Potential of THz-TDS for Crystallinity State Inspection of Active Pharmaceutical Ingredients in SmartFilms®

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***Abstract*— SmartFilms® with different loadings of L-tartaric acid as a model active pharmaceutical ingredient were prepared and investigated using THz-TDS as well as X-ray diffractometry. In addition, also tablets made from smartFilms as well as physical mixtures of L-tartaric acid and paper material were investigated. The results reveal that THz-TDS is an appropriate technique for nondestructive inspection of active pharmaceutical ingredient's crystallinity state in smartFilms and tablets made from them.**

I. INTRODUCTION

MAJORITY of newly developed active pharmaceutical ingredients (API) are poorly soluble in water and therefore exhibit low bioavailability [1]. A way to increase water solubility is to maintain API amorphous [2]. SmartFilm® technology uses ordinary paper as a matrix for loading API into the pores of paper in amorphous state [3]. These smartFilms can be easily compressed into tablets meeting the requirements of the European Pharmacopoeia (e.g. mass uniformity, resistance to crushing) [4]. However, verifying that the API is loaded amorphously either in a smartFilm or in a tablet made from smartFilms is essential. Furthermore, monitoring the state of the loaded API during storage is of interest. Here we investigate the potential of terahertz (THz) time-domain spectroscopy (TDS) as a nondestructive technique for investigation of an API's crystallinity state and compare it to the X-ray diffractometry (XRD) investigation. We choose L-tartaric acid (TA) as a model API, since its crystalline properties in the THz range are well-known. It also exhibits a prominent absorption peak at around 1.1 THz when in crystalline state [5].

II. EXPERIMENTAL PART

SmartFilms were prepared by applying 250 µl of 56 g/l TA (Carl Roth GmbH, Germany) aqueous solution on coffee filter papers (3.5 cm x 4 cm, Filtertüte 1x6/40 naturbraun, Melitta Europa GmbH & Co. KG, Germany). After drying, this resulted in a smartFilm being loaded with 1 mg/cm² of TA. Repeating the procedure resulted in higher loadings. In total 25 smartFilms with 5 different loadings (1, 2, 3, 4, 5 mg/cm²) as well as non-loaded filter paper were prepared. Additionally, physical mixtures in the corresponding weight proportions between TA and paper to those of smartFilms were prepared and compressed into tablets. These tablets were also spectroscopically investigated. Finally, a single smartFilm per loading was also compressed into a tablet and investigated.

III. RESULTS

The results of THz transmission measurements of smartFilms are shown in Fig. 1. The non-loaded filter paper showed featureless absorbance. The smartFilms loaded with 1 and 2 mg/cm² also showed featureless absorbance, however, higher than the non-loaded paper, indicating that the TA was in its amorphous state. For higher loadings of smartFilms the characteristic 1.1 THz absorption peak can be observed, meaning that crystalline TA was present. The same results were obtained for the compressed smartFilms (Fig. 2).

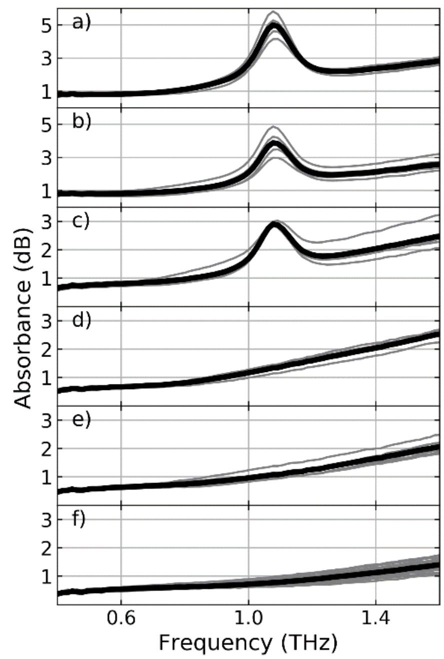

Fig. 1. Absorbance spectra for smart films with loading a) 5 mg/cm² b) 4 mg/cm², c) 3 mg/cm², d) 2 mg/cm², e) 1 mg/cm² and for f) non-loaded filter paper. The thin grey curves correspond to absorption of single smartFilms. The black thicker curves represent the mean absorbance of all smartFilms with the same loading.

