TERAHERTZ (THz) STUDIES OF REAL PHARMACEUTICAL TABLETS COMPRESSED WITH INDOMETHACIN AS AN ACTIVE PHARMACEUTICAL INGREDIENT (API)

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Abstract

Terahertz (THz) studies involving real pharmaceutical tablets have been undertaken. A total of 110 tablets which has been compressed with indomethacin as an active pharmaceutical ingredient (API) was used in this work. These 110 real tablets were grouped into four sets. In each sample set, at least one of the following tablet parameters were varied; porosity, $f$, API mass fraction, $k$ and height, $H$.

A home built THz spectrometer from the University of Cambridge was used to measure the THz time delay pulse for each of the samples. From the THz time delay pulse, the effective refractive index, $n_{\text{eff}}$, was calculated for each sample set. The linear correlation between the effective refractive index and the porosity for pharmaceutical tablets without API as reported by Bawuah et al. has been confirmed for these sets of real pharmaceutical tablets as well. Furthermore, a linear correlation was also found to exist between the effective refractive index and the API mass fraction.

The variation of the height had no effect on the effective refractive index. However, the height variation presented ways of checking the porosity variations when the height of the pharmaceutical tablet falls within an acceptable range. Of the two tablet parameters; porosity and API mass fraction, the porosity had a greater effect on the effective refractive index than the API mass fraction.
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Samuel Tweneboah
Dedication

This work is dedicated in loving memory of Dr. Thomas Tachie-Young (1950-2016) who has been my mentor and inspirer throughout my academic career. Unfortunately, he could not live to see this work. Dr. Young, may your gentle soul rest in perfect peace.
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Pharmaceutical tablets are solid dosage forms which may contain active and non-active ingredients. Usually, the active pharmaceutical ingredients (APIs) have the capability of curing diseases while the non-active constituents, called, excipients help in binding and aiding the compression and compaction of the tablets. Perhaps, pharmaceutical tablets are one of the most widely administered oral dosage forms. Other forms of oral dosages include suspensions, syrups, emulsions, and elixirs.

Since time immemorial, various pharmaceutical tablets have been used in curing different ailments such as common pains, malaria, bacterial infection, diarrhea, tuberculosis, to mention but a few. Virtually, tablets have been used in treating almost every disease that has confronted humankind and the availability of tablets in almost every household cannot be over emphasized. This widespread usage of pharmaceutical tablets has called on authorities to put measures in place to ensure uniformity and standardization during the tablet manufacturing process. From collecting raw materials to packaging and until the tablet reaches the final consumer, certain routine measures ought to take place in each of the manufacturing processes, with the aim of improving the efficiency and efficacy of the pharmaceutical tablets. In addition, these measures are needed in order to conform to the standardization proposed by the World Health Organization, WHO [1].

One of such measures is the quality inspection of each of the tablet manufacturing processes. The tablet manufacturing process undergoes series of quality inspections before they are finally released onto the market. Each stage of the tablet manufacturing process, be it a collection of raw materials, assembling of raw materials, compression, compaction and packaging should be carefully examined. These careful inspections aid in removing unwanted and sub-standardized materials and/or products during the manufacturing process. Such physical characteristics of the raw materials and/or products that are usually checked include their uniformity in size, color, shape, texture and other defects that may be present.

The quality inspection of a tablet has evolved over the past decades. Traditionally, tablet inspectors resorted to the use of visual inspection techniques in determining the variations of color, size, shape etc. within a batch of tablets. This technique involves one or more operators sitting behind a conveyor
belt and manually using their sight or vision to detect imperfections within the batch of the tablets. Alternatively, a camera was used to capture the tablets in the processing or assembling line and then the inspector manually removes defective tablets or tablets which differ from the others within the batch. This method is quite cost effective since it requires no sophisticated equipment. However, there is the need to employ a large number of people for inspection during a large-scale production of tablets. Therefore, this manual technique may have little importance in a large-scale manufacturing factory and there is the tendency for an increased cost of labor.

Other risks associated with the traditional inspection technique are the frequent medical check-ups that operators attend due to health risks such as backaches, long straining of the eye, etc., which in turn compounds to the labor cost in such manufacturing industries. Added to the huge labor cost is the subjective nature of this technique. Different inspection personnel may have different ways of seeing variations in shape, color, size, etc. What one inspector may see as defective, the other may see it otherwise, resulting in standardization based on the discretion of a particular inspector.

From the aforementioned challenges associated with the traditional inspection techniques, there is the need to develop tablet inspection techniques which are relatively fast, highly cost-effective, can be used for remote testing, non-destructive and most importantly, can be used in large-scale production of pharmaceutical tablets. Optical inspection techniques are highly suitable for meeting these demands.

In the tablet manufacturing processes, the quality inspection parameters include the dimensions of the tablets such as height, weight, and diameter. Other parameters include the particle size, dissolution and polymorphism of solid dosages [2], content uniformity, thickness, friability, coating uniformity and porosity [3]. The applicability of optical inspection techniques to determine these quality inspection parameters has been recorded and will be reviewed in the course of this thesis. One of such optical inspection techniques is the terahertz (THz) spectroscopy.

Pharmaceutical tablets are porous substances that contain inhomogeneities such as air voids, excipients, and APIs. The longer wavelength associated with the THz radiation permits the radiation to probe into the various inclusions of the pharmaceutical tablet with little or no scattering. No wonder THz spectroscopy has been used to study the tablet parameters of the various inclusions of a pharmaceutical tablet. A linear relationship that exists between the effective refractive, $n_{\text{eff}}$ and porosity, $f$ using THz time-domain measurements has previously been reported [4, 5, 6]. This thesis, which is a continuation of their work, aims to use THz time-domain (THz-TD) measurements to validate or otherwise the linear relationship that exists between the $n_{\text{eff}}$ and $f$ for a three-phase system.
(MCC + air + API). Further, the linear correlation between and effective refractive index and API mass fraction, $k$ as well as the effective refractive index and the height for a three-phase pharmaceutical tablet will also be investigated. The research objectives and research questions are presented in the following sections.

1.1 Research objectives

To be able to reach the desired aim of this study, this thesis aims to meet the following objectives;

i. To validate or invalidate the linear correlation between the effective refractive index and the porosity of a pharmaceutical tablet which has been compressed with an active pharmaceutical ingredient,

ii. To investigate the linear correlation between the effective refractive index and the API mass fraction for a three-phase pharmaceutical tablet,

iii. To estimate which of the two tablet parameters, that is, porosity and API mass fraction has greater effect on the effective refractive index.

1.2 Research questions

In order to achieve the objectives stated above, the researcher seeks to provide answers to the following questions;

i. Would the linear relationship between the effective refractive index and the porosity for a two-phase system also be valid for a three-phase system?

ii. What would be the correlation of the effective refractive index on the API mass fraction for a three-phase pharmaceutical tablet?

iii. Which of the two tablet parameters (porosity and API mass fraction) has a greater effect on the effective refractive index for a three-phase pharmaceutical tablet?

1.3 Overview of thesis

In this thesis, the optical inspection techniques in the pharmaceutical sciences are extensively reviewed in Chapter two. The main optical inspection technique which was employed in this thesis,
that is, THz-TD is reviewed in Chapter three. Chapter four presents the mathematical formulae and useful equations pertaining to the theory of THz radiation traversing through a slab. Also, an analogy is drawn between the propagation of THz radiation through a slab to a THz radiation traversing through a flat-faced pharmaceutical tablet in Chapter four. Furthermore, the various experimental techniques and materials that were utilized in this work are presented in Chapter five. Next, the various targeted or untargeted outcome of this thesis as well as an extensive discussion of these outcomes are presented in Chapter six. Finally, the conclusions, applicability and the future outlook of this work are outlined in Chapter seven.
In this Chapter, a comprehensive but inexhaustive review of the various optical inspection techniques which have wider applications in the pharmaceutical sciences are presented.

2.1 Evolution of optical inspection techniques

The manual visual inspection as described in the previous Chapter paved the way for an automated visual inspection [7]. The automated visual inspection comprises of high-quality cameras which are used for inspecting the surfaces of the entire tablets. These cameras are also capable of inspecting the edges of the tablets as well. With embedded sensors, such defects associated with shapes, imprints, cracks etc. of the tablets are easily detected. The color variations within a batch of tablets can also be detected with the automated visual inspection [8].

The scope of the development of the process analytical technologies (PAT), by the United States food and drugs authority (FDA), aims to improve the efficiency of processes by using scientific principles and tools that support innovation [9]. Since the traditional inspection techniques have drawbacks, there is, therefore, the need for the development of new inspection techniques for the pharmaceutical sector. Obviously, optical inspection techniques have the propensity of meeting the requirements of the PAT regulation. At the heart of the optical inspection techniques is an instrument called spectrometer.

