

NON-DESTRUCTIVE SYSTEMS AND METHODS FOR IDENTIFICATION OF PACKAGED MEDICINE

PRIORITY CLAIM

[0001] This application claims priority from Singapore Patent Application No. 10201707172U filed on 04 September 2017.

TECHNICAL FIELD

[0002] The present invention generally relates to sensors and sensing methods, and more particularly relates to systems and methods for non-destructive identification of packaged tablet, capsule and liquid medicine.

BACKGROUND OF THE DISCLOSURE

[0003] As medicines in pill and liquid form proliferate, there is a need for quality control through final batch inspection to batch quality check the packaged product. Previously, the pharmaceutical industry has manufactured finished products and then used laboratory analysis to verify their quality. The introduction of process analytical technology (PAT) provides a framework to obtain real-time information about drugs through inspection on the production line. Conventional techniques for such inspection can be categorized into near-infrared (NIR) spectroscopy, Raman spectroscopy and imaging, and mid-infrared spectroscopy with the use of chemometric techniques to identify and quantify the final product.

[0004] Optical techniques can probe the individual atomic bonds within a molecule. Oscillations of these atomic bonds generate discrete vibrational modes which characterize the material being probed. Traditionally, mid-infrared Fourier transform

or Raman spectroscopic techniques have been used for such characterization. However, Raman spectroscopy can create serious problems as the laser excitation used in Raman spectroscopy can induce a phase change or initiate a photochemical reaction in samples being interrogated, and fluorescence from the sample may swamp any Raman signal. More recently, there has been increased use of NIR spectroscopy; however, NIR spectroscopy also presents problems in that the spectra obtained will consist of many combinations and overtone bands of fundamental vibrations observed in the mid-infrared, thereby making analysis difficult.

[0005] The science of chemometrics can bring quantitative technology to manufacturing for qualitative and quantitative analysis of packaged products. Chemometrics combines chemistry and statistics of large datasets to design the best experimental procedures and provide maximum chemical information from experimental data. However, the technology is complex and requires considerable use of computers and software to perform the necessary computations.

[0006] Thus, what is needed is methods and systems for non-invasive identification of medicine within its packaging which provide reliable and consistent results and which is compatible with use during manufacturing and final batch inspection. Furthermore, other desirable features and characteristics will become apparent from the subsequent detailed description and the appended claims, taken in conjunction with the accompanying drawings and this background of the disclosure.

SUMMARY

[0007] According to at least one aspect of the present embodiments, a non-destructive system for packaged tablet, capsule and liquid medicine identification is provided. The system includes a femtosecond laser source, a THz transmitter, an

optical system, a THz receiver and a signal processing system. The femtosecond laser source generates a terahertz (THz) signal and the THz transmitter is coupled to the femtosecond laser source for emitting a THz radiation in response to the THz signal. The optical system includes an optical path and is arranged with respect to the THz transmitter to focus the THz radiation onto a sample placed in the optical path to illuminate the sample with the THz radiation, the sample including packaged tablet, capsule or liquid medicine. The optical system also includes a digital optical phase conjugation system configured to defocus the THz radiation to a sub-interface of packaging of the packaged tablet, capsule or liquid medicine while THz sampling of the sample to obtain information about the packaged tablet, capsule or liquid medicine. The THz receiver is coupled to the optical system and receives the THz radiation reflected from the sample. The signal processing system is coupled to the THz receiver to identify a type of medicine within the packaged tablet, capsule or liquid medicine in response to the THz radiation reflected from the sample. The signal processing system includes database storage means and processing means. The database storage means stores a database of THz reflectance spectra information for a plurality of medicines. The processing means is coupled to the database storage means and determines the type of the medicine within the packaged tablet, capsule or liquid medicine in response to the database of THz reflectance spectra information for the plurality of medicines.

[0008] According to another aspect of the present embodiments, a method for non-destructive packaged tablet, capsule and liquid medicine identification is provided. The method includes measuring THz radiation reflected from a surface of a sample of packaged tablet, capsule or liquid medicine and shifting a focal point of the THz radiation from the surface of the sample through the packaging until the focal point

focuses the THz radiation on a container/medicine interface of the sample of packaged tablet, capsule or liquid medicine. The method also includes measuring THz radiation reflected from the container/medicine interface of the sample of packaged tablet, capsule or liquid medicine, calculating an absorption spectra of the measured THz radiation, and auto-identifying by a processing device in response to the absorption spectra of the measured THz radiation a type of medicine within the sample of packaged tablet, capsule or liquid medicine in response to cluster analysis to group the type of medicine within the sample of packaged tablet, capsule or liquid medicine with respect to a database of THz reflectance spectra information for a plurality of medicines.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The accompanying figures, where like reference numerals refer to identical or functionally similar elements throughout the separate views and which together with the detailed description below are incorporated in and form part of the specification, serve to illustrate various embodiments and to explain various principles and advantages in accordance with present embodiments.

[0010] FIG. 1 depicts a block diagram of a system for non-destructive tablet, capsule and liquid medicine identification in accordance with a present embodiment.

[0011] FIG. 2, comprising FIGs. 2A and 2B depicts a method for non-destructive tablet, capsule and liquid medicine identification in accordance with the present embodiment, wherein FIG. 2A is a flow chart of the method for non-destructive capsule and liquid medicine identification and FIG. 2B is a diagram depicting defocusing to obtain a THz reflection signal from a subsurface of a sample.

