting phenomena is described as nuclear magnetic resonance. When the excitatory effect of RF radiation is ceased, the protons return to the metastable state by emitting RF radiation which can be determined and recorded as NMR signal. The emitted RF signal has the same frequency as that required for the excitation. It further decays progressively giving a unique waveform known as “free induction decay” signal. This results in a characteristic pattern in the form of a triangle. The base of the triangle reflects the initial magnetic moment magnitude of spinning nuclei prior to deflection, and the peak reflects the loss of proton resonance (temporal decay) (Tress and Brant-Zawadski, 1985).

NMR imaging is considered as an advancement over a conventional NMR spectroscopy. It provides additional data about the spatial distribution of protons. This makes it a valuable non-invasive technique in studying protons in the mobile water molecules which provides information regarding the temporal changes in solid dosage forms due to hydration, swelling and dissolution (Fahie et al., 1998). The NMR image resolution, contrast, and the measuring period depends on spin-lattice and spin-spin relaxation time, and the magnetic field strength (Djemai and Sinka, 2006). The spin-lattice relaxation is the time constant for restoring or building the initial parallel orientation of the nucleus net magnetic moment to the external field following RF induction. It directly influences the rate of data acquisition from consecutive NMR signals during image construction. The spin-spin relaxation time is the time constant required for temporal decay to occur and the generation of NMR signal after ceasing RF induction and influences the spatial resolution and signal/noise ratio of the signal.

A typical NMR imaging instrument is composed of a magnet, the radiofrequency electronics, magnetic field gradients, and a data acquisition system for signal processing (Figure 3). There are a wide variety of set-up configurations and specifications of the systems offered by

different manufacturers. However, the basic features are common between different systems (McFarland and Rosen, 1986). Most common applications of NMR imaging in pharmaceutical systems are directed towards studying the microstructure of tablets during drug release to gain an improved understanding of the drug-release mechanistics. Conventional techniques such as HPLC or UV spectroscopy provide general information about the drug diffusion process in tablets, whereas, NMR imaging provides a spatial characterization and detailed information on the distribution of elements in and around the tablet matrix.

Figure 3: Schematic representation of a typical NMR imaging instrument.

Several studies have reported the feasibility of NMR imaging as an ideal tool to monitor the swelling process of hydrophilic polymers in the modified-release tablets as a dissolution rate-limiting step (Bowtell et al., 1994; Rajabi-Siahboomi et al., 1996; Thérien-Aubin and Zhu, 2009; Thérien-Aubin et al., 2008; Wang et al., 2010). NMR imaging has also been used to measure the polymer concentration and distribution within different polymeric tablets, as well as the thickness of the hydrated gel layer (Baumgartner et al., 2005). In this study, the authors used combined NMR imaging and MRI to provide quantitative data about the swelling process. Fyfe et al. applied NMR imaging in recording the physical changes happening during the tablet dissolution within a flow-through apparatus as an approach to further understand the drug release mechanism (Fyfe et al., 2000). Fahie et al. reported the use of NMR imaging in identifying the cause for faster-than-expected release rate of some controlled release tablets (Fahie et al., 1998).

The obtained cross-sectional images of the prepared tablets at various time intervals showed that the presence of a highly porous coating layer, leading to a greater diffusion of dissolution medium to the core as a main cause of faster drug release. In addition to studying the functional attributes of tablets, NMR imaging has also been explored for analyzing the physical properties of tablets. Djemai et al. revealed the feasibility of NMR imaging in analyzing the density distribution in a tablet via 3D density mapping (Djemai and Sinka, 2006). This technique involved determining the compact porosity by impregnating them with a compatible liquid occupying the open pores, followed by imaging.

These studies show the potential of NMR imaging as a useful analytical technique for monitoring the properties of pharmaceutical tablets. Among the common benefits of this technique include non-destructive nature; analytical efficiency; and sensitivity to minor physical, chemical, and structural properties of the material. The NMR sample analysis requires no chemical additives, and multiple measurements are possible from a single sample. NMR imaging further provides highly valuable information on the internal features of the tested material (Dvinskikh and Furo, 2009). The limitations of NMR imaging as an analytical tool includes cost, and the requirement of a trained professional for operation and data analysis. Moreover, only a few studies have reported the applications of NMR imaging for the analysis of tablets. Thus, further studies are warranted to corroborate its utility in pharmaceutical applications.

3.5. Terahertz pulsed imaging

Terahertz (TZ) frequency is a region between the infrared and microwave segments of the radiation spectrum (1 THz are equivalent to a wavelength of 0.3 mm) (Chan et al., 2007). The lack of cost-effective TZ sources and detectors had limited the exploration of this region for the development of a feasible analytical technique for many years. The development of photoconductive antenna technology by researchers at the bell lab in 1980, using advanced optics and electronics, has resulted in the successful development of TZ-based analytical techniques (Fattinger and Grischkowsky, 1989). The availability and reduction in the cost and size of femtosecond lasers has recently spurred the evolution and applications of terahertz time-domain spectroscopy and terahertz pulsed imaging (TPI) techniques in the analysis of oral solid dosage forms.

The TZ radiation pulses are generated by directing ultra-fast femtosecond laser pulses of specific photon energy on a gallium-arsenide (Ga-As) semiconductor. This lead to acceleration

of charges through the semiconductor substrate, and generation of electron-hole pairs. The electron-hole pairs act like photo-carriers that allow the flow of transient current through a photo-conductive switch acting as radiating dipole antenna. This results in the generation of ultra-short TZ pulse (Haaser et al., 2013). The TZ pulse is detected and measured by special detectors using a solid-state receiver, the details of which are reviewed elsewhere (Zeitler and Gladden, 2009). This technique is characterized by a high signal/noise ratio, that allows direct extraction of absorption coefficient and refractive index of an analyte (Haaser et al., 2013). The basic configuration of the TPI instrumentation is shown in Figure 4.