Generally, spectrometers which use various sources of light are used in the inspection of pharmaceutical tablets. Usually, the intensity as a function of wavelength or frequency is obtained in a spectrum for measurements involving the use of a spectrometer. Typically, a spectrometer consists of light sources, dispersing or reflecting elements and detectors. The optical layout of a traditional spectrometer is shown in Fig. 2.1. This spectrometer consists of an entrance slit, collimating mirrors\lenses, a dispersing\reflecting element, a focusing lens\mirror and a detector as shown in Fig. 2.1. The wavelength range of the light source and the detectors in a particular spectrometer may give the name of the spectroscopic measurements that are carried out by the spectrometer. For example,
spectrometers that operate in the visible and ultraviolet regions of the electromagnetic spectrum give rise to the UV-Vis spectroscopy. Likewise, near-infrared spectroscopy (NIRS) uses spectrometers that work in the near-infrared region of the electromagnetic spectrum.

![Schematic diagram of a traditional spectrometer with a reflecting grating](image)

**Fig. 2.1:** A schematic diagram of a traditional spectrometer with a reflecting grating [10].

The quality inspection techniques are generally grouped into contact and non-contact measurement techniques. In the contact inspection measurement, a physical contact is made between the sample or object under study and the measurement device. In contrast, the non-contact measurement technique uses electromagnetic radiation in probing objects or samples. Therefore, all optical inspection techniques can be classified as non-contact measurement techniques. In the following sections, the general characteristics of non-contact optical inspection techniques such as x-rays, UV-Vis, near-infrared, mid-infrared, far-infrared, Fourier transform infrared and laser-induced breakdown spectroscopic techniques will be discussed. In addition, their peculiar characteristics that make them plausible for use in the pharmaceutical sciences will be explored. It is worth mentioning that the following review centers on the optical measurement techniques which have wider applications in the pharmaceutical sciences. A brief description about their location on the electromagnetic spectrum, their peculiar characteristics, the pros and cons of such non-contact measurement techniques are also provided in the following sections.
2.2 X-ray spectroscopy

The X-ray region has one of the shortest wavelength range in the electromagnetic spectrum, aside gamma rays. It covers the range between 0.01 nm – 10 nm and about $10^{19}$ Hz - $10^{16}$ Hz. Because of this higher energy associated with the x-ray, it has a high ionization potential and hence it is able to penetrate into many substances. For this reason, it has been extensively utilized in the pharmaceutical sciences for various purposes. When an x-ray beam interacts with a sample, the electronic states of the samples are then altered. This results in an energy loss by the x-ray beam. As a result, this energy loss may give information about the various components of the sample. A typical technique used in the x-ray spectroscopy in the pharmaceutical sciences is x-ray diffraction (XRD). X-ray diffraction concerns with the diffraction of the x-ray photon by a single crystal. When an x-ray beam interacts with a crystal, diffraction patterns are formed. The diffraction pattern formed is characterized by intensity positions that depend on the lattices of the crystals. Since most active pharmaceutical ingredients of pharmaceutical tablets are crystalline in nature, it makes XRD possible as an optical inspection tool in the pharmaceutical sciences. For example, XRD has been used to identify the drug content of pharmaceutical dosage forms [11]. Furthermore, x-ray spectroscopy has been used for the structural analyzes of the polymorphism, amorphousness, and nanocrystallinity of pharmaceutical solids [12-14]. Interestingly, Maurin et al. has employed x-ray powder diffraction to screen pharmaceutical tablets, with the aim of identifying counterfeit tablets [15]. Also, the trace element analysis of some metals has been carried out with the x-ray fluorescence (XRF) in the pharmaceutical sciences [16]. Despite its merits, x-ray spectroscopy has its own drawbacks such as its inability to treat more complicated amorphous systems [17, 13], the need for sample preparation and data interpretation techniques which are quite cumbersome. In addition, the high ionization energy may also be destructive to some samples and to humans as well.

2.3 Ultra violet-visible (UV-Vis) spectroscopy

Ultra violet-visible (UV-Vis) spectroscopy uses light sources in the visible and ultraviolet regions in the electromagnetic spectrum to measure absorption or reflection of liquids, solids, and gasses. It spans the wavelength range of about 190 nm – 750 nm and about $10^{15} – 10^{14}$ Hz in terms of frequency. When molecules interact with UV-Vis radiation, they undergo electronic transitions. The change in the energy associated with the electronic transitions results in absorption by the UV-Vis radiation. In the pharmaceutical sciences, UV-Vis spectroscopy has been used for assaying [18], analyzing drug
content [19, 20], determining drug purity [21] and quantification of drug formulations [22]. In addition, UV-Vis spectroscopy can be used for testing the dissolution of pharmaceutical tablets [23]. A major disadvantage of the UV-Vis spectroscopic technique is the spectral overlapping which is caused by the excipient matrices in pharmaceutical formulations [24].

2.4 Near-infrared spectroscopy (NIRS)

The near-infrared region of the electromagnetic spectrum spans from the 700 nm - 2500 nm range which corresponds to 14000 cm$^{-1}$- 4000 cm$^{-1}$. A typical property of this region is its broad absorption band and low absorption coefficient [25]. The low absorption coefficient in this region means that the electromagnetic radiations are able to penetrate deeper into substances (that is, there is high penetration depth). This high penetration depth aids in the direct analysis of strongly absorbing and highly scattering samples [25].

Quite recently, NIRS has gained popularity in the pharmaceutical sciences due to its rapidness, non-destructiveness and the minimal sample preparation associated with NIRS measurements [26]. In addition, NIRS allows for the measurement of the chemical composition of APIs and physical properties such as hardness and dissolution profile of pharmaceutical tablets [27]. Further, NIRS has been used in the pharmaceutical sector to identify raw materials [28] due to its capability of predicting the physical and chemical parameters from a single spectrum [25], and for selecting different polymorphs of tablets [29]. Moreover, for analyzing the tablet coating thickness, coating formulation and dissolution of tablets, the NIRS has been employed [30-33]. Likewise, NIRS has been used to access the blend uniformity [34] and online powder blending processes of pharmaceutical tablets [35-37].

The disadvantage associated with the NIRS is that the absorption bands are relatively weak and not clearly defined, which, in turn, makes quantitative calculations more complex [38]. In addition, calibration procedures associated with NIRS are somewhat tedious.

2.5 Mid-infrared (MIR) spectroscopy

The mid-infrared (MIR) region covers the spectral range between 2000 nm – 20000 nm which corresponds to the wavenumber range of 4000 cm$^{-1}$ – 400 cm$^{-1}$. In this spectral region, substances
undergo very strong molecular transitions and this makes it easy for the identification and characterization of such molecules. The first chemical map of a solid state sample in the mid-infrared region was recorded by Harthcock et al. in 1988 [38]. This technique is best suited for raw material identification and characterization and for process monitoring [39] in the pharmaceutical sciences. They are generally applicable to very thin layer samples [40]. A major technique used in the infrared spectral region is the attenuated total reflection (ATR) technique. With suitable beam splitters and detectors, the ATR technique can be used in the near, mid and far-infrared regions and this may lead to wider applications in the pharmaceutical sciences.

The materials which are capable of transmitting in the mid-infrared spectral region are relatively expensive, and thus, most chemical analysts may not prefer this analytical tool. Added to the expensive transmitting materials is that this region has strong absorbance spectrum for some samples. Since most materials absorb strongly in the mid-infrared region, it makes MIR impractical for in-line analysis of such solids [39, 40]. To curb the issue of strong absorption, spectroscopic analysts usually add the ATR accessory to take the measurements in the reflection mode [41].

2.6 Fourier transform infrared (FTIR) spectroscopy

Fourier transform infrared (FTIR) spectrometer is an instrument for measuring the infrared (IR) absorption spectra of solids, liquids, and gasses. It consists of a polychromatic infrared light source, beam splitters, two mirrors, and detectors. The beam splitters and detectors together with the two mirrors form an interferometer. The light source is split into two by the beam splitter and then sent onto the two arms of the mirrors. A classical interferometer used for this measurement is the Michelson interferometer. The Michelson interferometer is shown in Fig. 2.2.
The Michelson interferometer is made up of 2 mirrors; one fixed and the other movable. The collimated infrared light beam is split into two by the beam splitter and it propagates onto the two mirrors. The two mirrors then reflect the beam back onto the beam splitter, where recombination of the two beams occurs. Half of the recombined beam is transmitted while the other half is reflected by the beam splitter. Consequently, only one beam is transmitted through the beam splitter and then this beam interacts with the sample. The optical path length of the two arms of the interferometer is recorded. By scanning the movable mirror linearly, a time-dependent interferogram is formed. The interferometer provides information from the whole spectral range during the scanning. Through the mathematical process of Fourier transformation, the raw data (interferogram) is converted to actual spectrum.

The FTIR technique has also been extensively used as an optical inspection tool in the pharmaceutical sciences. For instance, FTIR has been used to monitor the dissolution and drug release of pharmaceutical tablets [42, 43] and also for extracting the API content from pharmaceutical formulations [44]. In addition, since the light source covers the entire infrared spectral region of the
electromagnetic spectrum, quality inspections that can be done using conventional near, mid and far-infrared spectrometers can also be done using FTIR with ease.