[0012] FIG. 3 depicts a block diagram of THz time domain system for non-destructive capsule and liquid medicine identification in accordance with a variation of the present embodiment.

[0013] FIG. 4 depicts a photograph of various capsule medicine packages.

[0014] FIG. 5, comprising FIGs. 5A to 5E, depicts graphs of THz frequency domain spectra of various capsule medicine packages obtained in accordance with the present embodiment from capsule forms of the medicines in the capsule medicine packaging of FIG. 4, wherein FIG. 5A is a graph of a THz frequency domain spectra of a capsule medicine package of Lovastatin, FIG. 5B is a graph of a THz frequency domain spectra of a capsule medicine package of Neuromethyn, FIG. 5C is a graph of a THz frequency domain spectra of a capsule medicine package of Calcigard, FIG. 5D is a graph of a THz frequency domain spectra of a capsule medicine package of Moxilen, and FIG. 5E is a graph of a THz frequency domain spectra of a capsule medicine package of Amlodipine.

[0015] FIG. 6, comprising FIGs. 6A to 6C, depicts graphs of THz frequency domain spectra of various medicines obtained in accordance with the present embodiment from capsule forms of the medicines in capsule medicine packaging (as pictured in FIG. 4) and not in capsule medicine packaging, wherein FIG. 6A is a graph of a THz frequency domain spectra of a capsule of Lovastatin with and without packaging, FIG. 6B is a graph of a THz frequency domain spectra of a capsule of Calcigard with and without packaging, and FIG. 6C is a graph of a THz frequency domain spectra of a capsule of Neromet with and without packaging.

[0016] FIG. 7 depicts a photograph of various liquid medicine packages.

[0017] FIG. 8, comprising FIGs. 8A to 8D, depicts graphs of THz frequency domain spectra of various liquid medicine packages obtained in accordance with the

present embodiment from liquid forms of the medicines in the liquid medicine packaging of FIG. 7, wherein FIG. 8A is a graph of a THz frequency domain spectra of liquid medicine packaging of vitamin B, FIG. 8B is a graph of a THz frequency domain spectra of liquid medicine packaging of ethicholine, FIG. 8C is a graph of a THz frequency domain spectra of liquid medicine packaging of adrenaline, and FIG. 5D is a graph of a THz frequency domain spectra of liquid medicine packaging of amiodarone.

[0018] FIG. 9 depicts a graph of six overlapping THz frequency domain spectra of a sample of a packaged 1mg tablet of Warfarin sodium in accordance with the present embodiments where three spectra are the package in a first orientation and the other three spectra are the package in a second orientation opposite from the first orientation.

[0019] FIG. 10, comprising FIGs. 10A to 10F, depicts graphs of THz spectra in accordance with the present embodiments, wherein FIG. 10A is a graph of a THz frequency domain spectra of a packaged 2mg tablet of Trihexyphenidyl (Benzhexol), FIG. 10B is a graph of a THz frequency domain spectra of a packaged 7.5mg tablet of Sennosides (SENNA), FIG. 10C is a graph of a THz frequency domain spectra of a packaged 50mg tablet of Atenolol, FIG. 10D is a graph of a THz frequency domain spectra of a packaged 625mg tablet of Calcium Carbonate, FIG. 10E is a graph of a THz frequency domain spectra of a packaged 300mg tablet of Allopurinol 300mg tablet, and FIG. 10F is a graph of a THz frequency domain spectra of a packaged 200mg tablet of Aciclovir.

[0020] FIG. 11 depicts a graph of six overlapping THz frequency domain spectra of a packaged medicine sample including Tranexamic Acid and Allopurinol in accordance with the present embodiments.

[0021] FIG. 12, comprising FIGs. 12A and 12B, depicts a graph of four overlapping THz frequency domain spectra of a packaged medicine sample including Calcium Carbonate, Sennosides, Atenolol and Aciclovir in accordance with the present embodiments, wherein FIG. 12A depicts a graph of the four overlapping THz frequency domain spectra covering the range of 0.0-1.7 THz and FIG. 12B depicts a magnified graph of the four overlapping THz frequency domain spectra in the middle THz range of 1.0-1.4 THz.

[0022] FIG. 13 depicts a graph of two overlapping THz frequency domain spectra of two different concentrations of Lorazepam in accordance with the present embodiments.

[0023] And FIG. 14, comprising FIGs. 14A and 14B, depicts packaged medicine samples of a 10mg tablet of Coveram at various stages of decomposition under ultraviolet light, wherein FIG. 14A depicts packaged 10mg tablets of Coveram exposed to 325nm ultraviolet radiation for (a) 5 minutes, (b) 10 minutes, (c) 15 minutes and (d) 20 minutes and FIG. 14B depicts a graph of four overlapping THz frequency domain spectra of the four stages of decomposition of the packaged 10mg tablets of Coveram in accordance with the present embodiments.

[0024] Skilled artisans will appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been depicted to scale.