Figure 4: Schematic of Terahertz Pulse Imaging (TPI) for pharmaceutical tablet analysis.

A frequently utilized TZ imaging approach, TPI, is based on the time-resolved analysis of TZ pulse back reflection after penetrating the samples. This technique is commonly used to analyze the internal microstructure of oral solid dosage forms (Zeitler et al., 2007). TZ radiation has unique properties, where it can easily penetrate through transparent materials such as plastics and polymeric excipients commonly used in tablets and tablet coatings (Zeitler and Gladden, 2009). This feature allows deep exploring of the sample structure using TPI. The submillimeter wavelength of TZ allows a high resolution imaging with minimum diffraction (Chan et al., 2007). Some materials have a characteristic fingerprint in the TZ region, which makes TZ an important technique for identification of various compounds.

The report by Zeitler et al. on the application of TPI in analyzing tablets was among the first such studies (Zeitler et al., 2007). This work demonstrated the feasibility of TPI in characterizing several dosage forms, including film coated tablets, and providing a whole-surface three-dimensional TZ mapping. Ho et al. used TPI to characterize sustained-release tablets by measuring tablet thickness, detecting any defects, and assessing the uniformity, distribution, and reproducibility of the coating layers (Ho et al., 2007). A comparison was made between the results obtained by TPI with conventional optical microscopy, and a showed good agreement. The microscopy technique however, was destructive and provided limited information about the sample. The data collected from TPI was significantly more useful, since TPI allowed multi-point measurements of the tablet surface. Spencer et al. examined the correlation between coating thickness and the dissolution of an enteric coated tablet, using TPI to outline the coating thickness over the entire tablet surface (Spencer et al., 2008). A subsequent study by Ho et al. further explored the aforementioned correlation between coating thickness and dissolution rate for tablets prepared on a lab scale with that for tablets prepared at a pilot scale (Ho et al., 2008). The rate and extent of dissolution for pilot scale tablets was found to be higher, although both batches had the same weight gain. TPI could effectively differentiate between the two batches based on their coating thickness and density. This study revealed a clear correlation between the mean dissolution time and coating thickness and highlighted the vital role of TPI in assessing the quality of film coated tablets. Pore et al. demonstrated the influence of excipients solid-fraction on the refractive index (RI) of tablets (Pore et al., 2007). The study reported an increase in the RI with increasing tablet breaking force in response to variations in the compression speed and force with different fillers. TPI was effectively employed to detect any defect/s within the tablets. These results were validated by X μ CT. Interestingly, TPI was found to be more efficient than X μ CT in the processing time. Quantitative frequency-domain composition calibration models using TPI, along with Chemometric tools such as PLS regression were developed to predict compact composition and to perform density analysis for a set of intact multicomponent tablets (Palermo et al., 2008). This approach allowed the preparation of the density map based on the refractive index, which exhibited a linear increase y with increasing compression force. Chemical mapping, based on reflection TPI, was used by Shen et al. to gain information about spatial distribution, as well as the chemical structure of individual component of a tablet in a single measurement (Shen et al., 2005). The authors reported the feasibility of TPI not only in

identifying the chemical components using spectral fingerprints, but also locating them within the dosage form. Maurer and Leuenberger reported the *off-line* application of TPI and NIR to assess the coating parameters such as thickness and homogeneity of film coated tablets as part of monitoring the coating process (Maurer and Leuenberger, 2009). TPI provided information about the whole tablet thickness, while NIR allowed the measurement of only the two tablet sides.

One of the first studies that reported the feasibility of using TZ probes for monitoring tablet coating *in-line*, was published by May et al (May et al., 2011). The study included random measurement of the coating thickness *in-situ* for 100 tablets in the coating pan without the need to establish calibration models. The authors later demonstrated the use of TPI for measuring tablet breaking force and surface density distribution and reported a high correlation between them (May et al., 2013). The authors recommended the use of TPI over conventional diametrical compression testing as a non-invasive analysis tool. A couple of studies published by Bawuah et al. showed the utility of Terahertz time domain spectroscopy in a transmission setup for measuring of the total porosity of pharmaceutical tablet *in-line* (Bawuah et al., 2014a; Bawuah et al., 2014b). The latter study additionally included measurement of the tablet absolute weight using Transmission terahertz time-domain spectroscopy. Recently, Yassin et al. demonstrated the use of TPI in reflection mode to monitor solvent diffusion and physical changes observed during the swelling of polymeric matrix tablets, and its impact on tablet dissolution (Yassin et al., 2015). The study employed three common excipients used in tableting; hydroxypropyl methyl cellulose (HPMC), Eudragit® RS PO, and lactose. Tablet porosity was also analyzed by X-ray microtomography, and the observations were correlated to the mechanism of diffusion detected by TPI.

TPI offers various advantages. Its high penetration power allows deep probing of the structure of solid dosage forms. It has high sensitivity to small changes in the refractive index as well as the physical-chemical attributes of the samples. TPI employs non-ionizing radiation. These radiations have unique, power energy (μW range), which doesn't induce a thermal stress within the inspected sample. Consequently, it is considered an attractive PAT tool for monitoring, quality assessing and investigating the microstructure of the solid dosage forms. This technique also has certain limitations, such as the relatively high wavelength (i.e., the spatial resolution limits). This limitation can be overcome by coupling with other techniques such as NIR imaging. Analyzing large-size samples are considered challenging to the current automated

imaging instruments. It can't be determined directly, except by manual imaging setup and data analysis, which requires experienced technicians. In the near future, more improvements are required to further allow using TPI as real-time and *on-line* PAT tool, and enhance its application in various aspects of pharmaceutical development.