### 2.7 Laser-induced breakdown spectroscopy (LIBS)

Laser-induced breakdown spectroscopy (LIBS) is a non-contact, destructive, at-line quality control inspection techniques which are used for elemental analysis of multi-component substances [45]. In LIBS, a laser is focused on the surface of the sample and then it forms a plasma. This plasma atomizes and excites the sample. The LIBS require little or no sample preparation and a relatively shorter time for analysis (~0.5 s) [46]. In the pharmaceutical setting, LIBS has been used in a variety of inspections such as determining multiple elements [47], coating thickness and coating uniformity [48-50] of pharmaceutical formulations. In spite of LIBS wider applications in the pharmaceutical sciences, it comes under scrutiny for causing tablet fragmentation, scattering and expulsion due to the laser radiation [46].

### 2.8 Raman spectroscopy

Raman is a vibrational spectroscopic technique which relies on the inelastic scattering of an electromagnetic radiation by a molecule. When a monochromatic light is illuminated on a sample, the scattered light is mostly Rayleigh scattering. However, very small photons of light with shifted frequency (energy) is observed. This inelastic scattering results in Raman scattering. Raman spectroscopy is inherently capable of detecting the fundamental molecular vibrations that are peculiar to the chemical properties of such molecules [46]. Other key advantages of this technique include its higher resolution, real-time measurement, no sample preparation and for remote monitoring. Perhaps, these inherent characteristics have contributed to its numerous applications as a non-contact measurement technique in the pharmaceutical sciences. From identification of raw materials to packaging and finally to consumers, Raman spectroscopy can be used to monitor some of the stages in the production line [51].

Typically, Raman measurements are taken in backscattering geometry. In this geometry, the Raman signals of the samples are collected directly from the illumination zone of the laser. This geometry is highly used for these reasons; ease of deployment and instrumental simplicity [52]. However, current advances in Raman spectroscopy has seen a switch to a more advanced measurement technique in a
spatially offset (SORS) and transmission mode. In Fig. 2.3, an illustration of the three Raman measurement techniques (backscattering, spatially offset Raman spectroscopy (SORS) and the transmission mode) are presented. The conventions used in Fig. 2.3 are \( R \) for the Raman light, \( L \) for the laser beam and \( \Delta s \) for the spatial offset.

![Fig. 2.3: Illustration of backscattering, spatially offset and transmission Raman spectroscopy [52].](image)

Generally, the fingerprints for most organic substances are in the wavenumber range of 500 cm\(^{-1}\) – 2000 cm\(^{-1}\). Since this wavenumber range falls within the Raman measurement spectral region, it makes Raman spectroscopy a suitable tool for characterizing and identifying these fingerprints of the molecules. Pharmaceutical tablets are multi-constituent formulations and hence Raman spectroscopy is capable of identifying each unique constituent within the formulations. In addition, Raman spectroscopy has been used for the quantitative determination and distribution of the API content within a pharmaceutical formulation [53-55]. Raman spectroscopy has also been extensively used online for quality control assessment [56] of pharmaceutical tablets, which in turn, is a major boost to the framework of PAT.

Furthermore, Raman spectroscopy has been used to non-invasively authenticate pharmaceutical products [57] and for the counterfeit screening of pharmaceutical tablets [58]. Currently, the applications of Raman spectroscopy have been extended to identifying the polymorphic forms [59, 60] of pharmaceutical tablets.
From the above review, it seems the applications of Raman in the pharmaceutical sciences are endless. Nevertheless, Raman spectroscopy is not devoid of disadvantages. Perhaps, the common drawback of this technique stems from the interference of the Raman radiation with the porous excipients, resulting in high scattering. Most common excipients that are widely used in pharmaceutical formulations undergo fluorescence [61, 52] under laser illumination in a Raman measurement, which in turn may make the spectrum noisy. In addition, Raman signals are quite weaker. Coupled with the weaker signal is that the choice of inappropriate excitation wavelength and laser power during measurement may cause the destruction of samples [51]. Typically for tablets and capsules, the Raman measurements are affected by severe sub-sampling [62, 63] due to the backscattering collection geometry that is used.

In the next Chapter, the main optical inspection technique that was employed in this thesis, that is, terahertz spectroscopy is reviewed.
The terahertz (THz) spectral region is located between the radio waves and the far-infrared region of the electromagnetic spectrum. With this location, it is possible that the THz region exhibits the characteristics of both the far-infrared and radio waves’ side of the electromagnetic spectrum [64]. The general wavelength range of THz spans from 3.00 mm - 0.01 mm (for which it is commonly referred to as the submillimeter wave). In terms of frequency, THz range is located between 0.1 – 30.0 THz and about 3.33 cm\(^{-1}\) – 1000 cm\(^{-1}\), in terms of wavenumber. However, the range between 0.1 – 3.0 THz (3.33 cm\(^{-1}\) – 100 cm\(^{-1}\)), which is called the THz gap, is widely used for material characterization and other analytical measurements. In Fig. 3.1, the location of THz on the electromagnetic spectrum is highlighted in red. In addition, the various appliances and/or technologies that are typically used in each of the frequency range in the electromagnetic spectrum is shown. Since spectroscopic analysts prefer working in diverse units, the conversion of THz to other units such as wavenumber, wavelength, and energy are also presented at the bottom of Fig. 3.1.
Fig. 3.1: Location of THz wave (indicated in red) on the electromagnetic spectrum. Conversion between THz to other spectroscopic units such as wavenumber, wavelength, energy and the various appliances and/or techniques that are used in each of the frequency range in the electromagnetic spectrum are shown [65].

Generally, the THz radiation has the following advantages over its counterparts in the infrared region.

i. THz radiation is abundant in nature.
ii. THz radiation has a longer wavelength.
iii. THz radiation excites the vibrational modes of molecules.
iv. It is highly sensitive to the presence of water and other polar substances.
v. Non-polar substances such as ceramics, plastics, etc. are transparent to THz radiation.
vi. The detection of THz radiation is coherent; both amplitude and phase measured.

When a molecule interacts with the THz radiation, the molecule absorbs the THz radiation and molecular vibrations occur within the molecules. As a result, the THz photons undergo changes in energy and frequency and this changes to provide information about the molecular interactions with the THz radiation. Unlike other optical inspection techniques, THz goes beyond spectral recognition alone.
In THz spectroscopy, the transient electric field itself is measured (other spectroscopic techniques measure the intensity of the electric field) and this determines the phase and amplitude of each of the spectral components [66]. From the knowledge of the amplitude and phase, one could extract the absorption coefficient and the refractive index of samples, without the need for using Kramers-Kronig relations. Terahertz time-domain spectroscopy (THz-TDS) is capable of getting the extinction and phase information, internal structures, impurities and conductivity of samples [67]. The THz spectra have low photon energy and it is non-ionizing, thereby, making it possible to interact with samples without destroying them.

Perhaps, scientists in the early years were not able to involve themselves in studies related to this part of the electromagnetic spectrum primarily due to the unavailability of suitable sources and detectors [68, 69]. The development of femtosecond lasers in the 1980s [70] presented new ways of harnessing the wider applications of THz spectroscopy. The typical generation and detection of THz radiation are presented in the ensuing sections.

### 3.1 Generation and detection of THz radiation

As highlighted above, the major challenge that hindered THz spectroscopy was the generation and detection of THz radiations. However, current advances in technology and sophisticated equipment has provided a solution to this obstacle. One way of generating a THz wave is the use of a photoconductive antenna (PCA). This generation technique, which has later been called terahertz time-domain spectroscopy (THz-TDS), relies on the optical excitations of PCA [71]. There are numerous ways of generating and detecting THz radiation recently [66, 71]. However, in this thesis, the generation, and detection by photoconductive antennas (PCAs), generation by optical rectification and detection by electro-optic sampling is considered. These generation and detection processes are presented in the subsequent sections.

#### 3.1.1 Generation and detection using photoconductive antenna (PCA)

A photoconductive antenna (PCA) or photoconductive switch is an antenna which is bridged by a semiconductor. A DC biased voltage is applied across the antenna. In a PCA generation of THz radiation, a laser pulse creates an electron-hole pair in the semiconductor. The generated electron-hole pairs result in creating electrical charges and hence increasing the conductivity of the
semiconductor. In order to generate a THz radiation, the laser pulse with a short duration in the range of sub-picosecond is needed. The PCA generation and detection of THz radiation is a resonant excitation one and thus it is limited by the laser pulse width and the response time of the material [66].

Until recently, the generation of a THz radiation with a PCA was in the spectral bandwidth of ~3.0 THz [72, 73]. However, current works have involved the use of low-temperature-grown GaAs (LT-GaAs) PCAs to generate and detect over 15.0 THz spectral broadband [74]. Other improved broadband detections of THz radiation of ~30.0 THz using electro-optic generation/PCA detection and PCA detection/electro-optic detection schemes have been reported [75-77].