DETAILED DESCRIPTION

[0025] The following detailed description is merely exemplary in nature and is not intended to limit the invention or the application and uses of the invention. Furthermore, there is no intention to be bound by any theory presented in the preceding background of the invention or the following detailed description. It is the

intent of the present embodiment to present a rapid, non-destructive, and non-contact technology for tablet, capsule and liquid medicine identification. Embodiments of systems and methods of the present technology operate in the THz range in the electromagnetic spectrum which lies between microwave and infrared frequencies and generally includes frequencies ranging from 100 GHz to 10 THz. In accordance with present embodiments, medication with irregular shapes and/or irregular packaging can be accurately and quickly identified providing systems and methods which can be widely utilized by medication manufacturers, hospitals, care- giving homes and similar institutions and companies to provide improved human health and wellness. For example, by facilitating medication safety and medication adherence, patients face less risk of being mis-medicated or over-medicated. In addition, both caregivers and consumers will be able to improve patient safety and family caregivers will face less stress as the present technology includes systems and methods which support such parties in ensuring safe medication for patients for whom they are caring. Further, consumers will have higher confidence in medication (and supplements) that are properly registered before they are released into the markets. Moreover, the present technology can be extended to food industries to provide system and methods for food inspection.

[0026] In accordance with present embodiments, terahertz pulsed spectroscopy (TPS), a new technique having much relevance to the process analytical technology (PAT) initiative, is used for safe, non-destructive tablet, capsule and liquid medicine identification. Terahertz (THz) radiation is electromagnetic radiation lying between the microwave and the infrared ranges of the spectrum (usually in the frequency range of 0.1–10 THz). Although this frequency band is present in our everyday life, it has remained unexplored until recently due to the lack of efficient and compact THz

sources and detectors. Major advances in both optical and microwave technologies, the former down converting higher frequencies and the latter encroaching up from the GHz domain, have led to further investigation of innumerable physical processes undergone by matter exposed to terahertz radiation. A multitude of organic compounds and simple molecules exhibit vibrational and rotational transitions under exposure to terahertz radiation causing phonon resonance in crystalline structures and bond vibrations in general solids and liquids.

[0027] Systems and methods for non-destructive tablet, capsule and liquid medicine identification in accordance with a present embodiment use a terahertz time-domain spectroscopy and/or a designed terahertz portable system for non-invasively measuring the composition for the tablet, capsule and liquid medicine while packaged. One exemplary system which provides tablet, capsule and liquid medicine identification includes a femtosecond laser source, a THz transmitter, an optical system, a THz receiver and a signal processing system. The femtosecond laser source generates femtosecond pulses and the THz transmitter is coupled to the femtosecond laser source for generating and emitting terahertz (THz) radiation. The optical system includes an optical path and is arranged with respect to the THz transmitter and a lens to focus the THz radiation onto a sample placed in the optical path to illuminate the sample with the THz radiation, the sample comprising packaged tablet, capsule or liquid medicine. The optical system also includes a digital optical phase conjugation system configured to defocus the THz radiation to a sub-interface of the packaged tablet, capsule or liquid medicine while THz sampling of the sample to obtain information about the packaged capsule or liquid medicine. The THz receiver is coupled to the optical system and receives the THz radiation reflected from the sample. The signal processing system is coupled to the THz receiver to identify a

type of medicine within the packaged tablet, capsule or liquid medicine in response to the THz radiation reflected from the sample. The signal processing system includes database storage means and processing means. The database storage means stores a database of THz reflectance spectra information for a plurality of medicines. The processing means is coupled to the database storage means and determines the type of the tablet, capsule or liquid medicine within its package in response to the database of THz reflectance spectra information for the plurality of medicines.

[0028] The sample may include a tablet medicine or a capsule medicine in, for example, an aluminium foil packaging. The optical system may include a lens, and the THz receiver receives a return THz radiation reflected from the sample, the return radiation comprising THz radiation focused through the lens. The optical system may also include a first pair of off-axis parabolic mirrors coupled to the THz transmitter to focus the THz radiation onto the sample and a second pair of off-axis parabolic mirrors coupled to the THz receiver to pick up the THz radiation reflected from the sample to provide the THz radiation reflected from the sample to the THz receiver. And the optical system may include an open space optical system or a fibre connected optical system.

[0029] The digital optical phase conjugation system may be configured to a THz time domain system sample while defocusing the THz radiation to the sub-interface of the packaging of the packaged tablet, capsule and liquid medicine to obtain information about the packaged tablet, capsule and liquid medicine. The processing means may determine the type of the tablet, capsule, tablet or liquid medicine within the packaging further in response to auto correction of the THz radiation reflected from the sample in response to the packaging. In addition, the processing means, in response to determining the database of THz reflectance spectra information does not

include the THz radiation reflectance spectra of the sample, may use cluster analysis to identify the medicine within the packaged tablet, capsule and liquid medicine and assign the THz radiation reflectance spectra of the sample to the database of THz reflectance spectra information. This can be done by cluster analysis of the THz reflectance spectra information corresponding to the THz radiation reflected from the sample in respect to THz reflectance spectra information of the database of THz reflectance spectra information.

[0030] Also, the processing means may determine any abnormal components within the packaged tablet, capsule and liquid medicine in addition to the type of the medicine within the packaged tablet, capsule and liquid medicine in response to the database of THz reflectance spectra information for the plurality of medicines. Finally, either or both of the THz transmitter and the THz receiver may include a THz antenna or a nonlinear crystal.

[0031] In accordance with present embodiments, the illumination system may include a THz generator head including a femtosecond laser and a nonlinear optical crystal. The optical system may include an illumination optical system configured to provide oblique-angle illumination of terahertz radiation of the sample of a packaged tablet, capsule or liquid medicine. The optical system may further include a pick-up optical system configured to provide return terahertz radiation. The illumination optical system may include a pair of off-axis parabolic mirrors and the pick-up optical system may also include a pair of off-axis parabolic mirrors. The detection system is configured to detect the return terahertz radiation within a frequency band of about 0.1 THz to about 10 THz.

