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Process analytical technology (PAT): Effects of instrumental and compositional variables on terahertz spectral data quality to characterize pharmaceutical materials and tablets

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Abstract

The aim of this study was to use terahertz spectroscopy to characterize pharmaceutical materials and tablets, and to understand the effects of measuring conditions and compositional variability on the data quality. Tests were performed on five formulation components (theophylline, lactose, starch, Avicel, magnesium stearate) and a series of tablets composed of various concentrations of theophylline and excipients. Transmission spectra of polyethylene (PE) disks derived from each of the samples were analyzed. Three factors (component loading, component chemistry, and disk drying time) were screened as critical factors associated with the magnitude and location of THz absorbance peaks. Applying the standard sample spectra divided by PE reference spectra ratio method revealed that, to a large extent, PE was responsible for the disk drying time dependence. Direct spectral feature analysis along with mass-transfer analysis of the disk drying process revealed THz absorption peak maxima of lactose (255 cm^{-1}) and water (54 and 210 cm^{-1}) which is also supported by literature values for the peak maxima assignment for water. Particle scattering due to specimen and PE was found to be also partially responsible for the observed spectral intensities. The importance of THz spectroscopy was demonstrated for characterization of pharmaceutical materials and tablet.
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Keywords: Process analytical technology (PAT); Terahertz spectroscopy; Measurement process; Crystalline materials; Amorphous state; Characterization; Mass-transfer analysis

1. Introduction

1.1. Regulatory relevance of pharmaceutical characterization

Pharmaceutical characterization is one critical aspect for a successful product and process development program, as it provides important physical, chemical, structural and property-related information of pharmaceutical components in formulated products. For both drug substances and drug products, there are pertinent regulations described in CFR 21§314.50(d)(1) *Chemistry, Manufacturing, and Controls section* to assure the identity, strength, quality, purity, and bioavailability of the drug product. However for the most part, more characterization emphasis has traditionally been put on active pharmaceutical ingredients (API) while less effort has focused on excipients, due perhaps to inadequate appreciation of the various roles excipients play in formulation and process. The gap between the CFR requirements and current industry practices in some cases may present potential risk to the public health in the event of introducing new excipient to a formulation during development (Baldrick, 2000) and unexpected appearance or disappearance of a crystalline form (Févotte, 2002). The scientific significance and regulatory relevance of pharmaceutical

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polymorphism characterization and pharmaceutical crystallization process control using process analytical technology (PAT) have been discussed in detail in the recent literature (Singhal and Curatolo, 2004; Yu et al., 2004; Wu and Hussain, 2005a; Wu et al., 2007a). Advanced process analyzers and spectroscopic techniques have been used for pharmaceutical applications (Roggo et al., 2005; Blanco and Alcalá, 2006; Eilertsen et al., 2000; Hausman et al., 2005) for probing molecular vibrational modes in the near- and mid-infrared regions of the electromagnetic spectrum for many years. However, studies using far-infrared or Terahertz (FIR or THz, 25–300 μm wavelength or 3–500 cm^{-1}) spectroscopic techniques had been limited due to the difficulty in accessing this low frequency range, especially below 50 cm^{-1}.

1.2. Terahertz spectroscopy and its pharmaceutical-related applications

Recently THz spectroscopy (Markelz et al., 2000) and THz time domain spectroscopy (THz-TDS) have received increasing interest for pharmaceutical polymorphism and crystallinity characterization (Haran et al., 1997; Taday et al., 2003; Walther et al., 2003; Strachan et al., 2004, 2005; Fitzgerald et al., 2005). It was demonstrated that THz-TDS is a useful technique for quantifying solid-state properties of pharmaceutical compounds. This is largely due to its unique capabilities of providing fundamental information that goes beyond the scope of other spectroscopic techniques. THz absorption spectra are directly related to the three-dimensional arrangement and low frequency motions of all the atoms in a molecule and it is also sensitive to the molecule's interaction with its environment, as demonstrated from THz biological and biomedical applications (Markelz et al., 2000; Kutteruf et al., 2003; Korter et al., 2005). Korter et al. (2005) discussed the difficulty for assigning the lowest frequency intermolecular phonon modes. Walther et al. (2003) reported the observations of a series of distinct absorption features originating from the lowest intermolecular vibrational modes in polycrystalline sugars and a broad, featureless absorption spectrum in amorphous sugars.

The THz-field transmitted through a sample is attenuated by dispersion and absorption in such a way that the ratio of the electric field strength before, $E_s(\omega)$, and after transmission, $E_r(\omega)$, is given by (Wallace et al., 2003):

$$\frac{E_s(\omega)}{E_r(\omega)} = T[n(\omega)] \exp\left[-\frac{\alpha(\omega)d}{2} + \frac{\mathrm{i}n(\omega)\omega d}{c}\right] \quad (1)$$

where d is the thickness of the disk sample, ω the frequency of the radiation, c the speed of light in vacuum and $T[n(\omega)]$ are the reflection losses at the sample surface. Therefore, for a given thickness of sample disk, any properties of materials that could influence $n(\omega)$ (refractive index), $\alpha(\omega)$ (absorption coefficient), and $T[n(\omega)]$, such as disk composition, particle size, etc., could ultimately impact the intensities and peak positions of the THz transmission spectra. The lack of a solid theoretical framework presents a significant barrier for understanding the detailed mechanisms that govern the THz transmission phenomena described at the microstructural level.

1.3. Challenges and opportunities of adapting terahertz spectroscopy as a pharmaceutical PAT tool

The majority of published work on THz pharmaceutical applications has been focused on differentiating polymorphism and determining crystallinity of APIs. Developing THz spectroscopic method as a quantitative pharmaceutical characterization tool for both crystalline and amorphous materials and/or excipients simultaneously merits much research and development. In the PAT domain, a thorough process understanding calls for the knowledge of both product (such as drug substances and drug products) and process (such as manufacturing and measurement process). For pharmaceutical application of an emerging technology such as THz spectroscopy, there are certainly some areas to be explored for enriching our understanding of the scientific merit of the application. From the risk-based approach highlighted in the FDA PAT Guiadance (FDA, 2004), incomplete information and knowledge of these two critical aspects may lead to process/product design issues and product safety issues, especially in the case of narrow therapeutic index (NTI) drugs and high potency drugs. Therefore, exploring the possibility of using THz absorption spectroscopy as an alternative technique for directly characterizing pharmaceutical materials and tablets would provide much insight for adapting THz spectroscopy as a potential PAT tool.

