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Detection of tulobuterol crystal in transdermal patches using Terahertz pulsed spectroscopy and imaging

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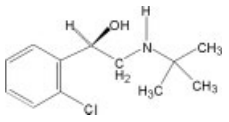
Applicability of a Terahertz Pulsed Spectroscopy (TPS) and a Terahertz Pulsed Imaging (TPI) for detection of tulobuterol (TBR) crystals in transdermal patches was investigated. Because TBR has high permeability in dermis, crystalline TBR in patch matrices contributes to controlling the release rate of TBR from a matrix. Therefore, crystalline TBR is one of the important factors for quality control of TBR transdermal tapes. A model tape that includes 5 w/w%, 10 w/w%, 20 w/w% or 30 w/w% of TBR was measured by TPS/TPI. TBR crystals in the matrices were successfully detected by TPI. Identification of TBR in an image of a crystal-like mass was done by comparison between the spectra of tapes and a TBR standard substance. These results indicate that TPS and TPI are applicable to identifying crystalline lumps of an active drug in tapes for quality control.

1. Introduction

Terahertz (THz) time-domain spectroscopy gives an electric field record of time delay due to the presence of material in a beam path with a higher refractive index when compared to a reference. Fourier-transformed waveforms from an electric field show a characteristic relationship between frequency and absorbance. Fourier-transformed waveforms provide information about not only intra-molecular vibration and lattice vibration, but also intermolecular forces and hydrogen bonds.

In the pharmaceutical industry, applications of TPS and TPI for discrimination of polymorphs (Taday et al. 2003; Walther et al. 2003; Strachan et al. 2004, 2005; Zeitler et al. 2005, 2006, 2007, Day et al. 2006) and for detecting unique waveforms of APIs have been reported. Thus, these technologies are expected to be used for qualitative and/or quantitative analysis (Taday et al. 2003; Upadhya et al. 2003; Ueno et al. 2006; Zeitler et al. 2006). In particular, THz spectroscopy has been used for detecting foreign materials in samples and for measuring the thickness of coatings (Fitzgerald et al. 2005; Zeitler et al. 2006; Ho et al. 2007).

Tulobuterol ((*R*,*S*)-2-tert-butylamino-1-(2-chlorophenyl) ethanol, TBR) transdermal tapes are used to cure bronchial asthma as a bronchodilator (β_2-blocker). TBR is one of the suitable compounds for systemic transdermal formulation because it has very high permeability into the keratin layer. The release rate of TBR from the matrix is controlled by the formation of lumps of TBR crystals. For this reason, crystallization of TBR in a matrix is an important factor assuring the quality of this tape. However, verifying the crystallization of an active drug is difficult because TDDS tapes (or patches) generally have a sandwich-like structure with a matrix between a liner and a supporting board. Although release testing is often used to evaluate "releasability", which is one of the physico-chemical properties of an active drug in transdermal pharmaceuticals, releasability is not a suitable parameter for evaluating crystallization of an active drug. In order to compensate for this disadvantage, development of an alternative method by which to observe crystallization of an active drug in a matrix through a liner and/or a supporting board is needed. This manuscript describes the applicability of one of the innovative non-destructive analytical techniques, TPS and TPI, for quality evaluation of TDDS tapes.



Tulobuterol

2. Investigations, results and discussions

2.1. THz pulsed spectrum of TBR obtained by TPS instrument

Fig. 1(A) shows the typical THz electric field records obtained from the TBR pellet and reference (PE pellet) by