In the LT-GaAs configuration, a Ti:sapphire laser produces a 15 femtosecond (fs) pulse duration. The output is split into two; a 400 mW beam which is focused onto the surface of a biased LT-GaAs photoconductive (PC) emitter for the THz generation and a 30 mW beam as the probe beam for gating the PC receiver antenna for detection [74]. To use this configuration in spectroscopic measurements, the emitted THz pulse is collimated and focused onto a sample by a pair of parabolic mirrors. The THz pulse is then transmitted through the sample. Another pair of parabolic mirrors is used to collect and focus the transmitted THz pulse onto the surface of the LT-GaAs antenna for detection. The receiver works in a similar manner as the detection; the only difference is that the transient electric field of the THz radiation, provides the DC bias voltage, rather than applying an external bias voltage [78]. Other PCAs that are commonly used for generating and detecting THz radiation are semi-insulating GaAs (SI-GaAs), radiation-damaged silicon-on-sapphire (RDSOS), LT-GaAsSb, LT-InGaAs, LT-InAlAs and ion-implanted InGaAs.

Similar generation and detection scheme in which the output of the fs laser has been divided into two; excitation and detection and the various optical layout has been reported by Tonouchi [79] and it is presented in Fig. 3.2. In this scheme, off-axis paraboloidal mirrors are used for collecting the emitted THz radiation. The time delay, as shown in Fig 3.2, aids in altering the time of arrival of the femtosecond pulse before it is detected.
3.1.2 Generation and detection by optical rectification (OR)

Another way of generating and detecting THz radiation is by focusing an intense laser pulse onto a non-linear crystal through the process of optical rectification. The optical pulses usually used in THz generation have significant optical bandwidths. The high-frequency component of the optical pulses mixes with the low-frequency components within a given pulse to produce a pulse at the difference frequency. This generated optical pulses contain a bandwidth of a few THz, therefore, the difference frequencies that is generated within the optical pulse also falls in the THz range [66].

In contrast to the photoconduction generation and detection of THz radiation, the optical rectification process is a non-resonant excitation one. The advantage of the non-resonant excitation is that the THz pulse width is limited only by the pulse width of the laser and the phonon-mode absorptions of the laser, but not the response time of the material [66].

For its detection, the optical rectification process relies on electro-optic sampling which is usually propagated through free space. The free space electro-optic sampling works on the principle of Pockel’s effect (the effect in which a detector crystal becomes birefringent when a voltage is applied). When the optical sampling pulse traversing through the crystal is in the same direction as the THz pulse, a slight rotation in the polarization of the optical sampling is created. Consequently, the magnitude and direction of the rotation of the polarization of the crystal are proportional to the magnitude of the THz field that is generated [66].
Typically, the non-linear crystals that are commonly used in generating and detecting the THz radiation include, ZnTe, CdTe, and GaAs. Other molecular organic crystals have been used in generating THz pulses via optical rectification [80, 81].

### 3.2 Terahertz time-domain (THz-TD)

The majority of the spectroscopic measurements carried out with THz is done by the time-domain technique. In terahertz time-domain (THz-TD), measurements are done in the time-domain, that is, it involves the use of time-resolved sub-picosecond THz pulses. This is analogous to Fourier transform infrared (FTIR) spectroscopy as described in section 2.6. From the Fourier transformation, one gets the frequency-dependent complex refractive index from the time delay measurements (since the THz pulse contains frequency components as well). The description of the THz-TD is similar to the detection and generation using the PCA, as presented in Fig. 3.2. In addition, the fs laser pulse provides the time resolution of the system and the time delay, as shown Fig. 3.2, can be altered. A typical sample is placed between the two off-axis paraboloidal mirrors. In the absence of a sample, the generated THz radiation passes through an empty space. When this happens, a reference THz pulse is said to have been measured.

Typical optics used in transporting the THz radiation from the emitter to the detector are the reflective and transmissive optics. The advantage of the reflective optics is that it has a low loss due to the fact that most of the mirrors used have high conductivity in the THz range. However, proper alignment in the reflective mode may somewhat be difficult [71]. In contrast, the transmissive mode is easier to align [71] and it gives a clearer picture of the light-matter interaction (due to the well-defined path length of the THz beam) [67]. For its disadvantage, the transmissive mode may be difficult in operating in high-frequency regions. This is as a result of the frequency-dependent absorption associated with this mode. In effect, the high-frequency components of the THz beam are attenuated [71].

The advantage of the THz-TD over its counterparts is that it is capable of determining both the absorption coefficient and the refractive index of samples without resorting to Kramers-Kronig relations. Further, THz-TD is capable of coherent synchronous detection which is immune to ambient black body radiation [66]. In addition, one can extract the frequency-dependent complex refractive index from the time delay measurements through the process of Fourier transformation.
3.3 Terahertz pulsed imaging (TPI)

Terahertz pulsed imaging (TPI) involves the use of sub-picosecond laser pulses with spectral content used for the analysis of samples via the reflection and transmission modalities [82]. This novel imaging technique focuses transient THz pulses which have been generated by the fs laser onto a diffraction-limited spot on the sample. The transmitted or reflected waveform is acquired and processed in real time at each point of the sample [83].

Further analysis is made on the temporal waveform which has been acquired through the transmission or reflection of the THz transients. The analysis can be done by using signal processing techniques such as Fourier transform, short-time Fourier transform (STFT), wavelet transform and wide band cross ambiguity function [84]. From such analysis, information about the chemical composition of such samples can be inferred. The first real imaging technique with TPI was demonstrated by Hu and Nuss in 1995 [83].

Figure 3.3 depicts a typical setup for the first real time TPI imaging system reported by Hu and Nuss in 1995 [83]. This consists of a femtosecond laser pulse, optically gated THz transmitter and detector, current preamplifier, analogue-to-digital (A/D) and digital signal processor (DSP) components and an optical delay line.

Fig. 3.3: A set up for the first real time terahertz pulse imaging system [83].
The femtosecond laser is used in exciting the THz transmitter. The transmitted THz radiation is collimated and focused to a diffraction-limited spot on the sample by using the appropriate optics. The sample is scanned in an x- and y-direction. The optical delay line is used in down converting the THz waveforms into audio waveforms [83]. The average photocurrent at the receiver is a function of the delay line and thus by sweeping the optical delay line, one acquires the THz waveform that has traversed through the sample [82]. The signal is amplified by the preamplifier, digitized and processed by the DSP. Finally, the spectral information at each pixel is obtained and processed by the appropriate software [83].

3.4 Pharmaceutical applications of THz time-domain (THz-TD) measurements

The pharmaceutical sector is one of the areas in which THz time-domain measurement is widely used. One of the products in the pharmaceutical sciences that has seen much application with THz time-domain measurements is the pharmaceutical tablet. This is due to the fact that the tablet is a heterogeneous mixture of multiple components. The inhomogeneities in a tablet may include excipients, air voids, and APIs. Such multiple constituents need to be individually accessed in order to ensure product efficacy and efficiency and at the same time, without causing destruction to the tablet. This is where THz comes in to non-invasively and rapidly provide such solutions to the pharmaceutical analyst.

This review will focus on identifying and characterizing the raw materials of pharmaceutical tablets viz. API, MCC etc. via their crystallinity and polymorphic states. In addition, the THz studies involving the determination of the optical constants, that is, refractive index and absorption coefficients, of the pharmaceutical tablets will be delved into. From this constants, the possible mechanical, chemical and physical tablet parameters that can be retrieved will be discussed. Finally, the application of THz to the post-tableting process; tablet coating and packaging inspection will also be highlighted.

3.4.1 Polymorphism and crystallinity of pharmaceutical tablets.

The active pharmaceutical ingredients of pharmaceutical tablets are usually crystalline in nature. The lattice vibrations of these crystals give rise to what is called phonons. Crystals that are insulators usually absorb THz radiation in a strong manner due to their phonon resonances. This strong
absorption is possible because the phonon lattice modes of the crystalline structures are probed directly by the THz radiation [85]. The measured THz spectra from such crystals can actually be used in differentiating the crystallinity of different substances, which are called polymorphs. With this capability of the THz region, researchers such as Strachan et al. have used THz spectroscopy in quantifying the polymorphism of pharmaceutical samples [86]. In a similar manner, the crystallinity of a cellulose (an MCC of pharmaceutical compact) has been studied using THz spectroscopy [87].

Different polymorphs have much importance regarding the dissolution of the typical crystalline active pharmaceutical ingredients (API) used in pharmaceutical tablets. Likewise, the physicochemical properties of crystalline inclusions in the pharmaceutical tablet affect their bioavailability, quality of products, therapeutic level, and the manufacturing process as well [88].

### 3.4.2 Determination of porosity of pharmaceutical tablets

Pharmaceutical tablets contain air voids (pores, cavities, channels etc.). These air voids may originate from the individual particles of the tablet inclusions (that is, intra-particle voids) or between the various constituents of the tablet (inter-particle voids). The ratio of the volume of the air voids to the total volume of the tablet is referred to as the porosity. Porosity has an effect on the performance of a pharmaceutical tablet. For instance, in the gastrointestinal tract, porosity affects the release of API from the pharmaceutical tablet [89]. Further, the porosity has been found to have an effect on the dissolution and disintegration of the pharmaceutical tablet [90].