[0032] A visible light source can serve as a stress trigger light and can be any wavelength of light in the visible range for the purpose of introducing elastic stress over the surface of the packaged tablet, capsule or liquid medicine.

[0033] The processing means of systems in accordance with present embodiments may include an algorithm for non-destructive packaged tablet, capsule or liquid medicine identification. In accordance with one aspect of the analysis, the THz detector picks up the THz signal difference between the packaged tablet, capsule or liquid medicine with and without light source stress measured by the THz detector.

[0034] The algorithm seeks to derive the tablet, capsule or liquid medicine identification parameters. More specifically, measurements on the elastic parameters of the packaged tablet, capsule or liquid medicine are based on a set of calibrated equations relating the THz signal difference between the packaged tablet, capsule or liquid medicine with and without stress. The calibrated equation may be modeled by means of data-fitting the THz signal difference against the actual tablet, capsule or liquid medicine elastic.

[0035] In yet another aspect of the analysis, the algorithm may seek to detect dubious cases associated with abnormal tablet, capsule or liquid medicine elastic or rigidity based on the THz signal differences of the packaged tablet, capsule or liquid medicine with and without stress. More precisely, the detection of abnormal elasticity is performed by evaluating whether the THz signal difference identity metrics as devised fall outside an acceptable range.

[0036] In accordance with another aspect of the present embodiments, methods for non-destructive tablet, capsule and liquid medicine identification may include measuring THz radiation reflected from a surface of packaging of a sample of packaged tablet, capsule or liquid medicine and shifting a focal point of the THz

radiation from the surface of the packaging through the packaging until the focal point focuses the THz radiation on a medicine/packaging interface of the sample of packaged tablet, capsule or liquid medicine. The methods may also include measuring THz radiation reflected from the medicine/packaging interface of the sample of packaged tablet, capsule or liquid medicine, calculating an absorption spectra of the measured reflected THz radiation, and auto-identifying by a processing device in response to the absorption spectra of the measured THz radiation a type of medicine within the packaged tablet, capsule or liquid medicine using cluster analysis to group the type of medicine within the packaged tablet, capsule or liquid medicine with respect to a database of THz reflectance spectra information for a plurality of medicines.

[0037] The methods may include before the auto identification step, the step of forming the database of THz reflectance spectra information for the plurality of medicines. In addition, calculating the absorption spectra of the measured THz radiation may include calculating the absorption spectra in response to Fast Fourier Transform of the measured THz radiation or may include calculating the absorption spectra in response to auto correction of the measured THz radiation in response to the packaging of the sample of the packaged tablet, capsule and liquid medicine. Further, the auto-identifying step may include auto-identifying by the processing device, in response to the absorption spectra of the measured THz radiation, the type of medicine within the packaged tablet, capsule and liquid medicine and any abnormal components within the packaged tablet, capsule and liquid medicine or may include auto-identifying the type of medicine within the packaged tablet, capsule and liquid medicine by a processing device in response to the absorption spectra of the

measured THz radiation a type of medicine within the packaged tablet, capsule and liquid medicine in response to cluster analysis and predetermined criterion.

[0038] Referring to FIG. 1, a block diagram 100 of a system for non-destructive tablet, capsule and liquid medicine identification in accordance with a present embodiment uses a THz time-domain (THz-TDS) system 102, a computer or other processing means 104 and an XYZ stage (105) to measure porosity of a sample based on a THz response with and without external perturbation.

[0039] The THz-TDS system 102 can be configured to reflect electromagnetic radiation 110 in THz range (i.e., THz radiation 110) from a THz transmitter or emitter 112 toward a surface of the sample 114 using a first lens 113 to focus the THz radiation 110 on the sample 114, receive the THz radiation 110 reflected from the sample 114 and focused onto a THz detector or receiver 116 by a second lens 115, and generate a signal 118 indicative of the received THz radiation 110 which is amplified and digitized by circuitry 120. The THz radiation 110 is generated by the THz transmitter 112 and pulsed in response to a signal from a femtosecond laser 122. The computer 104, which communicates with the THz-TDS system 102, can be configured to process the generated signal 118 and may further be configured for creating a visual imaging of the THz response from the sample 114. The XYZ stage 105 can be configured for holding the structure of the THz-TDS system 102, scanning the sample 114 and moving the THz focal point 124 from a surface of the packaging of the tablet, capsule and liquid medicine sample 114 to a surface of the tablet, capsule and liquid medicine within the packaging.

[0040] Referring to FIG. 2A, a flow chart 200 depicts an exemplary method for non-destructive tablet, capsule and liquid medicine identification in accordance with present embodiments. The method includes building up 202 a database of different

types of medicines as well as different types of containers and capsules. Next, a THZ signal is projected 204 onto a surface of a tablet, capsule or liquid medicine sample and the THZ signal is collected 206 to measure the tablet, capsule or liquid medicine. The THZ signal is then defocused 208 to the container medicine interface and the THZ signal is again collected to measure the tablet, capsule or liquid medicine a second time.