Given that THz spectra are information rich and provide enough chemical (formulation) and physical (processing) information to enable process engineers and pharmaceutical scientists to extract critical information for product/process design and process control, a few critical scientific questions may need to be answered first. For example,

(1) What measurement factors impact the quality, precision, accuracy, and repeatability of acquired THz spectra?
(2) How does one optimize these measurement factors for quantification purpose?
(3) How can process and product knowledge be brought into the spectral data analysis domain such that THz spectra can be better explained and interpreted?
(4) Can spectroscopic techniques and chemometric modeling methods be integrated to understand product and process interactions for PAT implementation?

In an effort to evaluate the feasibility of integrating THz spectroscopy and chemometric modeling methods for pharmaceutical characterization in support of FDA's PAT Initiative, an interagency agreement (IAG) was established between FDA and NIST in August 2004. This paper reports our findings for exploring critical THz measurement factors and interpreting THz spectra for PAT application.

2. Materials and methods

2.1. Pharmaceutical materials and tablets

The following pharmaceutical materials were used for this evaluation study: anhydrous USP grade theophylline (BASF,

Table 1
Direct compression tablet formulation compositions (mole fraction)

Formulation	Tablet code	Theophylline	Mg stearate	Avicel	Lactose
A	D1–3	0.616	0.004	0.000	0.380
B	D4–6	0.987	0.007	0.006	0.000
C	D7–9	0.759	0.005	0.002	0.234
D	D10–12	0.463	0.005	0.000	0.532
E	D13–15	0.979	0.010	0.011	0.000
F	D16–18	0.629	0.006	0.004	0.361

Minden, Germany); monohydrate UPS grade spray-dried lactose (Fast-Flo 316) (Foremost Farms, Baraboo, WI); corn starch powder and magnesium stearate (Spectrum Chemical, New Brunswick, NJ); microcrystalline cellulose (Avicel PH-102) (FMC Biopolymer, Newark, DE). Deionized water was used in the preparation of the starch paste in the wet granulation.

Theophylline tablets of various formulations were manufactured at a contract site using pre-defined protocols: powder blending, followed by either direct compression or wet granulation process then compression. Powder blending was performed in an 8 L bin blender (L.B. Bohle GmbH, Ennigerloh, Germany) at 25 rpm for 4 min. Magnesium stearate was added after the 4 min time point and blended for additional 30 s. Tablets were compressed at on an 18-station automated rotary tablet press (Elizabeth Hata, North Huntingdon, PA). Six stations were configured for manufacture. Tablets had a target weight of 300 mg per tablet and nominal hardness of 8, 11, 14 kp. The compression force was adjusted at-line such that target hardness of the tablets was achieved. Wet granulation was carried out in a planetary mixer (Hobart Mfg. Co., Model AS-200, Troy, Ohio) for 6 min. Throughout the granulation process, starch paste was added incrementally. The granule materials were tray dried at 60 °C in a forced air convection oven (Fisher Scientific, Model 838F, Pittsburgh, PA) until only approximately 1% unbound moisture was kept as determined by loss on drying (LOD) method. After drying, the granules were sized using a rotating cone mill at 20% power (Quadro Engineering Co., Comil, Waterloo, Ontario). Formulation and processing information are summarized in Tables 1 and 2.

2.2. *Terahertz spectroscopy and data analysis*

Fig. 1 shows the schematic of the THz instrument used for this work, which was a modified Nicolet Magna 550 mid-infrared Fourier transform (FTIR) system at NIST. Modifications include: (1) silicon-coated mylar broadband beam-splitter; (2) deuterated triglycine sulfate (DTGS) room temperature detector fitted with a high density polyethylene (HDPE) windows;

Table 2
Wet granulation tablet formulation compositions (mole fraction)

Formulation	Tablet code	Theophylline	Mg stearate	Starch	Lactose
G	W1–3	0.6245	0.0043	0.0002	0.3710
H	W4–6	0.6333	0.0044	0.0003	0.3620
I	W7–9	0.4701	0.0048	0.0002	0.5250
J	W10–12	0.4775	0.0048	0.0004	0.5173

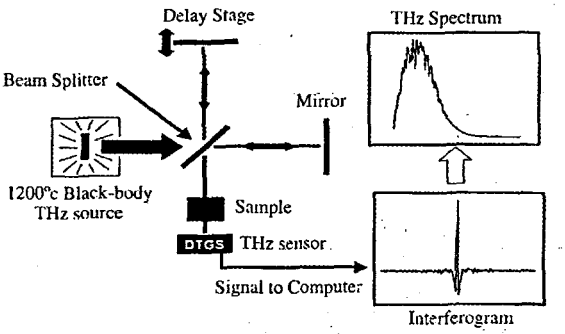

Fig. 1. Schematic of THz measurement system used in this study (using a modified FTIR spectrometer to perform Fourier transform infrared spectroscopy).

(3) spectral response from ~50 to 700 cm^{-1}. The modified instrument provides an improved advantage in terms of accessing a much wider THz spectral measurement range than methods previously reported using terahertz pulsed spectroscopy (TPS) (Taday et al., 2003; Strachan et al., 2004, 2005; Fitzgerald et al., 2005), where the frequency range was typically from 500 GHz to 3 THz (e.g., frequencies <100 cm^{-1}). As discussed later, this enhanced accessibility provides practical advantages for pharmaceutical characterization and future PAT application.