Conventionally, porosimetry refers to the measurement of pore size, volume, density and other porous-related properties of a material. A traditional porosimetric measurement uses the non-wetting and high surface tension property of mercury, Hg, to probe the pore spaces of a sample. On the contrary, this technique is destructive since an external pressure is needed in forcing Hg into the pore spaces of the sample. In addition, Hg poses health threats to humans.

Another technique used in measuring the porosity of samples is the Branauer-Emmett-Teller (BET), where gas adsorption is used in characterizing solid samples. The disadvantage of this technique is that the gas adsorption-desorption process is likely to contaminate the samples. In a similar manner, both the BET and the Hg porosimetry techniques may have problems measuring from the close pores of the tablets [91].
Building from the non-destructive, non-invasive, rapid and real-time optical measurements using THz spectroscopy, it is not surprising that THz has been used in the measurement of porosity of pharmaceutical tablets. It is worth noting that THz spectroscopy is not the only optical inspection technique that can or has been used to measure the porosity of pharmaceutical tablet. However, the various negative effects of some of the optical inspection techniques (as has been reviewed and described in this thesis) may not warrant pharmaceutical analysts in using such techniques.

Some studies have been done regarding the application of THz-TD in determining and estimating the porosity of pharmaceutical tablets. In 2014, Bawuah et al. estimated the porosity of MCC compacts (an inclusion of a pharmaceutical tablet) using THz-TD [4]. In that work, the intrinsic refractive index of the MCC was extracted from the time delay THz pulse using the effective medium theories such as Bruggeman model. In their recent work, which is currently under review and for which this thesis forms part, the estimation of the porosity using THz-TD has been extended to three-phase pharmaceutical tablets involving air voids, MCC and API [91]. In a related study, the broadening of a THz pulse has been found to correlate well with the porosity of pharmaceutical tablets by Peiponen et al. [92].

### 3.4.3 Tablet coating, coating thickness and packaging

Coating of a tablet refers to applying a thin layer of mixtures over the tablet in order to improve its shelf-life and efficacy. Coated tablets have the ability to protect the tablet against moisture, light etc. For a tablet inclusion that possesses unpleasant taste and/or odor, tablet coating may help to cover such smell or taste. Consequently, patients may be able to patronize such tablets, despite their smell and/or taste. Moreover, the coating thickness and coating uniformity may be related to the active functionality of the tablet. For instance, a too thick-coated tablet may slow the dissolution of the tablet. On the other hand, a very thin-coated tablet may not be able to protect the tablet against light and moisture and therefore decreasing the shelf-life of such tablets [93]. In addition, coating of a tablet has been found to affect the controlled release of APIs of pharmaceutical tablets [94].

In the context of using THz pulse imaging in determining the coating thickness and coating uniformity of the pharmaceutical tablet, the THz radiation is reflected back from different interfaces due to the differences in refractive indices when the THz radiation incidents on a coated tablet. Parts of the THz radiation is transmitted through the tablet until it encounters another layer or interface and then reflected. The reflected THz pulses for each layer are then detected. Each peak of the detected
THz pulse corresponds to the THz waveform for a different interface within the tablet. Using the peak-to-peak distance (time delay), the coating thickness of the tablet can be retrieved [85]. A TPI in a transmission mode is also possible in detecting the coating thickness and coating uniformity of pharmaceutical tablets [83].

In a similar manner, TPI can also be used to inspect the package of pharmaceutical tablets. The image is formed from the differences in the transmittance through the different materials of the pharmaceutical tablet (that is the coating, excipients, API, etc.) [83].

Terahertz pulsed imaging has been used to obtain the structural information (such as coating thickness, coating uniformity) of pharmaceutical tablets by Shen et al. [95]. In that article, the coating thickness and coating uniformity were directly obtained by analysis of the THz waveform. In addition, May et al. measured the direct coating thickness of pharmaceutical tablets using TPI without employing chemometric models [96]. Another interesting outcome of the work by May et al. was that these measurements were made in-line and in real-time. This is a very good step for THz measurements in the framework of the quality by design (Qbd) and process analytic technologies (PAT).
In this Chapter, the mathematical formulae governing the optical path length of a THz wave traversing through a slab for which the refractive index of the sample is deduced are presented. Added to the optical path length are the basics of the physical dimensions of the pharmaceutical tablet such as the height, volume, and area.

4.1 Concept of optical path length, refractive index and thickness of a slab

In optics, the optical path length refers to the product of the distance through which an electromagnetic radiation has traversed through a medium and the refractive index of the medium. Consider an electromagnetic radiation which has traversed through a slab with a true thickness, $h$, refractive index, $n$ and a small change in the thickness, given by $dh$ as illustrated in Fig. 4.1.
By integrating over the whole thickness, the optical path length, $L$ is given as

$$L = \int_0^h n(h) \, dh.$$  

(1)

However, for a homogeneous slab, the refractive index as a function of the thickness is constant. Hence, Eq. (1) is reduced to

$$L = nh.$$  

(2)
4.2 THz time delay through a slab and its connection with the optical path length of a slab

When THz pulses propagate through a slab, the time-of-flight of the THz radiation is measured. In the case where there are no sample slabs for the THz radiation to detect, a reference time-of-flight is obtained. The refractive index of the reference, which is usually a nitrogen gas, is equal to unity. Next, the sample slab is placed in the measurement compartment for the THz pulses to interact with. The time-of-flight of transmitted THz pulse is detected. Figure 4.2 depicts the propagation of a THz pulse through an empty compartment and then in the presence of a sample slab. The distance of propagation of the THz pulse through an empty compartment, that is a reference, \( x_r \) and distance of propagation through the sample, \( x_s \) is also noted in Fig. 4.2.

![THz pulse propagation](image)

**Fig. 4.2**: Propagation of a THz pulse through a reference and a sample slab.

The times of arrival of the THz pulse at the reference, \( t_r \) and through the sample, \( t_s \) can be deduced as

\[
\begin{align*}
t_r &= \frac{x_r n_r}{c}, \\
t_s &= \frac{x_s n_s}{c},
\end{align*}
\] (3) (4)

27
where \( n_s \) and \( n_r \) represent the refractive index of the sample and the reference respectively while \( c \) is the speed of light in vacuum.

The THz time delay, \( \Delta t \), is the difference between the times-of-flight between the reference and the sample and it is represented in Eq. (5) as

\[
\Delta t = t_s - t_r. \tag{5}
\]

Taking into account the different refractive indices for the reference and the sample and for a homogeneous slab, the change in the optical path length, \( \Delta L \), may be deduced as

\[
\Delta L = (n - 1)h. \tag{6}
\]

Moreover, using the analogy between distance, speed and time in mechanics, the change in the optical path length can be deduced as

\[
\Delta L = c \Delta t. \tag{7}
\]

By equating Eqs. (6) and (7), the relationship between the refractive index and the THz time delay is found to be

\[
(n - 1)h = c \Delta t. \tag{8}
\]

A diagram of the slab with its cross-sectional area, \( T \), and mass, \( m \), is presented in Fig. 4.3.
If the homogeneous slab has a cross-sectional area, $T$, then its volume, $V$ can be calculated as

$$V = Th.$$  \hfill (9)

In addition, one can obtain an expression for the mass once the density and the volume of the slab are known. In classical mechanics, the relationship between the mass and the volume of an object can be expressed as

$$m = \rho V.$$  \hfill (10)

Where the symbol $\rho$ represents the density of the object. Substituting Eq. (9) into Eq. (10), the expression for the mass can be found to be

$$m = \rho Th.$$  \hfill (11)

Subsequently, $h$ can be solved to be
Furthermore, substituting Eq. (12) into Eq. (8), one arrives at an expression for the refractive index of the slab, which is presented as

\[ (n - 1) \frac{m}{\rho t} = c \Delta t . \]  

By re-arranging Eq. (13), the following expression for the refractive index can be deduced.

\[ n = 1 + \frac{\rho t}{m} c \Delta t \]  

From Eq. (14), it is obvious that the refractive index is proportional to the density of the slab. In addition, a plot of \( n \) against \( c \Delta t \) will have \( \frac{\rho t}{m} \) as its slope.

### 4.3 Concept of porosity and effective refractive index of a pharmaceutical tablet

Intuitively, one can make an analogy between the propagation of THz radiation through a slab and a THz radiation propagating through a flat-faced pharmaceutical tablet. However, one has to be mindful that the cross-sectional area of the flat-faced tablet is a circular one and hence the appropriate expression for the area has to be utilized. On the contrary, one needs to redefine the concept of the refractive index. This is so because the flat-faced tablet is a porous medium (that is, it contains air voids). Figure 4.4 depicts the tablet with air voids and the concept of an effective refractive index.
Fig. 4.4: A diagram showing a tablet with air voids.