[0041] Referring to FIG. 2B, a diagram 250 depicts the defocusing step 208 in accordance with present embodiments. A THz focal point 252 is focused on a surface 254 of a target tablet, capsule or liquid medicine 256 in the sample 114 for the first measurement step 206. The THz radiation is defocused to provide a defocused focal point 258 at a container/medicine interface within the tablet, capsule or liquid medicine 256 for the second measurement step 208. Thus, it can be seen that, in accordance with the present embodiments, defocusing is a technique used to obtain the reflection signal from the subsurface of the sample 114 in order to avoid the direct reflection of the THz radiation 110. Normally the surface focusing (step 206) will be done first to obtain the highest THz radiation signal. Thereafter, a predetermined amount of focusing will shift focus to defocus a distance 260 into the subsurface of the tablet, capsule or liquid medicine 256. In this manner, the data collected from different samples shall be comparable.

[0042] Referring back to FIG. 2A, analysis of the signal 118 by the computer 104 is performed 210 using a novel algorithm as described above to identify the type of medicines and detect abnormal tablet, capsule or liquid medicine elastic extraction.

[0043] Referring to FIG. 3, a block diagram 300 depicts a THz-TDS system in accordance with present embodiments for reflectance mode examination of medicines as described hereinafter. All fifteen medicines examined were obtained from Einst

Technology Pte. Ltd, Singapore. Note that the side planar view of the XYZ stage 302 supports the sample 114. Note also that pairs of parabolic mirrors 304, 306 and 308, 310 are used to focus the THz radiation.

[0044] For examination of the fifteen medicines as described hereinafter the measurements were made under the following conditions. First, the spectrometer was purged with nitrogen gas in order to minimize the effects of water vapor which is highly absorbent in the THz range. Purging the spectrometer entails connecting a flexible plastic tube to a corresponding hole in the spectrometer and injecting nitrogen gas through the tube to displace air inside the spectrometer. Purging the spectrometer decreased the air to approximately two per cent humidity.

[0045] Second, a measure of the noise level was obtained by stopping the THz radiation with a metallic plate. As the incident radiation does not reach the detector, the measured signal only contains noise. Measuring the noise level allows determining the dynamic range of the device against frequency, i.e., the difference (in dB) between the intensity of the measured signal and the noise signal.

[0046] Third, pure high density polyethylene pellets are used as a reference upon which data of the samples are taken. This procedure suppresses any possible absorption features of the polyethylene used in the preparation of the samples.

[0047] Finally, ten measurements of each sample are undertaken. In each repetition, the sample pellet is extracted and reinserted in the sample holder. By averaging the spectra, systematic errors produced by wrong positioning, as well as present heterogeneities in the sample, are minimized.

Capsule Medicine Measurement

[0048] A total of five capsule samples were examined. FIG. 4 depicts a photograph 400 of the five of capsule medicine packages. In the photograph 400, the aluminum foil package side is shown. One of the packages (Amlodipine) is packed in aluminum foil on both sides. The other four packages are packed with one side being an aluminum foil package side and the other side being a plastic package side. For each sample, three positions are measured by THz radiation: the aluminum surface of the packaging, the capsule/medicine interface (i.e., the container/medicine interface) through the plastic package side, and deep focus on the capsule-medicine interfaces. All the measurements were done without opening the packages.

[0049] Referring to FIGs. 5A to 5E, graphs 500, 510, 520, 530, 540 depict THz frequency domain spectra of various medicines obtained in accordance with the present embodiments and the experimental method described above from the capsule forms of the medicines in the capsule medicine packaging of FIG. 4. FIG. 5A depicts a graph 500 of a THz frequency domain spectral of the capsule medicine Lovastatin. A curve 502 shows a measurement focused on the aluminum side, a curve 504 shows a measurement done by focusing on the plastic package side and capsule medicine interface. And a curve 506 shows a further deep focus in the medicine within the capsule. The graph 500 shows that when focusing on the interface of the capsule and the medicine through the plastic package side, the THz is already able to detect the medicine as shown by comparing the curve 504 to the curve 506.

[0050] FIG. 5B depicts a graph 510 of a THz frequency domain spectral of the capsule medicine Neuromethyn. A curve 512 shows a measurement focused on the aluminum side, a curve 514 shows a measurement done by focusing on the plastic package side and the capsule medicine interface. And a curve 516 shows a further deep focus in the medicine within the capsule. The graph 510 shows that when

focusing on the interface of the capsule and the medicine through the plastic package side, the THz is also already able to detect the capsule medicine Neuromethyn as shown by comparing the curve 514 to the curve 516.

[0051] FIG. 5C depicts a graph 520 of a THz frequency domain spectral of the capsule medicine Calcigard. A curve 522 shows a measurement focused on the aluminum side, a curve 524 shows a measurement done by focusing on the plastic package side and the capsule medicine interface. And a curve 526 shows a further deep focus in the medicine within the capsule. The graph 520 shows that when focusing on the interface of the capsule and the medicine through the plastic package side, the THz is also already able to detect the capsule medicine Calcigard as shown by comparing the curve 524 to the curve 526.

[0052] FIG. 5D depicts a graph 530 of a THz frequency domain spectral of the capsule medicine Moxilen. A curve 532 shows a measurement focused on the aluminum side, a curve 534 shows a measurement done by focusing on the plastic package side and the capsule medicine interface. And a curve 536 shows a further deep focus in the medicine within the capsule. The graph 530 shows that when focusing on the interface of the capsule and the medicine through the plastic package side, the THz is also already able to detect the capsule medicine Moxilen as shown by comparing the curve 534 to the curve 536.

