

Determining solid-state crystalline structure in pharmaceutical products

Summary

Terahertz pulsed spectroscopy (TPS) is used to non-destructively determine the polymorphic forms and crystalline state of active pharmaceutical ingredients (APIs). The analytical performance of TPS is equivalent to or better than traditional spectroscopic techniques.

Introduction

It has long been known that many pharmaceutical solids can exist in more than one crystalline form. These different forms or polymorphs have the same chemical composition but different crystalline structures which lead to different physicochemical properties. For example, different polymorphs may have different dissolution rates or bioavailability, and can affect the processibility and the stability of the API.

The formation of different polymorphs can be controlled during crystallization e.g. by changing solvent, the rate of cooling and the degree of supersaturation of the solution. However the polymorphic or crystalline state can change during subsequent processing stages e.g. milling, granulation, drying, or coating.

In contrast to other spectroscopic techniques, terahertz spectral features are directly related to intermolecular vibrations within the lattice structure rather than intramolecular vibrations. Hence TPS provides a unique opportunity to non-destructively acquire information about the polymorphic state and crystalline structure of APIs during chemical and pharmaceutical manufacturing. The information obtained is comparable to X-ray powder diffraction in terms of sensitivity to structural changes but with the fast acquisition of a spectroscopic technique.

Terahertz Pulsed Spectroscopy

Transmission spectra were collected from 0.06 THz to 3 THz (2 cm^{-1} to 100 cm^{-1}) at 0.03 THz (1 cm^{-1}) spectral resolution using a TeraView TPS spectra 1000 terahertz spectrometer. To remove spectral contributions associated with atmospheric moisture the sample chamber was purged with dry nitrogen (10 l/min) throughout the measurement. 20 mg of the sample material was physically mixed with 360 mg polyethylene (PE) powder and compressed to a 13 mm diameter pellet. Each sample spectrum was referenced against PE. For each rapid-scan spectrum the average of 1800 co-added scans was recorded in one minute.

Absorptions in the terahertz spectral region are associated with intermolecular interactions of the crystal structure. They predominantly represent differences in the oscillation of the crystalline lattice, resulting in phonon modes (Figure 1).

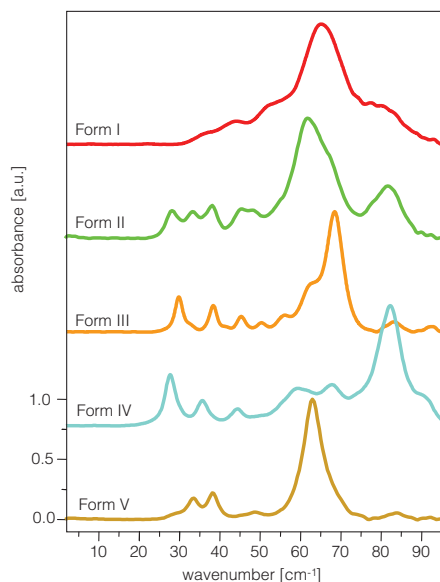


Figure 1.
Terahertz spectra of sulfathiazole polymorphic forms. Spectral features relate to intermolecular interactions. (Spectra offset for clarity.)



Results and discussion

Analysis of a polymorphic impurity

To determine the ability of TPS to detect polymorphic impurities, pellets containing carbamazepine form III and a small amount of form I as an impurity were prepared.

Pellets containing physical mixtures of carbamazepine forms I and III at six levels from 0% to 100% were prepared in triplicate.

In order to investigate the performance of TPS to quantify small amounts of one polymorphic form in the other a second set of pellets was prepared. This set again contained physical mixtures of carbamazepine forms I and III at six levels ranging from 0% to 10% form I. The measurements were performed in triplicate.

Representative spectra of the samples are shown in Figure 2. Unique spectral features are observed for form I at 1.26 THz (42 cm^{-1}) and 1.74 THz (58 cm^{-1}) and for form III at 0.96 THz (32 cm^{-1}) and 1.62 THz (54 cm^{-1}). In this spectral range forms I and III have no spectral features in common.

For quantitative analysis a partial least-squares (PLS) model was built. The spectra were pre-processed using mean centering and converted to first derivative. The spectral range included was 0.3 THz (10 cm^{-1}) to 2 THz (66 cm^{-1}). Cross validation was performed leading to a RMSECV of 2.00% and correlation coefficient R^2 of 0.996 for the 0-100% model (1 factor) and a RMSECV of 0.35% and R^2 of 0.991 for the 0-10% model (2 factors).

As shown in Figure 3, it is possible to detect the carbamazepine form I polymorphic impurity at a level of 1.17% relative to form III.