Spectrophotometric Grade PE (Aldrich Chemical, Milwaukee, WI) was used as-received. No further processing was applied to any of the five pharmaceutical components before it was mixed with PE to make transparent disks for THz measurement. Following similar procedure employed elsewhere (Taday et al., 2003; Strachan et al., 2005), the tablets received from the contract manufacturing site were manually crushed to a fine powder in a mortar and pestle, and mixed with polyethylene (PE) powder at ca. 4–12 wt.% (percentage of pharmaceutical materials). The mixture was compressed into disks of thickness 2 mm in a 13 mm die at approximately 200 psi pressure. Table 3 lists the weights of raw components and PE used for making the disks. Table 4 lists the weights of tablet and PE used for making the disks. All disks were made under lab humidity conditions (relative humidity (RH) = 40 ± 1%) using a portion from the crushed tablets and PE as received. All disks (including reference PE disks) were placed into the spectrometer under the same humidity conditions and then the sample compartment purged with dried-air (RH = 0%) at room temperature to remove interference from the gas phase water. THz spectra were recorded at 2 cm^{-1} spectral resolution and 64 spectral averages. In stan-

Table 3
The weights of raw components and polyethylene used for making the disks for THz measurement

Raw component name	Raw component weight (mg)	Disk total weight (mg)
Anhydrous theophylline	12	112
Monohydrate lactose	7	107
Microcrystalline cellulose (MCC)	5	105
Corn starch	10	110
Magnesium stearate	5.6	105.6

Table 4
The weights of tablet and polyethylene used for making the disks for THz measurement

Tablet code	Amount of tablet (mg)	Disk total (mg)
D1	11.1	106.4
D2	11.4	105.4
D3	10.9	102.1
D4	11.3	103.1
D5	11.3	102.7
D7	11.1	102.7
D8	11.14	102.8
D9	11.3	106.7
D11	10.7	100.8
D12	11.0	100.2
D13	11.4	106.5
D14	10.7	101.8
D15	11.1	101.3
D16	10.3	104.2
D18	11.2	104.1
W1	11.5	103.5
W2	11.2	102.4
W3	11.4	102
W4	10.9	104.7
W5	11.0	104
W6	11.5	105.6
W7	11.1	105.3
W8	11.0	103.5
W9	11.1	103.5
W10	11.0	104
W11	11.0	103.5

dard fashion, spectra were converted to optical density (OD) absorption units after ratioing raw sample disk transmission spectra (T_{sample}) to that of a pressed 100 mg polyethylene blank disk (T_{PE}) obtained under identical data acquisition conditions, according to the following formula:

$$OD = -\log_{10}\left(\frac{T_{sample}}{T_{PE}}\right) \quad (2)$$

3. Results and discussion

New analysis technologies lend themselves to further development and application alongside new systems that need to be studied. In the present case, a modified FTIR instrument was used for THz characterization and concentration determination of pharmaceutical materials and tablets. It is important to understand the effects of several instrumental and compositional variables for a meaningful interpretation of the THz spectral data. In order to address these issues, the following series of screening experiments were devised and employed.

3.1. Effects of component loading

The pressed disks consist of both pharmaceutical materials (crushed pharmaceutical tablets or as-received pure tablet components) and PE as a supporting matrix. Since PE may absorb or scatter THz radiation, it is expected that the component loading may impact the acquired raw THz transmission spectra. To examine the effect of component loading on theophylline spectra, two loading levels were tested: 4.5 and 12 mg. The results (data not shown) indicate that at lower theophylline loading (4.5 mg), the spectrum is of higher signal-to-noise (S/N) ratio and has a smoother undistorted baseline. The higher theophylline disk loading gives stronger signals for loading components, but suffered from higher THz baseline shifts due to component scattering of THz light, especially at higher frequencies. Such a screening procedure was applied to all other excipient components (lactose, MCC, starch, and Mg stearate) and it was noted that lactose, being the major excipient component in the formulation, displayed a similar trend. Therefore, to balance the S/N ratio, signal intensity, and baseline shift due to scattering, the minimum component loading was selected as 6 mg per 100 mg of PE.

3.2. Effects of component chemistry

Fig. 2 shows that for crystalline components such as theophylline and lactose, there are strong THz absorption peaks that arise from the vibrational motions of the molecular structure and its interactions with the surrounding solid medium (phonon modes). For amorphous and high molecular weight components such as starch and Mg Stearate, very few sharp THz characteristic peaks are observed. As might be expected, this fact may impose some difficulty for quantification purpose, in the event of applying a common univariate procedure to analyze a pharmaceutical dosage form which contains both crystalline and amorphous components. However, our work has confirmed that THz spectroscopy is suitable for characterizing pharmaceutical crystalline materials, as was demonstrated previously (Strachan et al., 2004; Fitzgerald et al., 2005; Wu et al., 2005a,b). As reported elsewhere (Wu et al., 2007b), applying multivariate methods and other data analysis method to the THz spectra allowed us to extract truly quantitative information from highly unselected spectra. The difference between the univariate procedure and multivariate procedure observed in our previous work agrees well with a recent IUPAC Technical Report (Olivieri et al., 2006).

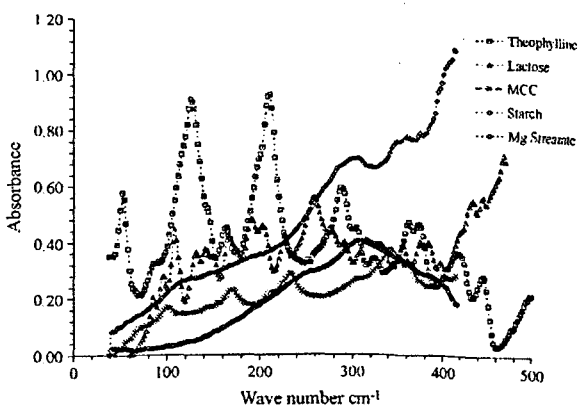

Fig. 2. Uncorrected raw THz spectra of pure pharmaceutical tablet components.

3.3. Apparent effects of disk drying time on pure component's raw THz transmission spectra

Within the scope of this study, the effect of disk drying time (t_{disk}) on the pure components' raw transmission spectral intensity (T_{sample}) varies and displays some interesting patterns, depending on the THz radiation frequency (ω) region and the type of component tested (e.g., whether they are crystalline materials or amorphous materials), as shown in Fig. 3a–f.