[0053] FIG. 5E depicts a graph 540 of a THz frequency domain spectral of the capsule medicine Amlodipine. The packaging of the capsule medicine Amlodipine has aluminum foil on both sides. A curve 542 shows a measurement focused on the aluminum surface and a curve 544 shows a measurement done when trying to focus on the capsule medicine interface through the aluminum foil side. The graph 540

shows that when the packaging of the capsule medicine has aluminum foil on both sides, one is unable to obtain ideal results using reflection mode.

[0054] Next, the packages were opened up and the THz measurements were performed on the capsule, the results shown in FIG. 6. From the graphs 600, 610, 620 of FIGs. 6A, 6B and 6C, respectively, one can see that the measurements on the capsules without packaging tally with the defocused measurements on the capsules with packaging. Thus, it can be seen that the THz is able to penetrate into the package and focus on the capsule measurement and directly and non-destructively obtain the capsule medicine information.

[0055] FIG. 6A depicts the graph 600 of a THz frequency domain spectral of the capsule medicine Lovastatin where a curve 602 shows a measurement of the capsule medicine Lovastatin within packaging and a curve 604 shows a measurement of the capsule medicine Lovastatin without any packaging. FIG. 6B depicts the graph 610 of a THz frequency domain spectral of the capsule medicine Calcigard where a curve 612 shows a measurement of the capsule medicine Calcigard within packaging and a curve 614 shows a measurement of the capsule medicine Calcigard without any packaging. And FIG. 6C depicts the graph 620 of a THz frequency domain spectral of the capsule medicine Neromet where a curve 622 shows a measurement of the capsule medicine Neromet within packaging and a curve 624 shows a measurement of the capsule medicine Neromet without any packaging.

[0056] In summary, for THz detection of capsule medicine within its packaging, when the THz radiation is defocused into the capsule/medicine interface (208, FIG. 2A), one can directly obtain an accurate measurement of the capsule medicine in a non-destructive, non-invasive method for medicine detection and identification in accordance with present embodiments. Furthermore, by focusing the measurement on

the capsule medicine interface through plastic packaging (i.e., through the plastic package side of the packaged medicine), an accurate signal can advantageously be detected without opening the packaging. It should be noted that it has been determined that the shape of the capsule medicine may have some effect of the measurement results as determined from tablet measurements.

Liquid Medicine Measurement

[0057] A total of four bottles of liquid samples were examined with two positions examined for each bottle. FIG. 7 depicts a photograph 700 of the four liquid medicine bottles. The liquid medicines were measured by reflection mode as the liquid medicines cannot be measured by transmission mode due to the long light path through the bottles and the absorption is too strong of the liquid in the bottle is too strong to allow a signal to be detected in the transmission mode. All the measurements were done without opening the packages.

[0058] Referring to FIGs. 8A to 8D, graphs 800, 810, 820, 830 depict THz frequency domain spectra of various liquid medicines obtained in accordance with the present embodiments and the experimental method described above from the liquid forms of the medicines in the bottle packaging of FIG. 7. FIG. 8A depicts a graph 800 of a THz frequency domain spectral of the liquid medicine Vitamin B. A curve 802 shows a measurement focusing focus on the bottom of the bottle while a curve 804 shows a measurement defocused to the liquid-glass bottle interface. The curve 804 shows that detected signal from the interface is from the liquid medicine Vitamin. Although resonance curves appear at the interface, there is an obvious 1.41 THz peak which is most likely indicative of the Vitamin B2 dominance.

[0059] FIG. 8B depicts a graph 810 of a THz frequency domain spectral of the liquid medicine Ethicholine. A curve 812 shows a measurement focusing focus on the bottom of the bottle while a curve 814 shows a measurement defocused to the liquid-glass bottle interface. The curve 814 shows that detected signal from the interface is from the liquid medicine Ethicholine. Although resonance curves appear at the interface, there is an obvious 1.32 THz peak which is indicative of the liquid medicine Ethicholine.

[0060] FIG. 8C depicts a graph 820 of a THz frequency domain spectral of the liquid medicine Adrenaline. A curve 822 shows a measurement focusing focus on the bottom of the bottle while a curve 824 shows a measurement defocused to the liquid-glass bottle interface. The curve 824 shows that detected signal from the interface is from the liquid medicine Adrenaline. Although resonance curves appear at the interface, there are obvious 1.23 THz peak and a 2.48 THz peak which are indicative of the liquid medicine Adrenaline.

[0061] FIG. 8D depicts a graph 830 of a THz frequency domain spectral of the liquid medicine Amiodarone. A curve 832 shows a measurement focusing focus on the bottom of the bottle while a curve 834 shows a measurement defocused to the liquid-glass bottle interface. The curve 834 shows that detected signal from the interface is from the liquid medicine Amiodarone. Although resonance curves appear at the interface, there are obvious 0.88 THz peak, 1.43 THz peak and 1.92 THz peak which are indicative of the liquid medicine Amiodarone.

Tablet Medicine Measurement

[0062] From the experimentation, it was determined that the repeatability for testing the tablet, capsule and liquid medicines is quite good. For example, the packaged

tablet samples were tested on one side and then turned to the other side to repeat the test with the process repeated three times. Referring to FIG. 9, a graph 900 depicts a graph of six overlapping THz frequency domain spectra of a tablet sample of a packaged 1mg tablet of Warfarin sodium in accordance with the present embodiments where three spectra are the package in a first orientation and the other three spectra are the package in a second orientation opposite from the first orientation.