3.6. Laser induced breakdown spectroscopy

When a material surface is irradiated with a high-powered laser pulse, the interaction results in minute material ablation at the focal spot. A shock wave is generated by the accumulation of the ablated material in the surrounding atmosphere. Consequent phenomena such as heating, melting, and evaporation locally follows. A plume like structure results from the expanded, evaporated material over the sample surface, which under the elevated temperature builds 'plasma'. This plasma is composed of excited species of the ablated material, electrons, and neutrons emitting light signal, which is detected and recorded. Several factors affect the properties of the laser-induced plasmas. These factors include operating parameters of the laser, such as wavelength (λ), duration of laser pulse (τ), laser energy (E), as well as the type of the material being irradiated, and the surrounding medium (i.e. composition and pressure) (Fortes et al., 2012). The commonly used Laser Induced Breakdown Spectroscopy (LIBS) techniques are double pulsed LIBS, Femtosecond LIBS, and resonant LIBS.

LIBS instrument consists of an automated pulsed laser of short duration, lenses for focusing laser beams, optics for capturing the emitted radiation from the plasma, which is then directed to a spectrum analyzer, and a detector (Figure 5). A highly focused single laser pulse is focused on the sample. This laser is of energy compared to the breakdown energy of the analyte. Consequently, the molecular structure of a small fraction of the sample breaks down, and this fraction is heated and vaporized. The material breakdown is induced when the free electrons accumulate and its density reaches 10^{18} cm^{-3} . This huge amount of electrons stimulates optical absorption in the plasma, which sustains the action of laser pulse on it through permitting its extension in the same direction of the laser light. Spectral lines emitted from the evaporated material may contain neutral atoms, ions, electrons, or molecular fragments. These lines carry analytical information about the sample. In addition, the applied laser pulse energy generates a plasma with high temperatures ($>10,000 \text{ K}$) that excites the vaporized elements. After losing the gained energy as emitted radiation, the plasma returns back to the lower energy level (Pasquini et al., 2007). The emitted signals are detected by LIBS. An advancement of LIBS described as

‘Time-Resolved Laser Induced Breakdown Spectroscopy’ (TRELIBS) allows monitoring the emitted waves against nanoseconds time resolution. TRELIBS facilitates the selection of the optimum sampling time for better data acquisition from the plasma (Castle et al., 1997; Radziemski et al., 1983). Modern detectors, consisting of intensified charge coupled devices (ICCD) arranged in series, provide data with a high resolution. The last two decades have witnessed an exponential growth and development of LIBS instruments. A large number of publications reporting about the fundamental applications of LIBS is a reflection of growing interest in this technology (Pasquini et al., 2007).

Figure 5: A schematic outline of a LIBS instrumentation.

LIBS has been widely used to monitor the distribution of drug and excipients within powder blends and pharmaceutical tablets (Anzano et al., 2009). Myakalwar et al. used LIBS coupled with several Chemometric algorithms to differentiate various marketed tablets (Myakalwar et al., 2011). PCA showed effective detection of similarities between tablets types, while *soft independent modeling of class analogy* (SIMCA) could determine the class group of the tested tablets. Additionally, LIBS have also been effectively used in the quantitation of drug within pharmaceutical tablets (Archambault et al., 2005). Yokoyama et al. examined the feasibility of LIBS in studying the migration of drugs within coated tablets (Yokoyama et al., 2010). The authors prepared tablets using yellow nicardipine powder and white excipients. The migration of drug was comparatively evaluated visually, FT-IR, and by LIBS. LIBS demonstrated superior performance than other techniques used in the monitoring of nicardipine migration to the surface of coated tablets. The method appeared to be the simplest, fastest and

most effective one for the purpose. St-Onge et al. showed the use of LIBS in the quantitative analysis of multi-component tablets (St-Onge et al., 2002). Mowery et al. reported the efficiency of LIBS as an *at line* analysis tool for simultaneous measurement of coated-tablet thickness, as well as detection of intra- and inter-batch coating homogeneity using the LIBS spatial resolution technique (Mowery et al., 2002). Madamba et al. demonstrated the feasibility of LIBS as a reliable PAT-based tool for a rapid, qualitative and quantitative characterization of tablet-coating, as well as monitoring of photo-degradation of API in the coated tablets. The LIBS-sensitive radiations emitted by the coating layer containing iron and titanium, increased in magnitude with increasing coating thickness. LIBS could thus effectively determine coating thickness and uniformity for these tablets.

Among the most attractive and valuable features of LIBS as an analytical tool is the relatively faster analysis time due to non-requirement of sample pre-treatment. Furthermore, current advancements in laser technology and detectors allows the analysis of distant samples (standoff detection). Thus, LIBS can be applied for *on-site* as well as remote analysis. Another important feature of LIBS is its capability to detect organic and inorganic components in the pharmaceutical tablets in a single step. (Pasquini et al., 2007).

Among the major drawbacks of LIBS include sample fractionation, where the ablation process could alter the sample composition in the formed plasma, and requires development of a theoretical calibration model for analysis. This limitation, however, could be overcome by applying short pulse laser such as femtosecond laser to reduce fractionation, and achieve accurate, calibration-free analysis (Samek et al., 2005). Other drawbacks observed with LIBS comprises complexity, requirement for highly skilled technician, relatively high cost of analysis, as well as power demands. Moreover, high sample temperature and increased mass of the ablated elements results in background noise, and could affect spectral line intensities and resolution. Using laser shots prior to the analysis is reported to reduce noise as well as the internal sample temperature (Pasquini et al., 2007).