For crystalline components such as theophylline and lactose, the sensitivity of T_{sample} over t_{disk} was observed to be ω dependent: for $\omega < 150\,cm^{-1}$ (approximately), it is relatively insensitive even when t_{disk} increases from 10 min to 14 or 15 h; when $\omega > 150\,cm^{-1}$ (approximately), it becomes sensitive. For example, at frequency $301\,cm^{-1}$, T_{PE} decreases from 32.1 to 20.0 (decrease 37.7%) when t_{disk} increases from 10 min to 14 h; $T_{theophylline}$ decreases from 9.52 to 6.97 (decrease 26.8%) when t_{disk} increases from 10 min to 4 h; while $T_{lactose}$ decreases from

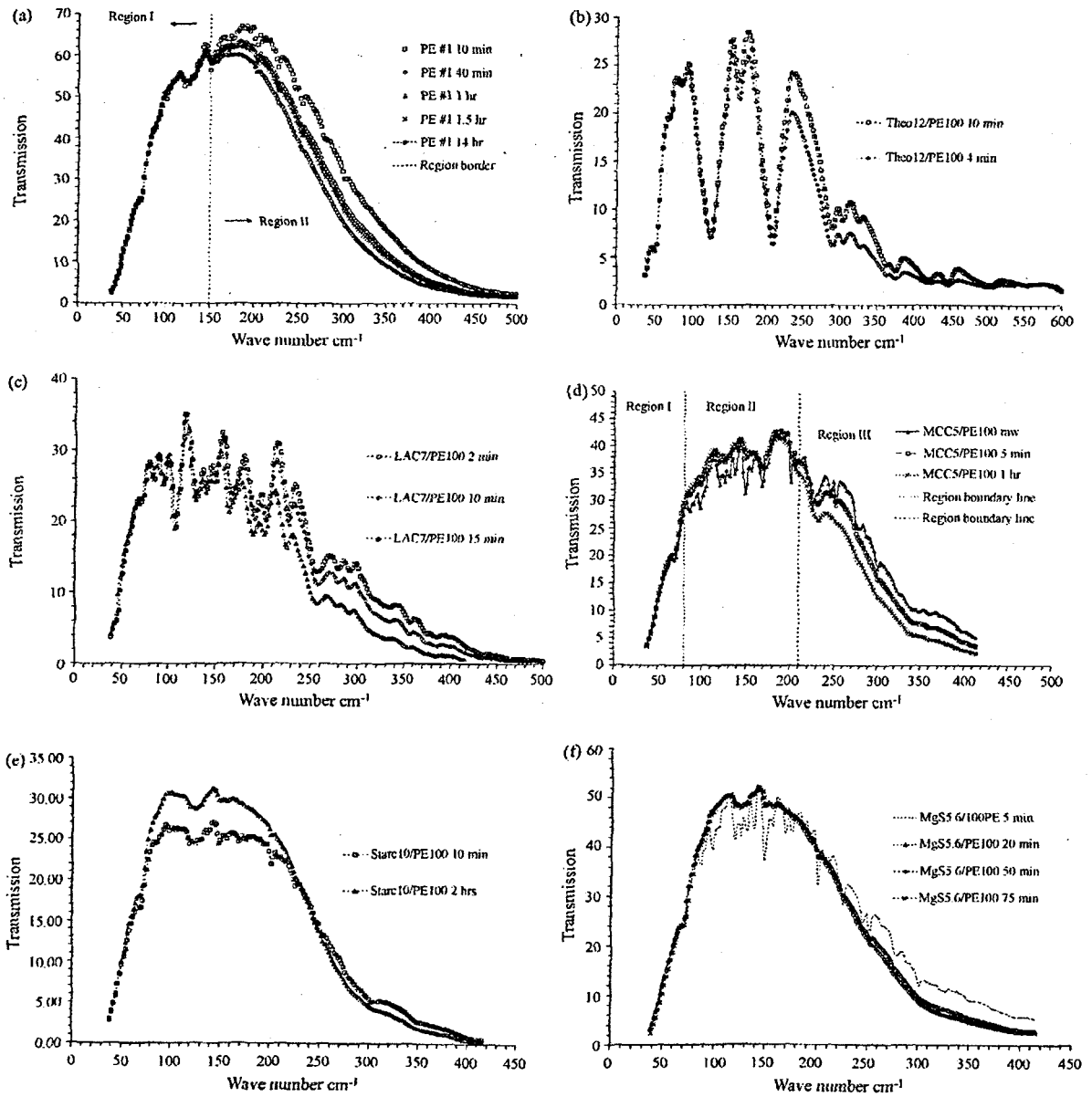

Fig. 3. Effect of disk drying time on THz transmission spectra of disks made from individual components mixed with polyethylene: (a) polyethylene disk (PE 105 mg); (b) 12 mg theophylline with 100 mg PE; (c) 7 mg lactose with 100 mg PE; (d) 5 mg MCC with 100 mg PE; (e) 10 mg starch with 100 mg PE; (f) 5.6 mg Mg stearate with 100 mg PE.

13.5 to 6.73 (decrease 50.1%) when t_{disk} increases from 2 min to 15 h.

For amorphous polymertic components such as MCC, starch, and Mg Stearate, the sensitivity of T_{sample} as a function of t_{disk} was also observed to be ω dependent also, but with three distinct spectral regions were identified: (1) for $\omega < 80\,cm^{-1}$, it is relatively insensitive even when t_{disk} increases from 10 min to 2 h; (2) for $80\,cm^{-1} < \omega < 210\,cm^{-1}$, T_{sample} increases with t_{disk}; (3) for $\omega > 210\,cm^{-1}$, T_{sample} decreases with t_{disk}.