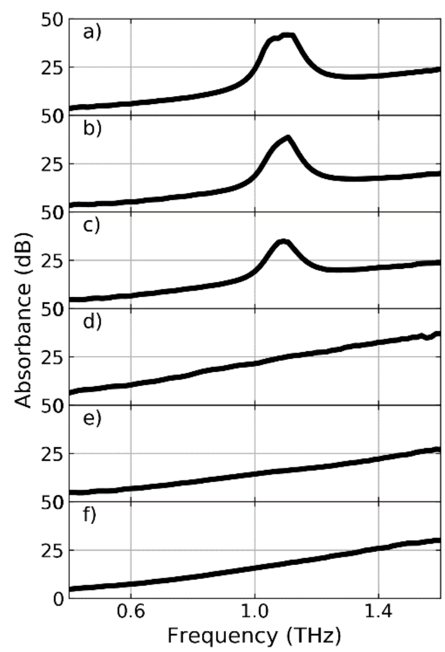

Fig. 2. Absorbance spectra for smart films pressed into tablets with loading a) 5 mg/cm² b) 4 mg/cm², c) 3 mg/cm², d) 2 mg/cm², e) 1 mg/cm² and for f) non-

loaded filter paper pressed into a tablet. Note that in case of a) 5 mg/cm² b) 4 mg/cm² the signal was attenuated to the noise level in the proximity of the 1.1 THz absorption peak, explaining its different peak shape.

On the contrary, for all physical mixtures, the characteristic absorption peak at around 1.1 THz could be clearly observed (Fig. 3), indicating that the system sensitivity was sufficient. The XRD investigation (not shown here) agreed with the THz-TDS investigation. For more information see [6].

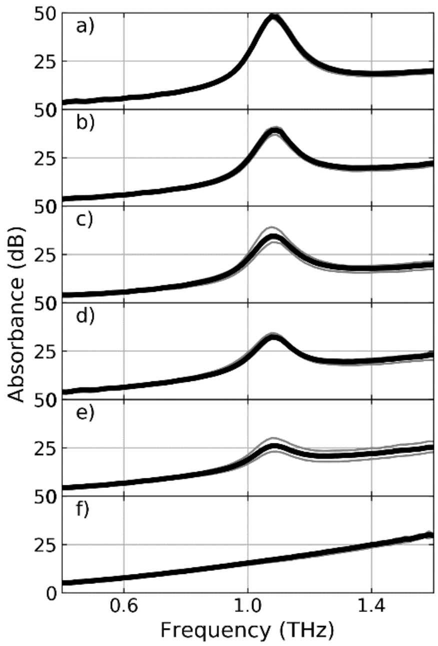

Fig. 3. Absorbance spectra for physical mixtures pressed into tablets corresponding to loadings a) 5 mg/cm² b) 4 mg/cm², c) 3 mg/cm², d) 2 mg/cm², e) 1 mg/cm² and for f) tablet made form pulverized paper only. The thin grey curves correspond to absorption of single samples. The black thicker curves represent the mean absorbance of three samples corresponding to the same loading.

IV. SUMMARY

The observed results confirm the potential of THz-TDS for nondestructive inspection of crystallinity state of an API loaded in a smartFilm and tablets made from them.

REFERENCES

[1] S. Stegemann, F. Leveiller, D. Franchi, H. de Jong, and H. Lindén, “When poor solubility becomes an issue: From early stage to proof of concept,” *Eur. J. Pharm. Sci.*, vol. 31, no. 5, pp. 249–261, 2007, doi: 10.1016/j.ejps.2007.05.110.

[2] B. C. Hancock and M. Parks, “What is the true solubility advantage for amorphous pharmaceuticals?,” *Pharm. Res.*, vol. 17, no. 4, pp. 397–404, 2000, doi: 10.1023/A:1007516718048.

[3] S. Lemke, E.-J. Strätling, H.-P. Welzel, and C. M. Keck, “Cellulose fibre based support matrices for layered products for oral and peroral application and their preparation: EP3192499A1,” 2016.

[4] F. Stumpf and C. M. Keck, “Tablets made from paper,” *Int. J. Pharm.*, vol. 548, no. 2, pp. 812–819, Sep. 2018, doi: 10.1016/J.IJPHARM.2018.05.071.

[5] E. M. Witko and T. M. Korter, “Investigation of the low-frequency vibrations of crystalline tartaric acid using terahertz spectroscopy and solid-state density functional theory,” *J. Phys. Chem. A*, vol. 115, no. 35, pp. 10052–10058, 2011, doi: 10.1021/jp204854e.

[6] J. Ornik, D. Knoth, M. Koch, and C. M. Keck, “Terahertz-spectroscopy for non-destructive determination of crystallinity of L-tartaric acid in smartFilms® and tablets made from paper,” *Int. J. Pharm.*, vol. 581, p. 119253, May 2020, doi: 10.1016/j.ijpharm.2020.119253.