

Evaluating lactose content within Avicel® PH-101 tablets by computational analyses of terahertz waveforms

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ABSTRACT

Using terahertz time-domain (THz-TD) transmission waveform analysis, a peak finding routine was used to monitor the known concentrations of lactose monohydrate in various tablets. By comparison, the same tablets were monitored having applied Fast-Fourier Transformation (FFT) of the waveforms. The accuracy of the two methods, determined with root mean square (RMS) error was 2.6% and $\pm 2.0\%$ for the comparator method.

INTRODUCTION

THz spectroscopy provides information on phonon modes in crystalline structures [1]. The phonon mode originates from van der Waals and hydrogen bonding between molecules within a crystal lattice structure. It represents an opportunity to fingerprint drug identity as well as assaying for content. The technique of THz pulsed technology has begun to contribute to in-process control during pharma manufacturing, in which drug uniformity during dry granulation (e.g. roller compaction) may present issues for product quality.

The aim of this work was to evaluate two methods of THz-TD waveform analysis for estimating the crystalline component of tablets. One method was based on the analysis of the THz-TD waveform signal intensity and the second, on principle component analysis (PCA) of the corresponding Fourier spectrum. A model tablet formulation was studied containing a crystalline component (lactose monohydrate) with known THz phonon vibrations, and Avicel® PH-101 which does not display any phonon modes within the THz spectrum.

MATERIALS AND METHODS

Seven 200 mg samples of Avicel and lactose monohydrate were weighed separately and mixed for 5 minutes before transferral into a 13 mm diameter die. The samples were pressed at 500 ± 1 kg at a rate of 20 mm/min on a single punch tablet press (Gamlen Tablet Press, Gamlen Tableting Ltd, Nottingham, UK) producing tablets with thickness $1.48 \text{ mm} \pm 0.1 \text{ mm}$ and densities of $1 \text{ mg/mm}^3 \pm 0.03 \text{ mg/mm}^3$. Allowing 48 hrs post-compaction for elastic recovery, the tablets were analysed with a TPS-3000™ (TeraView, Cambridge, UK) to record their TD waveform. **Method 1:** Maximum peak intensities were read from the TD waveform (See Fig.1) over a time period in which a ripple in waveform is witnessed, free of visible shoulders and inflexions. **Method 2** PCA was performed on the corresponding Fourier spectrum of each time domain waveform (Fig. 2), between wavenumbers 0 to 75 cm^{-1} . The PCA method involves the transformation on the orthogonal of the input data to find similarities in the variances of a given dataset.

RESULTS AND DISCUSSION

Waveforms of the 7 samples are shown in Fig. 1, where greater lactose content is denoted with lighter lines with 0% represented as black. The corresponding Fourier spectra are shown in Fig. 2.

For each method the peak intensities in the chosen regions of the waveforms and Fourier spectrum (respectively, methods 1 and 2) are presented in Fig. 3.

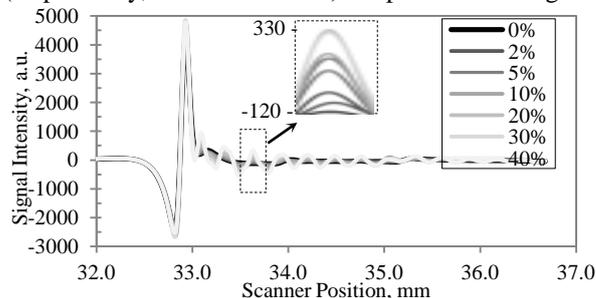


Figure 1: Compiled THz waveforms of tablets comprising of a binary mixture of lactose (expressed in % w/w) and Avicel® PH-101. Inset shows exploded image of the time region analysed in Method 1.

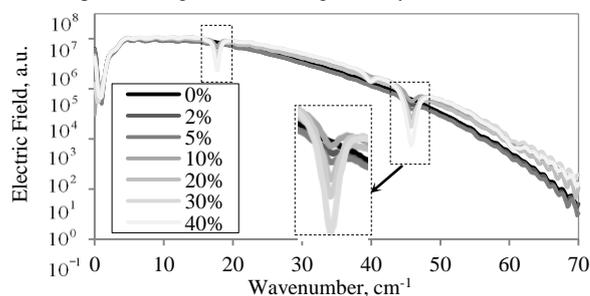


Figure 2: Compiled THz spectrum with lactose concentrations (% w/w). Inset boxes show wavenumber regions sensitive to lactose.

In the PCA analysis, the second component was chosen for subsequent regression analysis because it showed a good correlation between the characteristic peaks in the spectra at approximately 46 cm^{-1} and 19 cm^{-1} and the concentration of lactose (See Fig. 3).

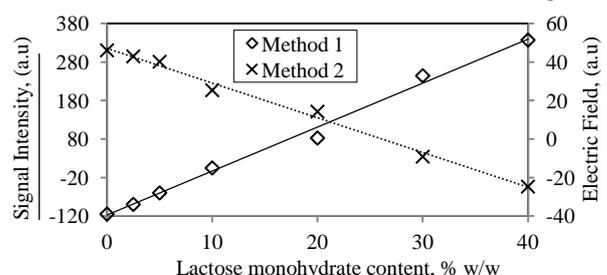


Figure 3: Calibration curve for Methods 1 and 2, where method 1 is measured against signal intensity and method 2, electric field.

From the RMS in the calibration curve for methods 1 and 2, the uncertainty of any concentration in the range studied was $\pm 2.6\%$ for method 1 & $\pm 2.0\%$ for method 2.

CONCLUSION

Although the RMS errors for both methods are similar, method 2 would be more suitable for the determination of concentration of one crystalline component in a binary mixture with another non-crystalline component. This is because PCA characterises the specific phonon vibrations from individual components directly on the Fourier spectrum and so has improved specificity.

REFERENCES

[1] Zhang, Y., et al. "A first principle study of THz spectra of acetophenone" *Chemical Physics Letters* **452** (2008) pp. 59–66