Given that the PE matrix material exhibits a prescribed THz absorption spectrum and other physical phenomena that could take place when scanning the disks, these apparently observed spectral patterns could be due to factors such as: (1) direct chemical and physical contributions from both PE and pharmaceutical components; (2) moisture level in the disk since components could interact or hydrogen-bond with residual moisture; or (3) some other competing spectral absorption modes, etc. Although theoretical differentiation of these mechanisms is out of the scope of this study, from the measurement perspective, in order to have a robust THz measurement protocol that is insensitive to t_{disk}, ideally we should take the THz measurement at frequencies below a certain value, in this case, $150\,cm^{-1}$ for crystalline materials and $80\,cm^{-1}$ for amorphous materials, if the selected frequency region provides sufficient necessary compositional and structural information. However, in reality, such a limited frequency region may not provide us sufficient information that enables us to perform quantitative characterization of a pharmaceutical system. Therefore, there is a practical need to push for a wider THz frequency region for pharmaceutical PAT application towards quantification of pharmaceutical systems. As discussed in Section 2.2, the modified FTIR instrument used in this study provided this practical advantage.

3.4. Apparent effects of disk drying time on tablet's raw THz transmission spectra due to particle scattering?

When analyzing raw transmission spectral data without normalizing PE contributions and t_{disk} increased from 1 min to 1 h, a maximal 65% and 50% spectral intensity change (based on 1hr drying time) was observed for disk made from wet granulation tablet W7 and disk made from direct compression tablet D3, respectively. Compiling all of the raw THz transmission spectra for disks made from tablets (both directly compressed tablets and wet granulated tablets) revealed that the trend of T_{sample} over t_{disk} could be identified in four distinct spectral regions. Taking Fig. 4a for a direct compression tablet and Fig. 4b for a wet granulation tablet as example:

(1) Region I ($38.6\,cm^{-1} < \omega < 80\,cm^{-1}$): insensitive.
(2) Region II ($80\,cm^{-1} < \omega < 140\,cm^{-1}$): increasing.
(3) Region III ($140\,cm^{-1} < \omega < 260\,cm^{-1}$): first increasing then decreasing.
(4) Region IV ($260\,cm^{-1} < \omega < 500\,cm^{-1}$): decreasing.

Although exact theoretical differentiation of possible mechanisms that could attribute to these spectral patterns seems to be difficult and out of the scope of this study, attempts were made to provide a qualitative explanation. In addition to residual moisture level in the disk, apparently particle scattering could be partially responsible for this effect. The particle size data (D_{50}) measured from sieve analysis for as received anhydrous theophylline, lactose monohydrate, Avicel PH-102, NF corn starch, and Mg stearate, are 164, 171, 128, 334, and 213 μm, respectively. The particle size of PE used (determined by microscopy) is also around 150 μm. Despite this wide particle size distribution, it is expected that the tablet crushing step used in the preparation of the disk reduces the constituent's particle size to only several microns. As a first approximation, the particle size data for the pure components can be useful for a qualitative discussion regarding whether there is any possible particle size effect on the raw THz transmission spectra. If the wavelength of THz radiation is significantly larger than the scattering structure, scattering effects of terahertz radiation should be considerably reduced in comparison with optical techniques using shorter wavelengths, e.g., near infrared or visible radiation (Han et al., 2000; Wallace et al., 2004). Region I probably falls into this category, because the wavelength (ca. 100 μm) is significantly larger than the particle sizes of crushed crystalline components, particle scattering may be ignored. Region II and III are cases where the particle size becomes comparable to the wavelength (ca.

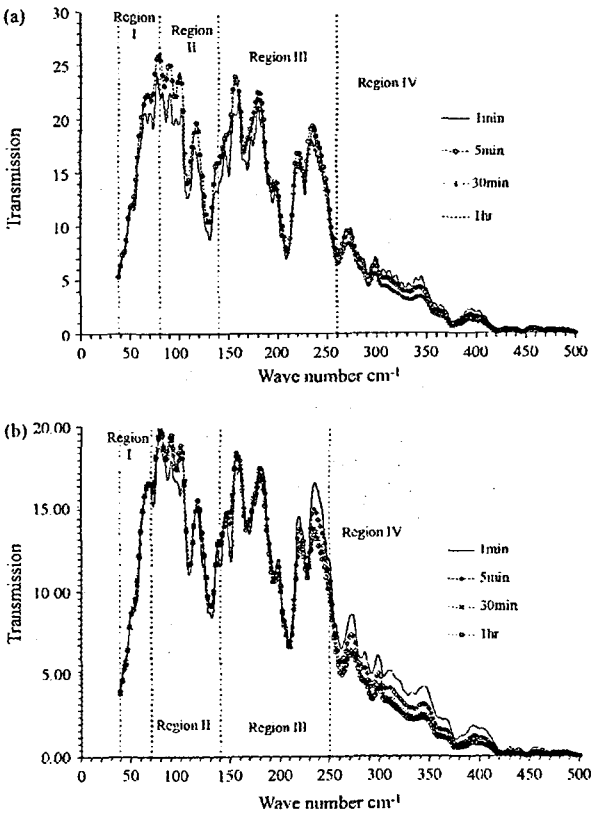

Fig. 4. When disk drying time increases, four distinct regions were observed on the transmission spectra of disks made from tablet and PE: (a) tablet D1; (b) tablet W2.

25–100 μm), so particle scattering gradually becomes important. For region IV, Rayleigh scattering (Drusch and Crewell, 2005) theory cannot be applied since the particle size is not small compared to the wavelength.

In summary, the magnitude of the apparent effects of disk drying time and particle scattering on tablet raw transmission spectral intensity is highly dependent on the THz radiation frequency region. Amongst them, the greatest impact was observed for the high frequency region IV, as demonstrated in Fig. 5a for disks made from direct compression tablets and Fig. 5b for disks made from wet granulation tablets at 301 cm^{-1}.

3.5. Apparent effects of disk drying time on tablet's corrected THz absorption spectra

To further investigate other possible causes that may be partially responsible for disk drying time dependence observed from the raw THz transmission spectra, the ratio method was applied to calculate the tablet optical density, or absorption spectral intensity according to Eq. (2). Spectra obtained through this ratio method are hereafter referred to being corrected THz absorption spectra hereafter.