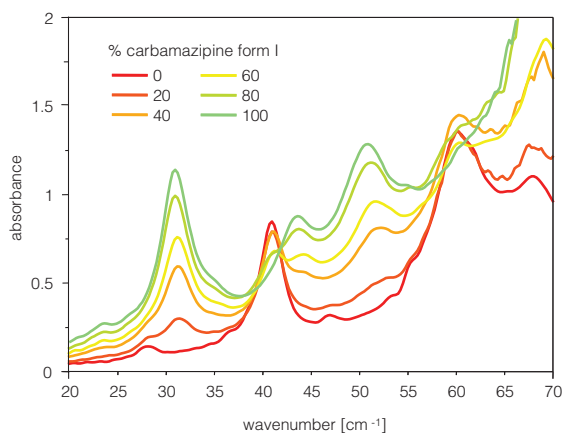


Figure 2.
Terahertz spectra of mixtures of carbamazepine polymorphs forms I and III.

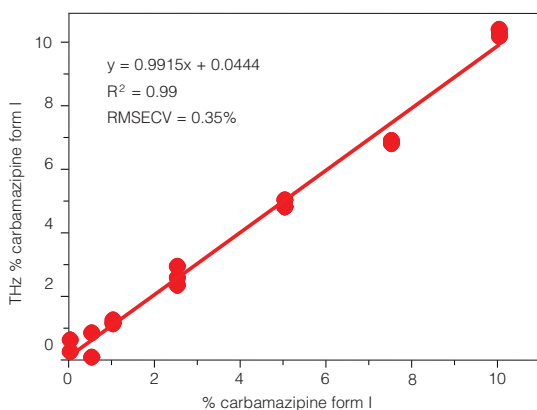


Figure 3.
Terahertz predicted concentration of carbamazepine polymorph form I in form III.

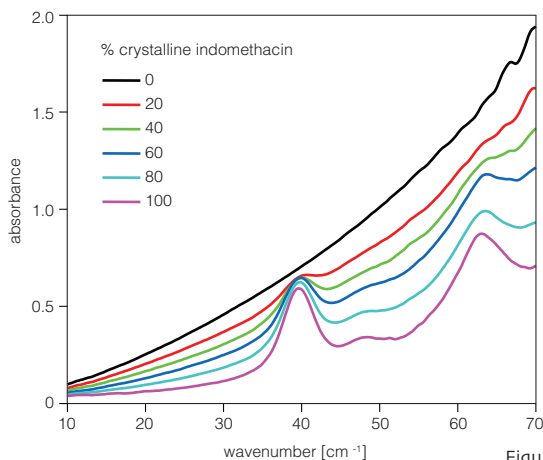


Figure 4.
Terahertz spectra of mixtures of crystalline and amorphous indomethacin.

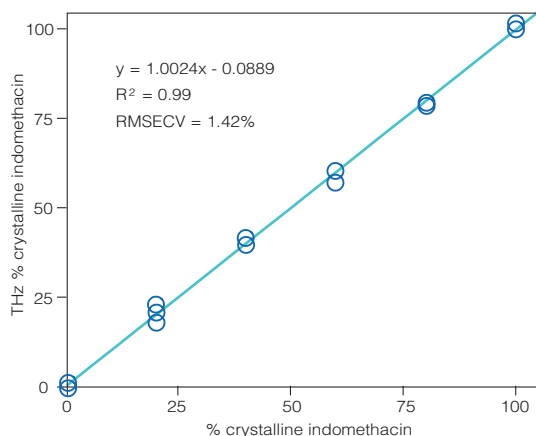


Figure 5.
Terahertz predicted concentration of crystalline content of indomethacin in mixtures of crystalline and amorphous indomethacin.

Detection of crystalline vs amorphous content

To assess the ability of TPS to distinguish between the crystalline and amorphous state, binary physical mixtures of crystalline and amorphous indomethacin were prepared and analysed by TPS. As can be seen in Figure 4, the lattice modes observed in the physical mixtures progressively weaken as amorphous content increases. Amorphous indomethacin exhibits no distinguishable spectral features as in this state no long range order can be observed and hence phonon modes can no longer be sustained. In contrast, for crystalline indomethacin the strong phonon modes contribute to unique spectral features located at 1.20 THz (40 cm⁻¹) and 1.92 THz (64 cm⁻¹). For quantitative analysis a PLS model including the spectral range 1.05 THz (35 cm⁻¹) to 2.10 (70 cm⁻¹) with 2 factors was built. The spectra were pre-processed using mean centering and converted to first derivative. Cross validation was performed leading to a RMSECV of 1.42% and correlation coefficient R² of 0.999 for the 0–100% mixtures (Figure 5).

Conclusions

Terahertz pulsed spectroscopy (TPS) can accurately detect polymorphic impurities and distinguish between crystalline and amorphous materials with levels of accuracy and precision equivalent to existing techniques. In addition, the unique spectral features observed in the spectral region provide the unique ability to identify further polymorphic forms.

Further Reading

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