# Terahertz Spectroscopical Investigation of Cocrystal Formation Process of Piracetam and 3-hydroxybenzoic Acid

**Yong Du** *, Huili Zhang, Zhi Hong

*Centre for THz Research, China Jiliang University, Hangzhou 310018, China*

***Abstract*—The cocrystal of piracetam and 3-hydroxybenzoic acid under grinding condition has been characterized by terahertz spectroscopical technique. Spectral results show that the vibrational modes of the cocrystal are different from those of the corresponding parent materials. The dynamic process of such pharmaceutical cocrystal formation has also been monitored directly with THz spectra.**

## I. INTRODUCTION

COCRYSTALLIZATION can improve physical and chemical properties of active pharmaceutical ingredient, and this feature has great potential in pharmaceutical development. Cocrystals formed from an active pharmaceutical ingredient (API) and a cocrystal former (CCF) show unique physicochemical properties compared to their parent APIs, such as dissolution rate, solubility, hydration stability and even bioavailability behavior[1-2].

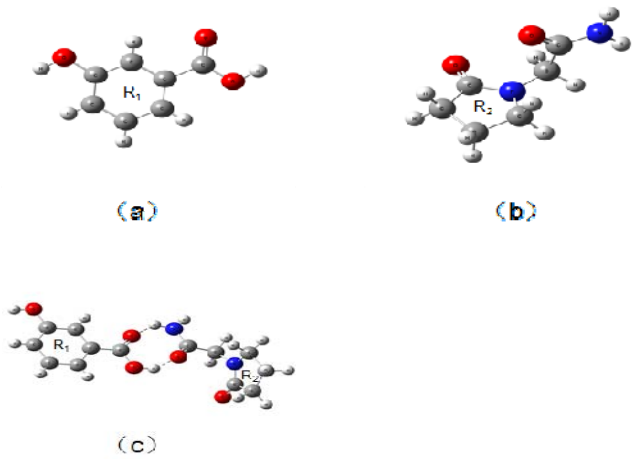


*Figure 1.* Molecular structures of (a) 3-hBA, (b) piracetam,(c) cocrystal of piracetam and 3-hBA

Candidates for crystallizing cocrystals with particular structural motifs for achieving desired physical properties are chosen according to the knowledge about intermolecular interactions between API and the appropriate CCF. Hydrogen bonds are among the strongest and most preferentially orientational intermolecular interactions, so that the presence of hydrogen bond donor and/or acceptor sites in API and CCF is usually a prerequisite factor in forming cocrystals. Piracetam is a cyclic derivative ofγ-Aminobutyric acid. It is widely used for the treatment of post-stroke aphasia, epilepsy, cognitive decline following heart and brain surgery, and dementia[3]. Based on the tendency of hydrogen bonding motifs between amides and carboxylic acids, piracetam (as API) and 3-hydroxybenzoic acid (3-hBA, as CCF), with the molecular structures shown in Figure 1, are chosen as suitable model molecules in this study to investigate the formation of corresponding pharmaceutical cocrystal with THz absorption spectroscopic technique directly.

## II. RESULTS

Terahertz radiation probes intermolecular and intramolecular interactions directly through crystal lattice vibrations, so THz spectroscopy is a sensitive and also attractive technique for differentiating and quantifying different solid-state forms of APIs and their cocrystals[4-8].

The THz absorption spectra of cocrystal formed between piracetam and 3-hBA distinguish at frequencies 0.52, 1.25 and 1.46 THz. It is well-known that the cocrystallization occurs as the result of intermolecular hydrogen bonding, nonconvalent interactions. The experimental results indicate that the vibrational modes observed are mostly intermolecular character resulting from intermolecular interactions between the parent 3-hBA and piracetam molecules.

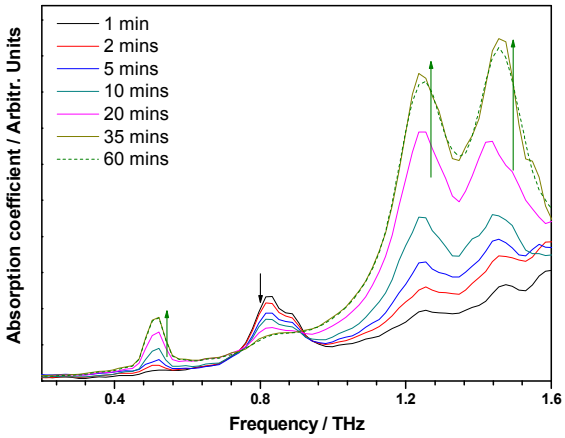


*Figure 2.* THz absorption spectra of cocrystal formed between piracetam and 3-hBA using grinding method at different reaction times (shown in the legend).