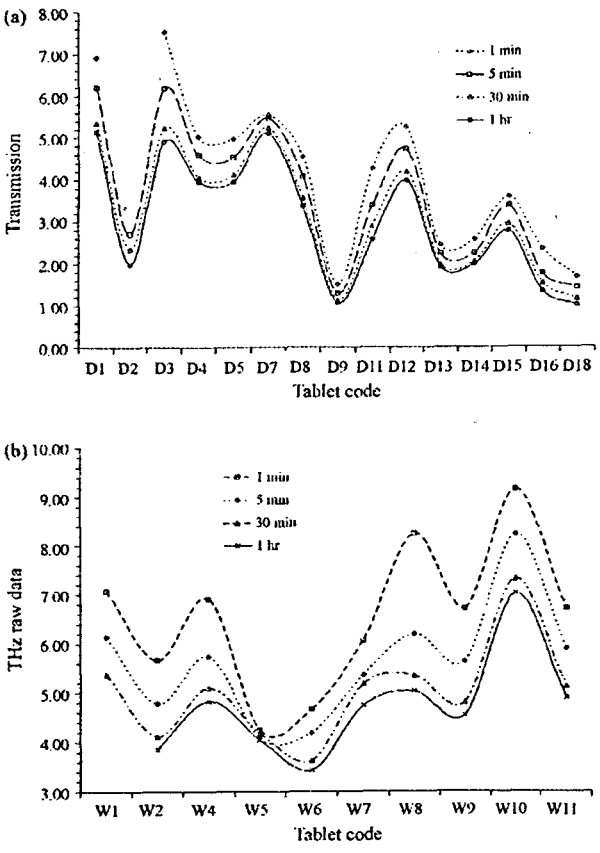

Fig. 5. Effect of disk drying time on tablet THz measurement transmission data at wave number of 301 cm^{-1} (without ratioing out PE contribution): (a) direct compression tablets; (b) wet granulation tablets.

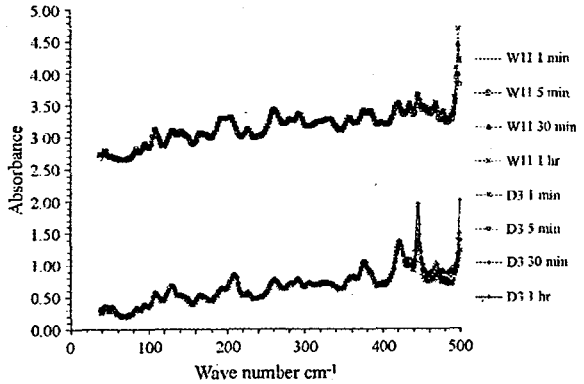

Fig. 6. Drying time dependence eliminated after ratioing out PE's contribution for direct compression tablet D3 (lower curve clusters) and wet granulation tablet W11 (upper curve clusters). For clarity, 2.5 units were added to the absorbance values of tablet W11 to upshift the spectra.

3.5.1. PE contribution

As shown in Fig. 6, the significant spectral differences on the raw transmission spectra for disks made from direct compression tablet D3 and wet granulation tablet W11 were almost completely eliminated after ratioing out the PE contributions, since the corrected THz absorption spectra for a tablet at different disk drying times match each other very well. This observation suggests that, to a large extent, PE is predominantly contributing to the observed spectral changes for increasing disk drying time for disks made from these two tablets. However, results from applying the ratioing method to disks made from other tablets show that spectral differences can only be partially eliminated after ratioing out PE contributions. For example, even after ratioing out PE contributions, a maximum of 20% difference in THz absorption intensity (based on drying time of 1 h) remained for disks composed of wet granulation tablet W4 and disks prepared from direct compression tablet D6, when t_{disk} increased from 1 min to 1 h. For disks made from other tablets, this difference is still quite noticeable although to a different extent, as shown in Fig. 7a and b. Therefore, there appear to be other responsible factors addressed below, in addition to the PE contribution identified here, that affect the overall measured spectral intensities.

3.5.2. Moisture effect

From the mass balance point of view, moisture absorbed by components (Hancock and Shamblin, 1998) and residual water in the tablets are inevitably carried into the disks when they are prepared for study. As stated in Section 2.2, all disks were made under lab humidity conditions (RH = 40 ± 1%), so before the disks were placed into the spectrometer's compartment, all disks especially the subsurface portions would contain a small amount of water. When the disk was placed into the spectrometer's compartment for dried-air (RH = 0%) purging, any subsurface water would diffuse out and evaporate into the gas phase in the compartment, and then quickly removed by the dried-air purging process, due to the gradient of water levels across the subsurface of disk and the gas phase according to the mass-transfer theory

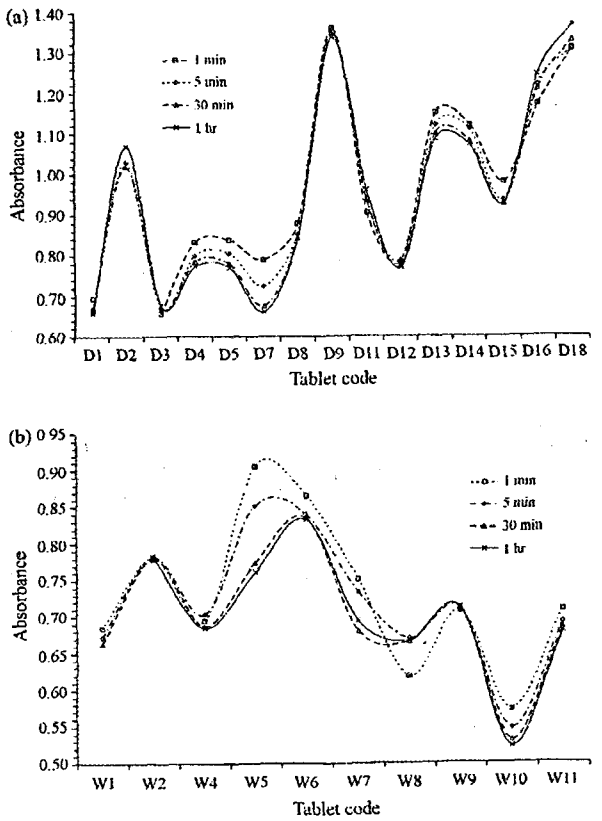

Fig. 7. After ratioing out the PE contribution, the observed effect of disk drying time on tablet THz absorbance intensity at wave number of 301 cm^{-1} was eliminated to various degrees for different tablets: (a) direct compression tablets; (b) wet granulation tablets.