3.7. Acoustic emission

Acoustics is an interdisciplinary science dealing with propagated mechanical waves such as sound waves. Acoustic techniques can be used in a passive mode (e.g. acoustic emission) or in an active mode (e.g. ultrasound). Acoustic emission (AE) is produced as a result of the rapid release of energy by a mechanical process or systems like cracks and degradation, without

applying stimulus. The common frequencies used for measuring AE are ranged between 100-700 KHz. AE could also be used to record waves with frequencies in the range of 0.03-1 MHz (Tsujimoto et al., 2000). Acoustic techniques depend greatly on the physical characteristics of solid materials e.g. mechanical strength, particle size, cohesivity, etc. Consequently, AE can be effectively used to monitor the quality of tablets. Vibrations carrying information about the physical and/or chemical attributes of the material are produced during the manufacturing process. These vibrations are analyzed by AE sensors and translated into relative information about material flowability, mixing progress, particle size, composition etc. (Leskinen, 2013).

AE involves the use of generated elastic waves due to changes in the solid state under stress during processing e.g. compaction, internal changes accompanied by dislocation motions, magnetic domain motions, crack formation, thermal expansions, contractions, or phase transformations. The propagated waves are detected and measured by specific transducers, and a temporal strain curve is generated (Wadley and Mehrabian, 1984). Acoustic emissions are classified into continuous or burst waves depending on the source of emission. For instance, cracks and fractures generate short events appearing in the form of bursts (Leskinen, 2013). The basic AE instrumentation consists of four essential parts; piezoelectric sensor, preamplifier, cables, and a data acquisition system. Any AE event associated with the process is detected by the sensor fixed against the equipment wall. The pre-amplifier is used to amplify the detected signals. The cables are made of special material and transfer the AE signals from emitting medium to the sensor and detector. The elastic AE signals are converted into electronic signals. These signals, after filtration undergo signals' parameters evaluation, data analysis, and charting by the data acquisition system (Fevotte et al., 2014).

AE is used for *in process* monitoring of material behavior such as deformation and fracture when subjected to mechanical testing such as stress (Wadley and Mehrabian, 1984). In addition, AE has been used to assess and quantify tableting materials' compressibility and brittleness, monitor stress relaxation and capping during tableting process, as well as detect endpoints of pharmaceutical unit operations such as fluidized bed drying, wet-granulation, and particle size reduction (Leskinen, 2013; Rue et al., 1979; Waring et al., 1987). Waring et al., used AE to assess the compressibility and detect the brittleness of different excipients like lactose, sodium chloride, microcrystalline cellulose, as well as an API (acetaminophen) during the three stages of compression cycle. AE waves were detected extensively from all materials during the

rearrangement stage (at low forces). AE have also been used previously to detect stress-relaxation in tablets during roller compaction, and in single-punch tablet machine (Hakanen and Laine, 1993, 1995; Salonen et al., 1997). Mellin et al. showed that the detection of stress relaxation via AE could be enhanced by using a preheated chamber along with the stimulation using halogen lamp (Mellin et al., 2001). Wong et al. reported the feasibility of AE in the analysis of the deformation behavior of common tableting excipients such as lactoses during single crystal compression studies (Wong et al., 1991).

Halstensen et al. designed and developed a new acoustic Chemometrics approach for particle size analysis and detection of critical endpoint in a fluid-bed granulator, such as lump formation leading to process failure (Halstensen et al., 2006; Halstensen and Esbensen, 2000). Whitaker et al. reported a strong correlation between AE and the physical properties, i.e. particle size, flowability and breaking force of the final tablets (Whitaker et al., 2000). Recently, Crouter et al. reported the feasibility of passive AE in studying, detecting, and *in-line* monitoring of changes in the particle flowability upon addition of lubricant using a V-blender (Crouter and Briens, 2016).

AE is characterized by being sensitive, inexpensive and a non-invasive analytical tool. The non-intrusive features of AE allow its use in harsh process conditions such as high pressures and temperatures, and in the presence of corrosive materials or media. It allows real-time evaluation and monitoring of several pharmaceutical processes *in line*. AE has limited applications, since some physical changes during processing may not generate detectable waves over the applied frequency range, and may result in false-negative observations (Wadley and Mehrabian, 1984). Furthermore, multiple physical sources could lead to the generation of AE noise that could be challenging to resolve and interpret (Fevotte et al., 2014). AE depends on stress differing with every procedure, which can hamper the reproducibility of results. Finally, AE is an indirect method in that it requires sophisticated multivariate modeling to analyze the obtained data.

3.8. Air-coupled acoustic characterization

Air-coupled acoustic emission is a type of active acoustic emission consisting the use of ultrasound coupled with air. Air has a low acoustic impedance (transmission coefficient) and high attenuation at frequencies higher than 1MHz. Thus, this technique requires the use of high energy input to overcome the transmission of weakly reflected signals from the examined

materials (Kommareddy et al., 2005). The technique is similar to acoustic emission except that it involves the use of an air-coupled transducer. This transducer generates an acoustic field in a specific frequency range enough to cause transient vibrations in a material and excite several vibrational modes. The setup components are mainly composed of a pulse-train stimulated air-coupled transducer, vibrometer controller, laser doppler vibrometer, digitizing oscilloscope, vacuum handling apparatus, non-contact laser interferometer, and a sample handling system. The air-coupled transducer is placed vertically to the tested material, and transmits acoustic waves with suitable frequency to cause vibrational excitement in the material. A non-contact interferometer measures the acquired material transit responses over a certain bandwidth. The recorded responses are then digitized by the oscilloscope to determine the resonance frequencies of the material and displayed on a computer (Akseli and Cetinkaya, 2008b).