[0063] Among the more than sixty tablets measured using THz spectroscopy, there are about six samples which demonstrated very similar spectral response. They are: Sennosides 7.5mg tablet (SENNNA), Trihexyphenidyl 2mg tablet (Benzhexol), Atenolol 50mg tablet, Allopurinol 300mg tablet, Aciclovir 200mg tablet and Calcium Carbonate 625mg tablet

[0064] Referring to FIGs. 10A to 10F, graphs 1000, 1010, 1020, 1030, 1040, 1050 depict THz spectra in accordance with the present embodiments, the graph 1000 is a graph of a THz frequency domain spectra of a tablet medicine package of a 2mg tablet of Trihexyphenidyl (Benzhexol), the graph 1010 is a graph of a THz frequency domain spectra of a 7.5mg tablet of Sennosides (SENNNA), the graph 1020 is a graph of a THz frequency domain spectra of a 50mg tablet of Atenolol, the graph 1030 is a graph of a THz frequency domain spectra of a 625mg tablet of Calcium Carbonate, the graph 1040 is a graph of a THz frequency domain spectra of a 300mg tablet of Allopurinol 300mg tablet, and the graph 1040 is a graph of a THz frequency domain spectra of a 200mg tablet of Aciclovir.

[0065] FIG. 11 depicts a graph 1100 of six overlapping THz frequency domain spectra of a sample including six tablets in accordance with the present embodiments where the curve 1102 denotes Tranexamic Acid and the curve 1104 denotes Allopurinol. When the six curves are drawn together, it can be seen that Tranexamic

Acid 1102 and Allopurinol 1104 can be easily distinguished based on the position of their peaks.

[0066] For the other four types of medicines, examination of the middle frequency or higher frequency can reveal their detailed differences. Referring to FIG. 12A, a graph 1200 of four overlapping THz frequency domain spectra of a sample including tablets of Calcium Carbonate, Sennosides, Atenolol and Aciclovir obtained in accordance with the present embodiments depicts the four overlapping THz frequency domain spectra within the range of 0.0-1.7 THz. Referring to FIG. 12B, a magnified graph 1250 of the four overlapping THz frequency domain spectra in the middle THz range of 1.0-1.4 THz clearly shows the different peaks among the four spectra. With the further improvement of THz sources in the middle frequency ranges (till 4THz) and higher frequency ranges (till 10THz), detection can be more precise, sensitive and reliable.

[0067] Referring to FIG. 13, a graph 1300 of two overlapping THz frequency domain spectra of two different concentrations of Lorazepam tablets (0.5mg and 1.0mg) in accordance with the present embodiments shows that the medicine's fingerprint peak positions 1302 will remain the same with only a shift in the intensities to demonstrate the difference between the different medicine strength.

[0068] In regards to the sensitivity of the method in accordance with the present embodiments, FIGs. 14A and 14B depict samples of a 10mg tablet of Coveram at various stages of decomposition under ultraviolet light. FIG. 14A depicts a photograph 1400 of packaged 10mg tablets of Coveram exposed to 325nm ultraviolet radiation for (a) 5 minutes, (b) 10 minutes, (c) 15 minutes and (d) 20 minutes and FIG. 14B depicts a graph 1450 of four overlapping THz frequency domain spectra of the four stages of decomposition of the 10mg tablets of Coveram in accordance with the

present embodiments. The strong UV introduces compound decomposition and as the UV damage increases, some peaks in the middle THz range disappear while some new peaks are generated, demonstrating that the THz spectra system and method in accordance with present embodiments is able to pick up the compound changes in the packaged medicine.

[0069] Thus, it can be seen that the present embodiments provide methods and systems for non-invasive identification of medicine within its packaging which provide safe, reliable and consistent results and which is compatible with use during manufacturing and final batch inspection. In accordance with present embodiments, medication with irregular shapes and/or irregular packaging can be accurately and quickly identified providing systems and methods which can be widely utilized by medication manufacturers, hospitals, care- giving homes and similar institutions and companies to provide improved human health and wellness.

[0070] While exemplary embodiments have been presented in the foregoing detailed description of the present embodiments, it should be appreciated that a vast number of variations exist. It should further be appreciated that the exemplary embodiments are only examples, and are not intended to limit the scope, applicability, operation, or configuration of the invention in any way. Rather, the foregoing detailed description will provide those skilled in the art with a convenient road map for implementing exemplary embodiments of the invention, it being understood that various changes may be made in the function and arrangement of steps and method of operation described in the exemplary embodiments without departing from the scope of the invention as set forth in the appended claims.

CLAIMS

What is claimed is:

1. A non-destructive system for packaged tablet, capsule and liquid medicine identification, comprising:

a femtosecond laser source for generating a terahertz (THz) signal;

a THz transmitter coupled to the femtosecond laser source for emitting THz radiation in response to the THz signal;

an optical system comprising an optical path and arranged with respect to the THz transmitter to focus the THz radiation onto a sample placed in the optical path to illuminate the sample with the THz radiation, wherein the sample comprises packaged tablet, capsule or liquid medicine, and wherein the optical system comprises a digital optical phase conjugation system configured to defocus the THz radiation to a sub-interface of the packaged tablet, capsule or liquid medicine while THz sampling of the sample to obtain information about the packaged tablet, capsule or liquid medicine;

a THz receiver coupled to the optical system to receive the THz radiation reflected from the sample; and

a signal processing system coupled to the THz receiver to identify a type of medicine within the packaged tablet, capsule or liquid medicine in response to the THz radiation reflected from the sample, the signal processing system comprising database storage means for storing a database of THz reflectance spectra information for a plurality of medicines, wherein the signal processing system further comprises a processing means coupled to the database storage means for determining the type of the medicine within the packaged tablet, capsule or liquid medicine in response to the database of THz reflectance spectra information for the plurality of medicines.