(Bird et al., 1960). Our experimental results on disk drying during THz measurement are in good agreement with a theoretical mass-transfer analysis, as discussed below.

Direct analysis of spectral features provided the following observations:

(1) An absorption peak at 255 cm^{-1} is characteristic for lactose, since it only shows up in spectra of disks made from tablets which have lactose as one of main components (by molar fraction) in the formulations (including A, C, D, F, G, H, I, J in Tables 1 and 2), but not in the spectra of formulations not having lactose as a component (including B and E in Table 1).

(2) For disks made from most direct compression tablets, the absorption intensity decreases quite notably when t_{disk} increases; for disks made from wet granulation tablets, the absorption intensity decreases when t_{disk} increases, but to a less extent compared to that of direct compression tablets. This difference is possibly due to an initial moisture level difference, as wet granules were dried to moisture level below 1% before tabletting, while raw materials for direct compression tablets did not undergo this pre-drying process.

3.5.3. Disk drying kinetics derived from the tablets' corrected THz absorption spectra

Previous studies (Rahman and Stillinger, 1971; Hasted et al., 1985; Thrane et al., 1995; Castner and Chang, 1995) revealed that two absorption bands centered at 50 and 200 cm^{-1} for liquid water are identified in far-infrared measurements. The band at 200 cm^{-1} was broad and corresponding to the stretching mode of the O–H···O unit of the water molecules. The exact position and width could vary slightly, depending on the chemical and physical environment. Our study shows that there are two bands with peak maxima located around 54 and 210 cm^{-1} on the tablet's corrected THz absorption spectra. Given the peak intensities and peak maxima locations, it is readily concluded that these two bands are not associated with any of excipients in the tablet formulations. Meanwhile, we observed two prominent peaks for the theophylline component around 52.1 and 210 cm^{-1}. Since theophylline is a stable component under our experimental conditions, it is difficult to conclude that the observed absorbance difference observed when t_{disk} increases was solely due to the contribution of theophylline. Most likely these two prominent theophylline bands were superimposed on the water bands in their vicinity around 50 and 200 cm^{-1}. Our drying process kinetics analysis below supports this rationale.

According to Beer's law, the spectral absorbance is proportional to the concentration of species being detected. Therefore, the absorbance difference at the peak maxima can be related to the mass change associated with the disk drying process over time. Thus, the absorbance difference divided by the drying time difference could be a measure of the drying rate, since it could be reasonably assuming that the disk surface area remains unchanged during this relative short period of drying time. Fig. 8a–d illustrates the relationship between this derived disk drying rate versus disk drying time. We can see that, for the bands centered around 54 and 210 cm^{-1}, most WG tablets and DC tablets exhibit a distinct two-stage drying process: (1) at the first stage, the absolute value of the drying rate decreases very quickly when t_{disk} increased from 5 to 30 min; (2) at the second stage, a nearly constant drying rate (almost zero) was exhibited when t_{disk} increased further to 60 min. This appears to agree well with the typical drying curve of materials at constant drying conditions, and could be well explained by the interphase mass-transfer theory in chemical engineering practice (Bird et al., 1960). Based on the literature data and the evidences obtained from both direct spectral feature analysis and drying process kinetics analysis discussed here, the bands located at 54 and 210 cm^{-1} identified in this study are interpreted as combinations of THz absorption features of theophylline component and moisture. However, the absorbance difference observed over disk drying time could be primarily attributed to residual water associated with the disk, although the amount of residual water does not appear to be significant.

The above analysis also suggests that the disk drying time should be larger than 30 min in order to enable a quantitative interpretation of THz spectra for extracting tablet concentration. All of our THz spectra used for tablet concentration quantification (Wu et al., 2007b) were acquired at 1 h disk drying time.