The distinctive spectral features from the absorption of cocrystal can be observed increasedly during grinding process shown in Figure 2. The intensity of the characteristic absorption peak of the physical mixture (at ~ 0.83 THz) decreases, while that of the cocrystal peaks (at ~ 0.52, 1.25 and 1.46 THz) increases gradually with the grinding time. There are two clear

isobestic points appearing at 0.74 and 0.91 THz position in the time-resolved changes of THz spectra and the arrows shown in Figure 2 indicate the change of absorption peaks due to physical mixture and cocrystal in the reaction process. It means that the starting mixture was consumed while a continuation of the cocrystal formation takes place.

The characteristic peaks in THz absorption spectra, 0.83 THz for the physical mixture and 0.52, 1.25 THz for cocrystal, are selected for quantitative analysis during the solid-state conversion process. The normalized change of the relative peak intensity for these distinctive features over grinding time is obtained, as plotted in Figure 3. Using this model it is possible to extract the cocrystal content information at every grinding time point during the grinding conversion process. Further work is needed to investigate such formation mechanism of cocrystal between piracetam and other conformers. It appears that the progress of the solid-state reaction from physical mixture to form cocrystal exhibits fast growth within in the beginning twenty minutes grinding time. And then the formation rate becomes slow. From the tentative changes shown in Figure 3 such solid-state pharmaceutical cocrystal transformation process and the corresponding dynamic information can be directly quantified and investigated.

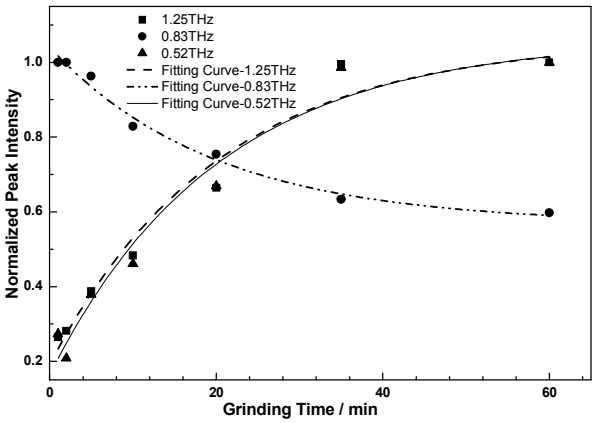


*Figure 3.* Observed normalized change of the relative peak intensity for the features at 0.83 THz (characterized feature for the physical mixture) and 0.52, 1.25 THz (characterized features for the cocrystal) in THz time-domain spectra as the grinding time.

## III. SUMMARY

Terahertz absorption spectra of cocrystal formed between piracetam and 3-hBA are obtained, and the dymanic process of such pharmaceutical cocrystal formation are monitored ditectly with THz-TDS technique. The results offer us the unique means to identify and characterize the cocrystal conformation from molecule-level, and also further real-time monitor the reaction dynamic of cocrystals in pharmaceutical industry.

## REFERENCES

[1]. K. L. Nguyen, T. Friscic, G. M. Day, L. F. Gladden, and W. Jones, "Terahertz time-tomain spectroscopy and the quantitative monitoring of mechanochemical cocrystal formation," *Nature Materials,* vol. 6, pp. 206-209, 2007

[2]. J. Lu, and S. Rohani, "Synthesis and preliminary characterization of sulfamethazine-theophylline co-crystal," *Journal of Pharmceutical Sciences,* vol. 99, pp. 4042-4047, 2010.

[3]. Y. Du, Y. Xia, H. Zhang, and Z. Hong, "Using terahertz time-domain spectroscopical technique to monitor cocrystal formation between piracetam and 2,5-dihydroxybenzoic acid," *Spectrochimic Acta Part A: Molecular and Biomolecular Spectroscopy*, vol. 111, pp. 192-195, 2013.

[4]. King, M. D., Buchanan, W. D., et al. "Understanding the terahertz spectra of crystalline pharmaceuticals: terahertz spectroscopy and solid-state density functional theory of (S)-(+)-ibuprofen and (RS)-ibuprofen", *J. Pharm. Sci.* vol.100, pp.1116-1129 , 2011.

[5]. Markelz, A., Whitmire, S., Hillebrecht, J., Birge, R. "THz time domain spectroscopy of biomolecular conformational modes," *Phys. Med. Biol.,* vol. 47, pp.3797-3805, 2002.

[6]. King, M. D., Hakey, P. M., et al. "Discrimination of chiral solids: A terahertz spectroscopic investigation of L- and DL-serine", *J. Phys. Chem. A.* vol.114, pp.2945-2953 , 2010.

[7]. Plusquellic, D. F., Siegrist, K., et al. "Applications of terahertz spectroscopy in biosystems." *Chem. Phys. Chem.* 8, 2412-243 (2007).

[8]. Baxter, J., Guglietta, G. "Terahertz spectroscopy." *Anal. Chem.* Vol.83, pp.4342-4368, 2011.

## ACKNOWLEDGMENT

This work was partly supported by National Natural Science Foundation of China (NSFC 21205110) and Zhejiang Province Science Foundation of China (LY15B050004).