Air-coupled acoustic emission technique finds wide applications in the characterization of pharmaceutical tablets. It has been used in measuring tablet coating thickness, tablet mechanical properties, tablet integrity, detection of tablet structural defects (e.g. cracks, lamination, capping, etc.), and characterization of other tablet core and coating properties (Akseli et al., 2008). Akseli et al. carried out several studies utilizing air-coupled acoustic emission technique for analyzing the physical-mechanical properties of pharmaceutical compacts (Akseli and Cetinkaya, 2008a, b; Akseli et al., 2010; Akseli et al., 2013; Akseli et al., 2008). In one of the studies, they studied the use of air coupled acoustics to analyze tablet coating thickness using tablets with varying coating thicknesses (Akseli and Cetinkaya, 2008b). They developed an iterative procedure using Newton's and finite element methods to determine the tablet coating thickness from their recorded resonance frequencies. A remarkable shift in the resonance frequencies with no overlapping was reported within $\pm 20\%$ variation of coating thickness. The reported results were in agreement with commonly used destructive methods for measuring tablet thickness. In another study, they demonstrated the utility of air-coupled acoustic emission in monitoring the quality of the tablets via detecting the structural defects in tablets, as well as estimating the extent of damage (Akseli et al., 2008). The tablet defects were assessed by evaluating the frequency domain quadratic norm, the similarity norm, and the coefficient at 0th time shift; and comparing the observations to that of intact tablets. In general, the evaluated defects included any cracks, holes, or chipping defects. This approach demonstrated the ability to

successfully distinguish defective tablets from intact ones, and determine the type of defect from the similarity measure values.

Later, Akseli et al. used air coupled acoustic emission for the analysis of the mechanical attributes of coated and bilayered tablets (Akseli et al., 2010). The mechanical attributes, measured as the Poisson's ratio, density, and the Young's moduli, were extracted from the corresponding resonance frequencies in the specific bandwidth using computations based on Newton's methods and finite element analysis. The obtained results were compared with time-of-flight measurements using contact ultrasonic technique to verify the accuracy and precision of experiments, and showed a high similarity. This study demonstrated the feasibility of air-coupled acoustic emission in monitoring the mechanical characteristics, defects, and the shape and dimensions of each layer of the bilayer tablets (Akseli and Cetinkaya, 2008a; Akseli et al., 2010).

Air-coupled acoustic emission technique allows *in line* monitoring of tablet properties. It is an efficient, non-destructive, and cost-effective technique for studying tablet compression, as well as testing finished tablets. The technique is versatile in terms of effectively characterizing tablets with different dimensions (e.g. oval, atypical etc.) and different physical make up (e.g. coated, multilayered, etc.) (Akseli and Cetinkaya, 2008a). A major limitation of this technique is that most of the energy generated by air transducers is reflected at the interface, and the relatively small portion is transmitted through the test material with high density. This drawback can be overcome by applying frequencies lower than 1MHz (Kommareddy et al., 2005).

3.9. Contact and wireless ultrasonic testing

The basic principle of contact ultrasonic technique is similar to the acoustic emission, except a contact transducer, directly attached to the sample, is used to generate pulses of acoustic waves of ultrasonic frequency. The ultrasonic waves are focused on the surface of materials, which propagate through its different layers. The same transducer could be used to record the reflected waves using a digitizing oscilloscope. This is known as pulse-echo measurement system (Figure 6). If the configuration employs the use of two transducers for transmitting and detecting the ultrasonic waves, it is called pulse-catch ultrasonic mode (Liu and Cetinkaya, 2010). A delay line transducer is usually used to avoid echo overlapping by creating a time gap between the transmitted and the reflected waves. Additionally, it generates ultrasonic waves of short wavelength that make it applicable for penetration through different layers of materials. Acoustic couplant material (e.g. gel, glycerin, or adhesive plastic tape) is applied to enhance the

transmission of ultrasonic acoustic waves by the transducer to the material. An ultrasound scan is used to measure the time of flight (TOF, travel time) within the sample, as well as the amplitude of the reflected waves (Akseli et al., 2009). The set-up for this technique is composed of a pulser/receiver unit, ultrasonic piezoelectric cell, and an oscilloscope.

The velocity of transmitted ultrasonic waves is reported to be influenced by the internal microstructure of tablets. Hence this technique was explored in differentiating tablets based on their solid fraction and particle size (Hakulinen et al., 2008). This study showed the velocity of ultrasound waves correlating with the tablet porosity, irrespective of the tablet composition. Contact ultrasound testing was employed by Akseli et al. in the characterization of the physical-mechanical attributes of coated tablets (Akseli et al., 2009). The study involved the use of a delay-line transducer containing active element in a series of contact pulse/echo ultrasonic waves focused onto the tablet surface. The transmitted waves were reflected back at the core-coat interface in the tablet and recorded by the same transducer. The detected overlapping waveforms were analyzed to determine the transmission coefficients of the interface and the Young's moduli. The test was repeated using air-coupled acoustic emission for comparison and the obtained results showed good agreement. Liu and Cetinkaya demonstrated the use of pulse-catch and pulse-echo modes of contact ultrasonic technique in measuring the thickness and mechanical properties of controlled release tablets (Liu and Cetinkaya, 2010). The thickness results provided information on the eccentricity and concentricity of tablets. The results were compared with those from destructive methods for measuring tablet thickness, and showed good agreement. The authors suggested that further advancement in the technique could allow contact ultrasonic testing being used in real time online monitoring of tablet quality through integration with traditional die-punch set.