Since the pharmaceutical tablet consists of air voids, excipients, and active pharmaceutical ingredients, the refractive index can be considered as an effective refractive index. The validity of this assumption relies on the fact that the THz radiation is not scattered or has very weak scattering when the THz radiation is transmitted through the tablet [69]. In such a scenario, the refractive index is termed as an effective refractive index, $n_{\text{eff}}$. It is interesting to note that the effective refractive index depends on the porosity of the tablet [4, 5, 6]. Under the assumptions of the effective medium model and the effective refractive index, Eqs. (8) and (14) can be rewritten as Eq. (15) and Eq. (16) respectively.

$$\left(n_{\text{eff}} - 1\right)h = c\Delta t. \tag{15}$$

$$n_{\text{eff}} = 1 + \frac{\rho_T c}{m} \Delta t. \tag{16}$$

The next Chapter deals with the materials and methods that were used in this work.
In this Chapter, the various materials that were used coupled with the THz techniques are chronologically presented.

5.1 Materials

The materials used in this study were sets of tablets which have been compressed with indomethacin as an active pharmaceutical ingredient. The nominal diameter, $d$, of all the tablets, were 13 mm. These sets were compacted from microcrystalline cellulose, MCC (Avicell PH101, FMC BioPolymer, Philadelphia, USA) as the excipient. The active pharmaceutical ingredient (API) used is indomethacin, which is produced by Hangzhou Dayangchem Co. Ltd, Hangzhou, China. The MCC grade, Avicell PH101, has a nominal particle size of 50 µm and a true density of 1.56 gcm$^{-3}$ whereas the indomethacin, which is mostly used as a painkiller, in its crystalline gamma polymorph has a true density of 1.37 gcm$^{-3}$. A total of 110 tablets were used in this study. For each sample under consideration, the measurement for five different tablets was taken and its average was found in order to affirm the repeatability of our measurements. In this thesis, the average data for each of the samples are presented.

The MCC has been widely used as a filler, binder and a disintegrant for compressing tablets due to its compactibility and flowability [97, 98]. Microcrystalline cellulose (MCC) also exhibits crystallinity. Indomethacin can exist as a crystalline substance and an amorphous substance as well [99, 100]. These characteristics of the indomethacin and MCC make it ideal for the THz radiations to probe into them. This assertion is buttressed by the works of Strachan et al. [86] and Vieira et al. [87] in using THz pulsed spectroscopy in quantifying the polymorphism and crystallinity of both indomethacin and MCC. The various descriptions of the four sets of tablets are presented in the following sections. At least, one of the tablet parameters, height, $H$, API mass fraction, $k$, and porosity, $f$ were varied in each of the sets.
5.2 Set A

Twenty (20) tablets grouped into 4 were included in this set. Both the $k$ and $f$ were kept at a constant value of 10 wt% and ~36 % respectively. The height was varied between 2 - 4 mm. The average value for each sample is presented in Table 1.

Table 1: Average data for set A. The data presented are the weight, $M$, diameter, $d$, height, $H$, API mass fraction, $k$, porosity, $f$, pulse delay, $\Delta t$ and the effective refractive index, $n_{\text{eff}}$.

<table>
<thead>
<tr>
<th>Sample number</th>
<th>$M$ (mg)</th>
<th>$d$ (mm)</th>
<th>$H$ (mm)</th>
<th>$k$ (wt%)</th>
<th>$f$ (%)</th>
<th>$\Delta t$ (ps)</th>
<th>$n_{\text{eff}}$</th>
</tr>
</thead>
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<td>3.927</td>
<td>10</td>
<td>36.439</td>
<td>7.023</td>
<td>1.535</td>
</tr>
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</table>

5.3 Set B

This set consists of 25 tablets grouped into 5 samples with a constant nominal diameter of 13 mm. In this set, the parameter varied is the porosity, $f$ whereas the API mass fraction, $k$ and the height, $H$ were kept at a constant value of 10 wt% and ~3 mm respectively. The $f$ value ranges between 36 % - 46 %. Table 2 presents the average data for the five samples in this set.
Table 2: Average data for set B tablets. The data presented are the weight, $M$, diameter, $d$, height, $H$, API mass fraction, $k$, porosity, $f$, pulse delay, $\Delta t$ and the effective refractive index, $n_{\text{eff}}$.

<table>
<thead>
<tr>
<th>Sample number</th>
<th>$M$ (mg)</th>
<th>$d$ (mm)</th>
<th>$H$ (mm)</th>
<th>$k$ (wt%)</th>
<th>$f$ (%)</th>
<th>$\Delta t$ (ps)</th>
<th>$n_{\text{eff}}$</th>
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<td>1.527</td>
</tr>
</tbody>
</table>

5.4 Set C

The highest number of tablets were measured in this set. About 40 tablets grouped into 8 different samples were measured. Both $H$ and $f$ were kept constant at a value of ~3 mm and 36 % respectively while the $k$ was varied between 0-15 wt%. In Table 3, the average data for set C tablets are presented.
Table 3: Average data for set \( C \) tablets. The data presented are the weight, \( M \), diameter, \( d \), height, \( H \), API mass fraction, \( k \), porosity, \( f \), pulse delay, \( \Delta t \) and the effective refractive index, \( n_{\text{eff}} \).

<table>
<thead>
<tr>
<th>Sample number</th>
<th>( M ) (mg)</th>
<th>( d ) (mm)</th>
<th>( H ) (mm)</th>
<th>( k ) (wt%)</th>
<th>( f ) (%)</th>
<th>( \Delta t ) (ps)</th>
<th>( n_{\text{eff}} )</th>
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<td>5.372</td>
<td>1.521</td>
</tr>
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</table>

5.5 Set \( D \)

All three parameters (that is \( H, f, \) and \( k \)) were varied in this set. The \( H \) ranged between 2 - 4 mm, \( f \) between 28 % - 50 % and \( k \) was varied between 9 - 11 wt\%. A total of 25 tablets were measured in this set and they were grouped into 5 samples. The average data are presented in Table 4.
Table 4: Average data for set D tablets. The data presented are the weight, $M$, diameter, $d$, height, $H$, API mass fraction, $k$, porosity, $f$, pulse delay, $\Delta t$ and the effective refractive index, $n_{eff}$.

<table>
<thead>
<tr>
<th>Sample number</th>
<th>$M$ (mg)</th>
<th>$d$ (mm)</th>
<th>$H$ (mm)</th>
<th>$k$ (wt%)</th>
<th>$f$ (%)</th>
<th>$\Delta t$ (ps)</th>
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</tbody>
</table>

5.6 Measurement of height, weight, diameter, density, refractive index and porosity of the tablets

The following dimensions of the tablets were measured; height, $H$, and diameter, $d$. The tablet dimensions were measured with a micrometer (Digitrix, NSK, Japan) whereas an analytical balance (Mettler Toledo AG245, Schwerzenbach, Switzerland) was used for the weight measurement. From the measurement of the height, weight and diameter, the density of the tablet were calculated. However, in this thesis, the data for the calculated density were not presented. The true density of MCC was defined using a helium pycnometer (MVP-1 Multipycnometer, Quantachrome, Syosset, NY), and the porosities of the tablets were calculated from the true density of MCC and API which was given by the manufacturers. These measurements have previously been described by Ervasti et al. [6]. In addition, using Eq. (15) the effective refractive index for the tablets was calculated, after the THz time measurements of the tablets have been taken.

For each tablet sets, errors in the calculations made for the nominal porosities are as follows: diameter $\pm$ 0.008 mm, height $\pm$ 0.005 mm (standard deviation of the sample mean), weight $\pm$ 0.01 mg (readability of the scale), porosity $\pm$ 0.2 % (calculated using the error propagation law) and refractive index $\pm$ 0.002 [6]. It is worth noting that the measurements of the dimensions of the tablet were taken, a day after the compaction of the tablets. This was to ensure that mechanical relaxation after the compaction process had no or minimal effect on the tablet dimensions.
5.7 Tablet compaction

All the sets were compacted with a compaction simulator (PCS-1, PUUMAN Ltd., Kuopio, Finland). Similar to what was described by Ervasti et al. and Simonaho et al. [6, 101], a cylindrical 13 mm punch was used in this compaction. The lower punch was kept stationary while a triangular-wave compaction profile was used for the upper punch and a constant compaction velocity of 100 mms\(^{-1}\) was maintained throughout the compaction process. The effect of an application of speed during compaction (compression) on pharmaceutical tablets has been shown [102, 103] and a punch velocity between 30 - 640 mms\(^{-1}\) has been found to yield a good compaction for pure drug and formulations [104]. Hence, the punch velocity (ca. 100 mms\(^{-1}\)) used in this work is found to be in the range and it can effectively reproduce a well-compacted tablet. In order to change some physical properties of the tablet such as the height and porosity during compression, the mass of the MCC and API was changed. The compaction profile of the upper punch was varied while the lower punch remained stationary. An added advantage of the compaction simulator is one’s ability to control the tablet parameters and its repeatability of the measurements. The use of the compaction simulator on an MCC has been reported in the literature [105, 106].