2. The system in accordance with Claim 1 wherein the packaged tablet, capsule or liquid medicine comprises a tablet medicine.

3. The system in accordance with Claim 1 wherein the packaged tablet, capsule or liquid medicine comprises a capsule medicine.

4. The system in accordance with Claim 2 or 3 wherein the packaging of the tablet medicine or the capsule medicine comprises an aluminium foil package side and a plastic package side.

5. The system in accordance with Claim 1 wherein the packaged tablet, capsule or liquid medicine comprises liquid medicine and the packaging of the liquid medicine comprises a bottle.

6. The system in accordance with Claim 1 wherein the optical system comprises a lens, and wherein the THz receiver receives return radiation of the THz radiation reflected from the sample, the return radiation comprising THz radiation reflected through the lens.

7. The system in accordance with Claim 1 wherein the optical system comprises a first pair of off-axis parabolic mirrors coupled to the THz transmitter to focus the THz radiation onto the sample and a second pair of off-axis parabolic mirrors coupled to the THz receiver to pick up the THz radiation reflected from the sample to provide said THz radiation reflected from the sample to the THz receiver.

8. The system in accordance with Claim 1 wherein the optical system comprises an optical system selected from the group consisting of an open space optical system and a fibre connected optical system.

9. The system in accordance with Claim 1 wherein the digital optical phase conjugation system is configured to THz time domain system sampling of the sample while defocusing the THz radiation to the sub-interface of the packaged tablet, capsule or liquid medicine to obtain the information about the packaged tablet, capsule or liquid medicine.

10. The system in accordance with Claim 1 wherein the processing means determines the type of the medicine within the packaged tablet, capsule or liquid medicine further in response to auto correction of the THz radiation reflected from the sample in response to the packaging.

11. The system in accordance with Claim 1 wherein the processing means, in response to determining the database of THz reflectance spectra information for the plurality of medicines does not include THz reflectance spectra information corresponding to the THz radiation reflected from the sample, identifies the medicine within the packaged tablet, capsule or liquid medicine and assigns THz reflectance spectra information corresponding to the THz radiation reflected from the sample to the database of THz reflectance spectra information in response to cluster analysis of the THz reflectance spectra information corresponding to the THz radiation reflected

from the sample in respect to THz reflectance spectra information of the database of THz reflectance spectra information.

12. The system in accordance with Claim 1 wherein the processing means determines the type of the medicine within the packaged tablet, capsule or liquid medicine and any abnormal components within the packaged tablet, capsule or liquid medicine in response to the database of THz reflectance spectra information for the plurality of medicines.

13. The system in accordance with Claim 1 wherein either or both of the THz transmitter and the THz receiver comprise a THz antenna.

14. The system in accordance with Claim 1 wherein either or both of the THz transmitter and the THz receiver comprise a nonlinear crystal.

15. A method for non-destructive packaged tablet, capsule and liquid medicine identification comprising:

measuring THz radiation reflected from a surface of a sample of packaged tablet, capsule or liquid medicine;

shifting a focal point of the THz radiation from the surface of the sample through the packaging until the focal point focuses the THz radiation on a container/medicine interface of the sample of packaged tablet, capsule or liquid medicine;

measuring THz radiation reflected from the container/medicine interface of the sample of packaged tablet, capsule or liquid medicine;

calculating an absorption spectra of the measured THz radiation; and
auto-identifying by a processing device in response to the absorption spectra of the measured THz radiation a type of medicine within the sample of packaged tablet, capsule or liquid medicine in response to cluster analysis to group the type of medicine within the sample of packaged tablet, capsule or liquid medicine with respect to a database of THz reflectance spectra information for a plurality of medicines.

16. The method in accordance with Claim 15 further comprising before the auto identification step, the step of forming the database of THz reflectance spectra information for the plurality of medicines.

17. The method in accordance with Claim 15 wherein calculating the absorption spectra of the measured THz radiation comprises calculating the absorption spectra in response to Fast Fourier Transform of the measured THz radiation.

18. The method in accordance with Claim 15 wherein calculating the absorption spectra of the measured THz radiation comprises calculating the absorption spectra in response to auto correction of the measured THz radiation in response to the packaging of the sample of packaged tablet, capsule or liquid medicine.

19. The method in accordance with Claim 15 wherein the auto-identifying step comprises auto-identifying by the processing device in response to the absorption

spectra of the measured THz radiation the type of medicine within the sample of packaged tablet, capsule or liquid medicine and any abnormal components within the sample of packaged tablet, capsule or liquid medicine.

20. The method in accordance with Claim 15 wherein auto-identifying the type of medicine within the sample of packaged tablet, capsule or liquid medicine comprises auto-identifying the type of medicine within the sample of packaged tablet, capsule or liquid medicine by a processing device in response to the absorption spectra of the measured THz radiation a type of medicine within the sample of packaged tablet, capsule or liquid medicine in response to cluster analysis and predetermined criterion.