Figure 6: Schematic of contact ultrasonic setup for measurement in a ‘pulse echo’ mode.

Recently, Stephens investigated contact ultrasonic testing for real-time monitoring of physical-mechanical behavior of tablets during compression (Stephens et al., 2013b). The study included a transducer for the generation of ultrasonic waves, directly connected to the upper punch of the tablet compression machine. The ultrasonic waveforms are obtained, and the time-of-flight (TOF) of the waves propagating through the tablet is estimated as the function of compression force. Ultrasonic waves were reflected at the interface of the punch tip-powder and their reflection coefficient were extracted. It was observed that as the compaction force increased, the reflection coefficient was reduced due to solidification of the tablet. Young’s moduli of the compacts were extracted using data acquisition methods during the compaction and decompression processes. In a subsequent study, Stephens et al. reported the use of wireless transceiver for analyzing of tablets’ geometric and microstructural properties in real-time (Stephens et al., 2013a). Ultrasonic pulses were generated by a transducer fixed to the upper punch. The same transducer detected the waves reflected at the junction between the lower punch and the tablet, and transmitted *via* a wireless electromagnetic connection to a computer for further analysis. Similar to the earlier study, this approach was successful in determining Young’s moduli of the tablets from the measured TOF of ultrasonic waveform during a complete compaction cycle. Akseli et al. utilized contact ultrasonic testing technique for the prediction of

tablets capping, and quantitative correlation of capping with the viscoelastic characteristics of tablets such as Young's effective elastic and shear moduli, measured axially and radially (Akseli et al., 2013). The utilized approach depends on calculating dimensionless elastic-shear moduli (EG) ratio and cap value which refer to tablets' integrity, the likelihood of capping, and the ability of the tablet to expand to relieve acquired stress from compression. The measured EG ratio was correlated to the anisotropic properties of tablets, a major cause of capping. It was observed that higher the EG ratio, lower the anisotropy of compressed powder, and lower capping tendency. Additionally, it was reported that as the cap value increased, the tendency of capping increases. The results of this study showed a high correlation between the actual and predicted capping tendency.

The major advantages of contact ultrasonic technique in the evaluation of tablet properties are its speed and simplicity. The technique doesn't require a calibration model, sample preparation, or numerical simulation (e.g. finite element analysis) to determine Young's moduli. Furthermore, it is relatively economical compared to other methods, such as air coupled acoustic emission. However, unlike NIR, contact ultrasonic testing cannot be used for the chemical analysis of pharmaceutical tablets. In addition, due to direct contact, the likelihood of damage to the sample is higher. Using an adhesive tape instead of a gel as a couplant could overcome this limitation.

3.10. Photo-acoustic testing

Photo-acoustic testing is another example of active acoustics which involves stimulus transmitted to the material under investigation. The principle of photoacoustic testing is similar to air coupled acoustic emission with some exceptions. This technique involves the use of shorter laser pulses for shorter durations (nanoseconds) as a source of electromagnetic energy and excitation. The electromagnetic energy leads to thermo-elastic expansion after absorption by the samples, and generates a broadband ultrasonic signal. The emitted acoustic signal is recorded by oscilloscopes and analyzed to obtain structural information about the material (Leskinen et al., 2010).

Varghese et al. reported a photoacoustic platform to monitor the mechanical properties of tablet and coating integrity (Varghese and Cetinkaya, 2007). The authors used two different pulsed laser techniques as a source of energy to cause transient vibrational excitations detected by laser interferometer. The transient surface displacement and resonance frequencies were

measured, and compared to tablet defects. It was observed that, unlike defective tablets, defect-free tablets were characterized by quite consistent transient responses. Consequently, this study demonstrated the feasibility of the photoacoustic approach in detecting mechanical defects such as change in tablet breaking force due to core irregularities, or coating defects such as small shallow circular holes. Photoacoustic testing was also observed to be an effective tool to monitor and evaluate the elasticity and integrity of the tablets. For instance, it could detect subtle variations in porosity/density of pharmaceutical tablets (Ketolainen et al., 1995). The viscoelastic behavior of tablets such as Young's and shear moduli were successfully evaluated by analyzing the amplitudes and ultrasonic velocities of the generated acoustic waves.

While photoacoustic testing as a tablet evaluation tool has limitations due to low efficiency in producing ultrasound ($<0.1\%$), the above examples prove its value for non-invasive analysis of tablets' integrity, elasticity, and other mechanical properties (Thompson and Chimenti, 2012).

3.11. Acoustic resonance spectroscopy (ARS)

Another recently explored acoustic technique for the evaluation of tablet properties is Acoustic Resonance Spectroscopy (ARS). Generally, when a material is exposed to acoustic waves, it leads to particle movements either closer or farther from each other, and appears in the form of local expansion or contraction in the medium. The transmission of sound waves through a tablet results in a resonant frequency that depends on the velocity of transmitted sound. Material compressibility/bulk modulus influences the magnitude of this phenomena. For instance, materials of low compressibility allow propagation of sound waves faster than materials of higher compressibility (Medendorp and Lodder, 2006).