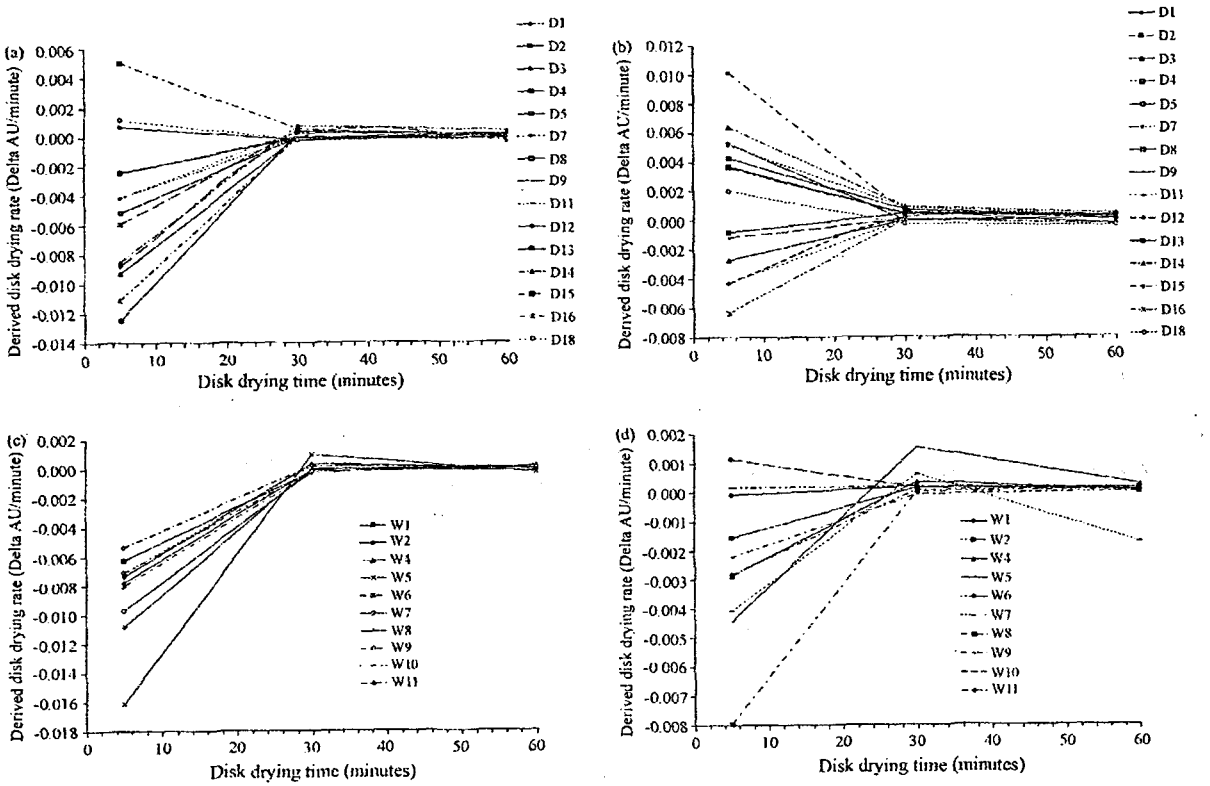

Fig. 8. Apparent disk drying rate curves derived from absorbance data at THz bands around 54 and 210 cm^{-1}: (a) DC tablets at 54 cm^{-1}; (b) DC tablets at 210 cm^{-1}; (c) WG tablets at 54 cm^{-1}; (d) WG tablets at 210 cm^{-1}.

3.5.4. PE particle size and hardness effects

In addition to the PE loading and component particle size identified in the raw transmission spectra and moisture level identified in THz absorption spectra, there might be other factors that could be contributing to the observed changes in the raw transmission spectra as t_{disk} increases. Recent results from NIST Physics Laboratory show that for polyethylene powder with particle size smaller than 5 μm, there is minimal scattering effect on the transmission data, resulting in no t_{disk} dependent spectral changes.

The nominal values of the original tablet hardness were 8, 11, and 14 kp. During sample disk preparation, the original tablet was crushed and milled to fine particles then mixed with PE powder and pressed into a sample disk. Presumably, the likelihood of seeing the impact of original tablet hardness in the sample disk's raw transmission or absorption spectra should be very low. Therefore, no attempt of comparing differences associated with hardness was made during this analysis.

3.6. PAT considerations for a THz spectroscopy measurement process

Design of experiments (DOE) as an important multivariate statistical tool has been highlighted in the FDA's PAT Guidance. Successful applications of DOE in process/product development, scale-up, and manufacturing can bring tremendous benefits to the industry, such as developing a robust process, improving process performance (Fraleigh et al., 2003), reducing materials and resources usage, and optimizing process recipes (Vannecke et al., 1999), etc. However, for an actual process involving multiple factors and levels, to balance the cost of multiple runs associated with DOE and the resolution and robustness of the models to be built, process engineers typically start with an univariate method for quick screening and then develop a DOE based on the screening study. In this work, a screening study was conducted to identify critical process variables (Wu and Hussain, 2005b) for pharmaceutical THz measurement process, such as tablet loading, disk drying time, and component chemistry, etc. This constitutes one critical element for evaluating emerging technology for pharmaceutical application. Measurement process optimization based on this screening study would ensure repeatability, reproducibility, and process robustness from an engineering perspective (Taguchi et al., 2000). It will help to interpret THz spectra successfully, and to extract quantitative process and product information from THz spectra.

Our current work serves as a starting point. Other pharmaceutical systems consisting of both crystalline and amorphous components should be characterized by this emerging technology in order to develop its full capability for the pharmaceutical PAT application. The methodology study of using THz spec-

troscopy merits it as a promising approach for both scientific research and development in the area of pharmaceutical process/product characterization in the PAT domain.

4. Conclusions

In this study, measurement process conditions and PAT considerations of using THz spectroscopy to characterize pharmaceutical materials and tablets were explored with the goal of evaluating THz spectroscopy as an emerging technology for potential pharmaceutical PAT application. Our study revealed that three factors including component loading, component chemistry, and disk drying time have significant impacts on the raw THz transmission spectra of disks. Crystalline materials and amorphous materials absorb THz radiation very differently, as evidenced from both their number of characteristic peaks and their apparent dependence on disk drying time. Results from applying the spectral ratio method demonstrated that the disk drying time dependence could be largely eliminated for the majority of the disks made from both direct compression tablets and wet granulation tablets, and could be completely eliminated in a few cases. Direct spectral feature analysis on the corrected THz absorption spectra along with the mass-transfer analysis of the disk drying process provided evidence for the peak assignment of both lactose ($\sim$255 cm^{-1}) and disk moisture ($\sim$54 and 210 cm^{-1}), although these two water peaks may overlap with theophylline peaks in their vicinity. Furthermore, our assignment of water peak maxima in the far-infrared region is in good agreement with literature assignments (Hasted et al., 1985). Lastly, specimen or PE particle size may contribute to these observed spectral changes in part from effects described by particle scattering theory.

Although ideally one should choose a drying time-insensitive region to simplify the quantification process, in practical accessing a wider THz frequency region is warranted due to limited characteristic features available in the time-insensitive region. Doing so would enable us to collect THz spectra of embracing rich chemical information of a pharmaceutical dosage form, although the spectra may convey the dosage form's physical information such as particle size scattering and moisture content. With the help of multivariate statistical data analysis methods performed on similar data and samples described here and demonstrated elsewhere (Wu et al., 2007b), this complication could be handled effectively such that quantifying concentrations of pharmaceutical dosage forms from THz absorption spectra is indeed feasible. This constitutes one important element for THz spectroscopy measurement process and should be taken into account when developing a robust analytical/testing protocol for a pharmaceutical PAT application.

Disclaimer

The views and opinions expressed in this paper are only of the authors, and do not necessarily reflect the views or policies of the FDA.

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