5.8 Terahertz (THz) time-domain measurements

A home built THz time-domain spectrometer from the University of Cambridge was used to conduct the transmission measurements used in this study. The refractive index can be directly measured from the measured time-domain THz signals without resorting to any complex data analytical tool. Using Eq. (15), one can calculate the effective refractive index when the THz time delay pulse has been measured. Since the THz pulse consists of a broadband of THz frequencies, the effective refractive index reported in this work is given at a virtual frequency.
The variation of the product of the speed of light and the THz time pulse, $c\Delta t$ as a function of $H$ for set $A$ tablets are discussed. These sets of tablets have a varying height but constant porosity and API mass fraction. Since the $f$ and $k$ for this set are constant, the effective refractive index is almost constant [107] (due to the linear dependence of the $n_{eff}$ on both the $f$ and $k$). In effect, the THz time pulse ($c\Delta t$) depends on the height [91] of this set of tablets, taking reference from Eq. (15). This linear dependence of the $c\Delta t$ on the height with an additional ‘anchor’ points is illustrated in Fig. 6.1. This additional ‘anchor’ point comes from theory. From Eq. (15), when the height of the tablet is zero, its equivalent THz pulse delay will also become zero and thus, the plot of the data will pass through the origin as it is demonstrated in Fig. 6.1.

![Graph showing linear dependence of $c\Delta t$ as a function of $H$ for set $A$ tablets. A slope (m) of 0.536 is obtained.](image)

**Fig. 6.1:** A linear dependence of $c\Delta t$ as a function of $H$ for set $A$ tablets. A slope (m) of 0.536 is obtained.
By rearranging Eq. (15), one can get

\[ c\Delta t = (n_{eff} - 1)H, \] (17)

where \( n_{eff} \) is the effective refractive index of the tablet. A plot of \( c\Delta t \) as a function of \( H \) will have \((n_{eff} - 1)\) as its slope. Such a plot is presented in Fig. 6.1 with a slope of 0.536. The linear best fit of the data for set \( A \) can be used as a calibration line. Equating

\[ n_{eff} - 1 = 0.536, \] (18)

the estimated value of \( n_{eff} \) was found to be 1.536, which is consistent with the average of the \( n_{eff} \) recorded in Table 1, with a difference in the order of \( 10^{-3} \). Thus, by keeping both the \( f \) and API mass fraction constant and varying only the height, one can get information about the effective refractive index. This is interesting since tablet makers may set an optimal height for a batch of tablet and hence one can use this idea to get the \( f \) (due to the linear correlation between the effective refractive index and the porosity) of such batch of tablets or vice versa [91]. In order to test the validity of this argument, an optimal height (~3 mm) and a corresponding optimal \( c\Delta t \) for set \( B \) was used, as illustrated with a horizontal dashed line in Fig. 6.2. The value of the optimal \( c\Delta t \) was found to be 1.609 mm.
Fig. 6.2: Variation of $c\Delta t$ as a function of $H$ for set A tablets with a slope (m) of 0.536. The dashed line indicates the optimal points. Additional data points for set B tablets are also plotted. A value of $\sim3$ mm is used as an optimal point for the height. Points (2), (3), (4) and (5) which have deviated from the calibration line is due to their different porosities.

The data of set B with almost constant $H$ are also plotted in Fig. 6.2. If one assumes that the optimal height of all the tablets in this set should be 3 mm and their corresponding $c\Delta t$ range being $1.609 \pm 0.03$ mm, then samples (2), (3), (4) and (5) in Fig. 6.2 have deviated from the optimal line while sample (1) seems to be closer to the optimal point. This deviation can be attributed to the differences in $f$ of these samples in the batch.

Hence, with a priori known height, one can get information about the variation of the pulse delay which is due to the porosity of the tablets or vice versa. The application of this demonstration is obvious; tablet makers may have the option of keeping a tablet parameter such as $f$ or $k$ constant and then check the effect of the other parameter such as $H$ on the tableting process or vice versa. In addition, this demonstration can nondestructively be used in checking the presence or otherwise of...
an unacceptable height within a batch of tablets. For instance, if the aim is to have constant $f$ for a batch of tablets, then other samples that may fall outside the calibration line (due to height variations) may easily be detected and removed from the batch. Alternatively, if the aim is to get a uniform height for all the tablets, then such variations that may arise in the plot are as a result of the differences in the porosities of such samples.

The knowledge of the variation of the height is crucial during post-tableting processes such as packaging. Tablets with the same height may be able to be placed in the same blister packs [91]. For tablets that over- or under-fill the spaces in the blister packs, one can conclude on the possible disparities in their heights.

Further, the variation of the $n_{\text{eff}}$ with porosity by considering set $B$ which has a constant API mass fraction, $k$ but varying porosity, $f$ is discussed. Similarly, Eq. (17) was used in calculating the $n_{\text{eff}}$ values and an illustration of the variation of the $n_{\text{eff}}$ with $f$ is shown in Fig. 6. 3. With a known height and THz time pulse traversing through this samples ($\Delta t$), the $n_{\text{eff}}$ for this batch of tablets were calculated. The values for the effective refractive index are tabulated in Table 2.
Fig. 6. 3: Linear correlation between the effective refractive index and the porosity for set B tablets and the extrapolation of the refractive index at zero porosity of MCC, \( n(0)_{MCC} \) for the set of tablets with constant API mass fraction but varying porosity. The extrapolated \( n(0)_{MCC} \) is 1.844. The slope \( m \) of the figure is -0.009.

In Fig. 6. 3, the linear correlation between the \( n_{eff} \) and \( f \) is clearly manifested. Thus, it is possible to use this linear correlation to estimate the refractive index of MCC at a constant \( k \) (\( n_{MCC} \)) or the refractive index at zero porosity, \( n(0) \), similar to such an extrapolation utilized in [90, 106]. Since this thesis deals with a three-phase system (that is MCC + air + API), the refractive index at zero porosity means that the tablet has now been reduced to only 2 inclusions (MCC and API). In other words, if porosity is zero percent at \( n(0) \), then the tablet contains purely MCC and API only. The \( k \) values for this set of tablets were kept at a constant value (ca. 10 wt%), therefore, the refractive index at zero porosity, \( n(0) \) for the MCC is presented as the refractive index at zero porosity of MCC at a constant \( k = 10 \) wt% as labelled in Fig. 6. 3. To arrive at the refractive index at zero porosity, the porosity was plotted in the range of 0 % - 100 %. The numerical value obtained for the \( n(0)_{MCC} \) is 1.844.

This further extrapolation is critical in evaluating the upper and lower limit of the refractive index (and hence the porosity) of tablets with a constant API mass fraction. For instance, in Fig. 6. 3, it is obvious that the maximum refractive index for such tablets with constant API is 1.844 while the minimum is \(~1.000\). Thus, for a very porous tablet (100 % porous), that is air, its refractive index is \(~1.000\) whereas for tablets with only MCC (and constant API) as inclusions, its refractive index is \(~1.844\). In effect, the more a tablet becomes porous, the lesser its refractive index becomes and vice versa for this set of tablets. This argument further augments the linearity between the effective refractive index and porosity of pharmaceutical tablets [20]. In the tablet manufacturing process, porosity is a critical quality attribute (CQA) and hence this information may be vital in setting the required porosity so as to enhance the easy dissolution of pharmaceutical tablets.

As an example, if the target for the tablet manufacturer is a 60 % porous tablet, then its corresponding effective refractive index can be extrapolated from Fig. 6. 3. The corresponding effective refractive index for a 60 % and 10 % porous tablets as targets are illustrated in Fig. 6. 4. The values extrapolated are respectively 1.316 and 1.756 as labeled as \( a \) and \( b \) in Fig. 6. 4.
Fig. 6.4: Extrapolation of the effective refractive index of a 60 % and 10 % porous tablets as targets during the tablet manufacturing process. The corresponding effective refractive indices are 1.316 and 1.756 for the 60 % and 10 % targets respectively.

In order to verify the possible linearity or otherwise between the effective refractive index and the API mass fraction, $k$, set $C$ was used in making such analysis. This set consists of a constant porosity but varies in its API mass fraction. The range of variation of $k$ is between 0 - 15 wt %. The variation of the effective refractive index as a function of the API mass fraction is shown in Fig. 6.5.
Almost all the 8 samples in set C exhibit the linearity between the effective refractive index and the API mass fraction as seen in Fig. 6.5. The negative slope (m = -0.002) clearly indicates the effect of an increasing API mass fraction on the effective refractive index of the tablet. That is, at a higher API mass fraction, the effective refractive index becomes smaller and vice versa for this set of tablets. Hence, one can use this figure in extrapolating the effective refractive index for tablets with only API (100 wt%). In addition, the effective refractive index of tablets without any API or tablets with only MCC (0 wt%) can also be estimated. Such an estimation is illustrated in Fig. 6.6, where the API mass fraction, k has been extended to 100 wt %. 

**Fig. 6.5:** Linear correlation between API mass fraction, k and effective refractive index, $n_{eff}$ of set C tablets.
Fig. 6.6: Extrapolation of the effective refractive index for tablets which contain API + air only, MCC + air only and a 50 % API and MCC. The vertical and horizontal dotted lines represent the estimate for the 50 % mixture of both API and MCC. The respective effective refractive indices were found to be 1.392, 1.542 and 1.467 for API + air, MCC + air and a 50 % mixture of API and MCC. The corresponding $n_{\text{eff}}$ for set $A$ which contains a constant 10 wt % API is also extrapolated with a horizontal dash-dot.