The difference in acoustic velocity could be easily and effectively used in the identification, characterization, and monitoring of tablets. Moreover, ARS spectrum, highly correlates with the chemical composition of the tablets. Consequently, it can be used in quantitative and qualitative evaluation of tablets. When tablet compositions differ chemically, these differences affect the physical characteristics such as density, mass, and compressibility which can be observed and recorded in the form of ARS spectra. The differences in the physical attributes of tablets containing same API can be analyzed by studying the linkage between chemical and physical characteristics of the used excipients (Medendorp and Lodder, 2006). Medendorp and Lodder examined the feasibility of using ARS in the identification of tablets, and

differentiation of the tablets with similar dimensions (Medendorp and Lodder, 2006). This study was based on the use of integrated sensing and processing (ISP), which is a concept of applying mathematics and Chemometrics directly to design sensors with an aim to reduce data. This method is considered easy, simple, and leads to a significant shortening of the analysis time. Three different sources of acoustic waves were tested; radio, white noise generating Zener diode amplifier circuit, and a functional generator. The physical properties of five different types of tablets including, mass, thickness and density were accurately determined using ARS spectra with <10% error. The study exhibited a correlation between the physical properties of tablets and the obtained acoustic spectra. The ARS results were compared with those obtained from NIRS. While NIRS evaluation showed a better median inter-tablet and intra-tablet separation, the authors noted the high cost and integration time associated with NIRS. Moreover, the NIRS-associated advantages were outweighed by the efficiency, economy, durability, and interference-free observations obtained with ARS.

The accuracy, precision, low cost, and non-destructive features of ARS makes it a promising tool for monitoring pharmaceutical tablets, and ensuring the production of defect free tablets with optimal and standard quality. The only reported drawback of ARS is that it is considered relatively slow in comparison to other commonly used techniques (Leskinen et al., 2010).

3.12. Light induced fluorescence (LIF)

Among the lesser explored techniques for the analysis of the physical-mechanical properties of pharmaceutical tablets is Light Induced Fluorescence (LIF). The technique generally depends on irradiation of sample surface with light at a specific excitation wavelength (depending on the sample components), and monitoring the sample fluorescence of the emitted light at a higher wavelength during relaxation. The excitation of electrons and their transition to a higher energy level occur when the energy difference between the excited singlet state (S'_1) and the fundamental electronic state (S_0) is equivalent to the energy of the absorbed photons, which is related to the excitation pulse wavelength (Guay et al., 2014). A few seconds after the excitation, partial relaxation occurs via vibration which terminates at the lowest energy level of the singlet state (S_1). At this point, three possible events could occurs. They are *quenching*, *Stoke's shift* and *photo bleaching*

(Valeur, 2004). The first is non-radiative, while the latter two are radiative and of high interest in LIF technique.

The excited molecules lose the acquired energy in the form of fluorescence and returns back to the ground state. The emitted radiations are of a longer wavelength as the energy of S_1 is lower than S_0 . *Stoke's shift* is the distance between the maximum excitation and emission. In some cases, the excited electron is converted from the singlet to a triplet excited state. This phenomenon is known as inverse spinning and is characterized by a longer lifespan. This state is considered as an energy storage state, and could undergo excited-state reactions known as '*photo bleaching*'.

Generally, the instrument setup involves positioning of LIF directly above the sample, which can be easily re-adjusted using rotating disk. A support jack allows controlling the distance between the sample and LIF instrument (Domike et al., 2010). Optic filters sets are used to select the optimum light wavelength according the sample fluorescence spectra. Radio frequency is used to transmit the collected data to a computer for processing and analysis using specific software.

To our knowledge, there are only a handful of publications reporting the application of LIF in the pharmaceutical tablets. Moreover, all of the reported studies explores the utility of LIF for the chemical analysis, or analyzing the API content of tablet formulation, rather than the physical-mechanical characterization of tablets. This could be probably related to the lack of commercial LIF analyzers. Most of the reported studies use specific purpose-built LIF sensors (Shah et al., 2015). The feasibility of a LIF instrument to analyze API in a sample depends on the relative fluorescence strength of API in comparison to the other components of the sample (i.e., excipients (Domike et al., 2010). It has been reported previously that about 60 % of the commonly used APIs fluoresce. On the other hand, most excipients that are used in tablets such as celluloses, lactose, starch, etc. don't fluoresce (Lai et al., 2004). Domike et al. effectively used LIF technique for the estimation of total API concentration in tablets (Domike et al., 2010). The study involved testing two sets of tablets containing different API. The results were compared to the total drug content measured using conventional analytical techniques. The results revealed the accuracy of LIF in estimating the drug concentration in the whole tablet. An interesting study carried out by Lai et al. demonstrated the use of LIF technique in qualitative *online* evaluation of drug

content uniformity of compressed pharmaceutical tablets (Lai et al., 2004). The study involved the production of homogenous compressed tablets as well as non-homogenous tablets containing a layer of known concentration of API using 3D Printing technology. The non-homogenous tablets were used to study the penetration depth of the light radiation as well as evaluation of the emitted fluorescence. The total drug content was determined using spectroscopic analysis for verification. A good correlation was observed between LIF signals and the total drug content of the tablets. This study highlighted the feasibility of this approach for *online* monitoring of drug content that could be implemented during tablet manufacture.

Despite the fact that there are only a limited number of reported studies about LIF, however, it is still considered an emerging, advanced technology with several advantages. LIF allows direct monitoring of fluorescent API with high speed, sensitivity, precision and relatively low cost. The sensitivity of LIF is much higher than other conventional techniques such as absorption spectroscopic methods specially in the analysis of potent drugs (Karumanchi et al., 2011). In addition, it has several advantages over UV spectroscopy and NIR. The *Stoke's shift*, which is a characteristic feature of fluorescence, and results in the difference between the absorption and emission wavelength, has a significant role in reducing the background noise and enhancing its sensitivity and detection limits. Moreover, the collection of fluorescent signal occurs at 90° angle from the incident light (Shah et al., 2015). This obviously leads to the reduction of the amount of scattered light captured by the detector, as well as increasing signal to noise ratio. Unlike UV spectroscopy and NIR, the increase in the intensity of incident radiations in LIF is accompanied by an increase the fluorescence intensity which result in better detection. This has been proven mathematically through the equation of fluorescent equation:

$$I_f = P_0 \gamma \phi \epsilon b C = k P_0 C$$

Where, I_f is the fluorescent intensity, P_0 is the incident irradiance or power per unit area, γ is the fluorescent collection efficiency, ϕ is the fluorophore quantum efficiency, ϵ is the molar absorptivity at the fluorophore excitation wavelength, b is the optical path length, C is the concentration of the fluorophore, and k is the proportionality constant (Shah et al., 2015).

However, LIF has some limitations due to its sensitivity to pH and temperature; any fluctuation in them could affect the fluorescence intensity. In some cases, the intensity of the emitted fluorescence could significantly decrease with an increase in the concentration of fluorophore. This is known as *self-quenching* and it occurs when the absorption of light increases faster than the emission. In addition, saturation of the detector could occur if the concentration of the fluorophore is high, leading to a non-linear detector response (Karumanchi et al., 2011).

4. Conclusions

Early and efficient assessment of the physical-mechanical characteristics of tablets are of prime importance in the drug product development and pharmaceutical manufacturing. **Moreover, about a decade ago, USFDA introduced a scientific, risk-based framework, i.e. Quality-by-Design (QbD) to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The FDA published guidance documents on QbD and Process Analytical Technology (PAT) tools aimed at achieving a thorough understanding of the Critical Quality Attributes (CQAs) of the finished dosage forms. This framework is based on the vision that through process understanding, control strategies, and measurement of critical attributes of materials and processes, drug manufacturing will improve and final product quality can be assured. Real-time monitoring and non-destructive analysis of tablet properties affirms this vision. Currently utilized pharmacopeial and non-pharmacopeial techniques, while being highly informative and useful, lack resolution and sample-sparing attributes. Moreover, these traditional techniques are not adaptable to the FDA's PAT initiative.** Newer techniques exploiting the interaction of material with electromagnetic spectrum, sound waves, etc. have emerged as potential non-invasive tools for analyzing tablet properties. Most of these techniques are currently used as supportive tools to the existing traditional techniques. Complete integration of these techniques into the tablet manufacturing process will require improvements in operational complexity, analytical efficiency, and adoption/operational costs. As observed with the exponential progress in design improvements, instrumentation, and software, it is not unreasonable to foresee these techniques being integrated into mainstream tablet quality control paradigm.

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Response to the Reviewers' comments:

Reviewer #2: This review work provides a comprehensive overview of recent works on the subject matter. It is well-organized and coherent. Illustrations are clear.

RESPONSE: The authors thank the reviewers encouraging comments.

The following points can be improved:

(i) Regulatory issues are overlooked. What is the links between the parameters of interest (density, porosity, breaking force, viscoelastic properties,...) and the regulations.

RESPONSE: The authors did not intend to overlook the regulatory issues. Considering the scope/length of the article, and the fact that regulations related to tablet properties have been around for decades (well known among the individuals involved with tablets research and/or manufacturing), authors had intended to avoid redundancies. Brief statements pertaining to these regulations are now included.

(ii) FDA's position on the subject matter. The status of the PAT initiative with respect to the parameters of interest (density, porosity, breaking force, viscoelastic properties,...) and their quality implications.

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(iii) LIF is another method that was proposed some time ago. Its status is somewhat unclear at the moment, but it could be worth mentioning.

RESPONSE: LIF, as an analytical tool for evaluating the physical-mechanical properties of tablets is yet to be established. Authors have added a section on the current state of LIF in relation to tablet analysis.

(iv) "Conclusion" section can include deeper arguments. Additional comments on the future of real-time monitoring should be discussed in more detail.

RESPONSE: further arguments have now been added to the 'conclusion' section.

(v) Some projections as to where the technologies are going could be useful.

RESPONSE: some projections as to where the technologies are going are now been added to the 'conclusion' section.

(vi) Some discussions on additive manufacturing/3D printing could be valuable, as a lot of attention has been focused on such technologies and their innovative uses. One specific application. For example, how the parameters of interest(density, porosity, breaking force, viscoelastic properties,...) can be tailored with additive manufacturing/3D printing technologies.

RESPONSE: While the reviewer points to additive manufacturing/3D printing as an important technology in tablet manufacture, the authors believe that discussions related to 3D printing are beyond the scope of current article. Moreover, the use of modern analytical technique for the evaluation of 3D printed drug products is in its inception stages. This could however be an interesting topic of another review in coming months.

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Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Reflector

Focusing
lens

Optic
Collector

Broadband spectrometers

Data acquisition

LIBS
spectrum

Figure 6

Figure1: Basic configuration of a NIR spectrometer.

Figure 2: A schematic representation of x-ray microtomography for the analysis of pharmaceutical tablets

Figure 3: Schematic representation of a typical NMR imaging instrument.

Figure 4: Schematic of Terahertz Pulse Imaging (TPI) for pharmaceutical tablet analysis.

Figure 5: A schematic outline of a LIBS instrumentation.

Figure 6: Schematic of contact ultrasonic setup for measurement in a ‘pulse echo’ mode.