Since set $C$ consists of tablets with a constant $f$ (36 %), $n_{\text{API + air}}$ and $n_{\text{MCC + air}}$ shown in Fig. 6.6 are the refractive index of API only and MCC only at $f$ = 36 %. Similar extrapolation techniques are employed to extract the refractive index at zero porosity for MCC, $n(0)_{\text{MCC}}$ and API, $n(0)_{\text{API}}$ for this same set of tablets. Such an extrapolation which yielded 1.850 and 1.636 for the $n(0)_{\text{MCC}}$ and $n(0)_{\text{API}}$ respectively, is illustrated in Fig. 6.7.
Fig. 6.7. An illustration of the use of the linear extrapolation technique in the estimation of the zero-porosity refractive indices of MCC, \( n(0)_{\text{MCC}} \) and API, \( n(0)_{\text{API}} \) for set C tablets. Also included are the refractive indices of both MCC and API at \( f = 36\% \).

The linear correlation between the effective refractive index and the porosity has been established in this study and other studies as well [4, 5, 6, 92, 108-110]. Thus, the corresponding effective refractive index of a 36 % porous tablet can be estimated from Fig. 6.4. Then, the \( k \) value of the estimated effective refractive index from Fig. 6.4 can be extrapolated in Fig. 6.6. Alternatively, for a tablet set with a known \( k \), one can estimate its \( n_{\text{eff}} \) value. As an example, let’s take tablet set A which contains a constant API mass fraction of 10 wt % and extrapolate its \( n_{\text{eff}} \) value using our calibration line in Fig. 6.6. The value for this estimate is 1.527 and it is clearly shown in Fig. 6.6. Coincidentally, the average of the effective refractive indices for the four samples presented in Table 1 is 1.534. The difference between the effective refractive index estimated using the calibration line and the average effective refractive indices for the four samples reported in Table 1 is in the order of \( 10^{-3} \). Moreover, the effective refractive index difference between the samples in Table 1 is also in the order of \( 10^{-3} \).
Hence, the accuracy of the calibration line in Fig. 6. 6 has been tested. Herein, the accuracy of the calibration line in Fig. 6. 6 has been confirmed by confirming the average effective refractive indices for set $A$ and the order of differences correlate well.

To further validate the linear correlation between the tablet parameters in this study, that is porosity $f$, API mass fraction $k$, height, $H$ and effective refractive index, $n_{\text{eff}}$, sets of tablets in which all these parameters have been varied are discussed. This set is labeled as set $D$. First, the linear correlation between the $n_{\text{eff}}$ and $f$ for this set of tablets is checked. Figure 6. 8 illustrates the effect of changing the porosity on the effective refractive index for this set of tablets.

![Fig. 6. 8: The linear correlation between the effective refractive index and porosity for a set of tablets in which the porosity, height, API mass fraction and effective refractive index have been varied. The extrapolated refractive index of MCC, $n_{\text{MCC}}$ is 1.850. The blue dash line represents $n_{\text{eff}}$ at $f = 10 \%$. The $k$ value of 10 wt% used in this figure is the average of the $k$-values presented in Table 4.](image)

The linear correlation between the effective refractive index and the porosity is obvious even for sets of tablets with varying $k$, $f$, $n_{\text{eff}}$ and $H$ as depicted in Fig. 6. 8. The refractive index of MCC, $n_{\text{MCC}}$ at
$k=10$ wt% was estimated to be 1.850. However, the extrapolated $n_{MCC}$ in the case of set $B$ at $k=10$ wt% was found to be 1.844 (see Fig. 6. 3). The comparison between the extrapolated effective refractive indices of MCC, $n_{MCC}$ in sets $B$ and $D$ is possible because the $k$ value in the case of set $B$ was constant (10 wt%) while the average of the $k$ values in set $D$ was also found to be 10 wt%. A difference of value between $n_{MCC}$ in sets $B$ and $D$ in the order of $\sim 10^{-3}$ was obtained. Perhaps, this difference may be attributed to the variation of the porosity of the tablets. In set $B$, the porosity was varied between 36 % - 46 % and this resulted in an $n_{MCC} = 1.844$ whereas in set $D$, the porosity was varied between 28 % - 50 %, producing $n_{MCC} = 1.850$. This further augments the effect of porosity on the effective refractive index. In addition, measurement errors associated with this work might have contributed to this refractive index difference.

In a similar manner, the linear correlation between the effective refractive index and the API mass fraction for this same set of tablets is presented. This effect is shown in Fig. 6. 9.

![Fig. 6. 9: The linear correlation between the effective refractive index and the API mass fraction for set $D$ tablets in which all parameters have been varied.](image-url)
The linear relation between the effective refractive index and the API mass fraction is still valid for a set of tablets in which all three parameters have been varied (that is, $f$, $k$, and $H$). However, comparing the slopes for sets $D$ and $C$, it can be observed that the slope of set $D$ (see Fig. 6.9 with $m = -0.101$) is greater than that of set $C$ (see Fig. 6.5 with $m = -0.002$). Perhaps, the greater slope observed in the case of set $D$ is due to the effect of the individual parameters on the effective refractive index.

Furthermore, comparing Fig. 6.3 ($m = -0.009$) with Fig. 6.5 ($m = -0.002$), one can observe the effect that both $f$ and $k$ have on the $n_{\text{eff}}$. The magnitude of the slope in Fig. 6.3 is bigger than that in Fig. 6.5. It can then, generally, be concluded that the figure with a greater magnitude in terms of the slope has a greater effect on the effective refractive index than the other. Thus, of the two parameters; $f$ and $k$, the porosity has a dominant effect on the effective refractive index than the API mass fraction.

It is worth highlighting that, part of the results and discussions of this thesis including the variation of the effective refractive index with the API mass fraction and the porosity, and the non-destructive determination of the presence or absence of height variations within a batch of tablet constitute a manuscript which has been submitted for review and it is hereby referenced as [91].
CHAPTER VII

CONCLUSION AND FUTURE WORK

This thesis was aimed to study the linear correlation between tablet parameters; porosity, $f$, API mass fraction, $k$, height, $H$ and effective refractive index, $n_{\text{eff}}$ for a three-phase system (that is MCC + air + API) by using four real sets of pharmaceutical tablets compressed with indomethacin as an active pharmaceutical ingredient. The sets of tablets were labeled as $A$, $B$, $C$ and $D$ and each set consisted of 4-8 samples. For each sample number, about 5 tablets were compressed and the data of the average values for each sample number is presented. At least one of the three parameters were varied in each of the sets of tablets. It is worth noting that the works of Bawuah et al. [4], Juuti et al. [5] and Ervasti et al. [6] have previously validated the linear correlation between the effective refractive index and the porosity for a pharmaceutical tablet. However, their work was limited to only a two-phase system (that is MCC + air). Hence, this is a continuation of their work in predicting the validity for the linear correlation between the effective refractive index and the porosity for sets of pharmaceutical tablets which have been compressed with an active pharmaceutical ingredient (API).

In addition, this work also sought to find the linear correlation between the effective refractive index and the API mass fraction and the effective refractive index and the height of the four sets of pharmaceutical tablets which have been compressed with an active pharmaceutical ingredient (API). Thus, the present study uses a three-phase system in further validating the linear correlation that exists between the effective refractive index and other tablet parameters such as height, porosity and API mass fraction.

Obviously, there is still a linear correlation between the effective refractive index and the porosity, effective refractive index and the API mass fraction, even for a set of tablets compressed with an active pharmaceutical ingredient. There was no effect of the variation of the height on the effective refractive index. However, the height variation presented an estimate on the porosity of pharmaceutical tablets. This is useful in setting an optimal height for a batch of tablets and then the porosity of such batch of tablets could be obtained or setting an optimal porosity in order to estimate the height of such tablets. This idea may also be paramount in checking post-compressional problems associated with the manufacturing of tablets since a change in height due to mechanical relaxations will have an effect on the porosity of the tablet and its dissolution.
Moreover, the height variations can be used to nondestructively detect the presence or otherwise of an unacceptable height variation within a batch of tablets. Such detections may aid in post-tableting activities such as packaging.

Of the two parameters, that is porosity and API mass fraction, it was observed that the porosity had a dominant effect on the effective refractive index than the API mass fraction.

The promising outcome of this study will go a long way in providing non-contact, real-time, rapid, non-destructive, and cost-effective measurement techniques for critical quality attributes of pharmaceutical tablets in the pharmaceutical sciences.

Despite the promising outcome of this study, it is, however, limited to only flat-faced tablets. In the pharmaceutical sciences, curved tablets exist as well. Hence, this work can be extended to cover curved-surface tablets as well. This will be the basis and motivation for future studies. Another likely future outlook of this work is to quantitatively measure the effect of the effective refractive index on the porosity and API mass fraction for both a flat-faced and curved-surface tablet as well.
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