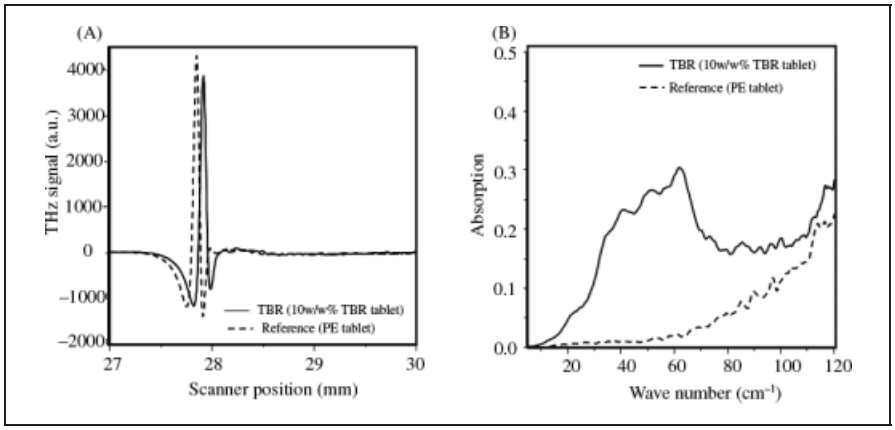


Fig. 1:
THz electric field records (A) and Fourier-transformed THz waveforms (B) of the TBR pellet and reference (PE pellet). The unique absorbance range, from 40 cm^{-1} to 70 cm^{-1}, is available to detect TBR absorbance

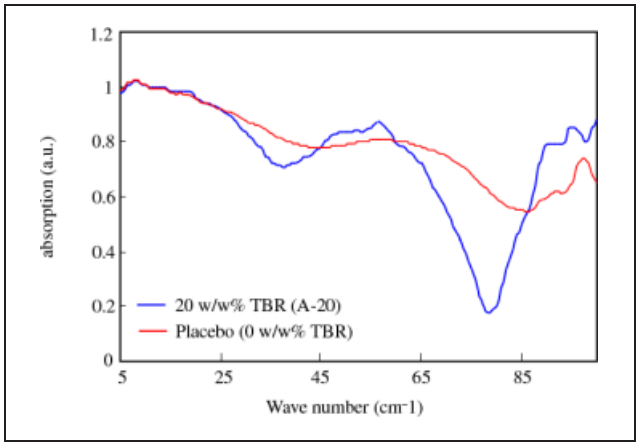


Fig. 2: THz spectra of model tape (20 w/w%, A-20) and placebo tape (0 w/w% TBR) obtained with quartz. The characteristic THz spectral range of TBR (from 45 cm^{-1} to 70 cm^{-1}) is best observed when etaloning effects are not dominating the range due to the thinness of the sample, as was the case here

the TPS 1000. The THz electric field record of the TBR pellet was shifted compared with that of the reference and the unique Fourier-transformed THz waveform of TBR was observed compared with that of the PE reference (Fig. 1(B)). This unique absorbance range, from 70 cm^{-1} to 45 cm^{-1}, seemed to be available to detect TBR absorbance from the total waveform of tapes.

2.2. THz image and spectra of TBR crystal in matrix

Fig. 2 shows the Fourier-transformed THz spectra of the placebo tape (the red line, an acrylic matrix) and the model tape (the blue line, 20w/w% TBR in an acrylic matrix, A-20). The fingerprint-like waveform of TBR from 70 cm^{-1} to 45 cm^{-1} was observed in the THz spectra obtained from the A-20. This observation suggests that chemical information of TBR can be detected in a tape. A lump of TBR crystals was detected at the top left of the image (Fig. 3(A)). The TPI contrast derives from refractive index differences. Therefore, it was presumed that the edge of the lumps of the TBR crystals contributed to making the definite contrast of shift of the refractive index. However, the image that is made from the shift of a refractive index would not provide chemical information about the lumps of TBR crystals. In order to identify the origin of the lumps of crystals, the THz spectra obtained from pixels which are located inside the lumps or outside the lumps were compared. Both spectra are shown in Fig. 3(B). The waveform indicated as the blue line represents the THz spectrum obtained from the pixel that is located inside the lump of crystals. The red line indicates the spectrum obtained from a pixel that is located outside the lump of crystals. The THz spectrum from the crystal shows a characteristic waveform range from 70 cm^{-1} to 45 cm^{-1}, almost the same as that of TBR standard substance. This observation strongly suggests that an image could be obtained from the crystal formed from TBR.

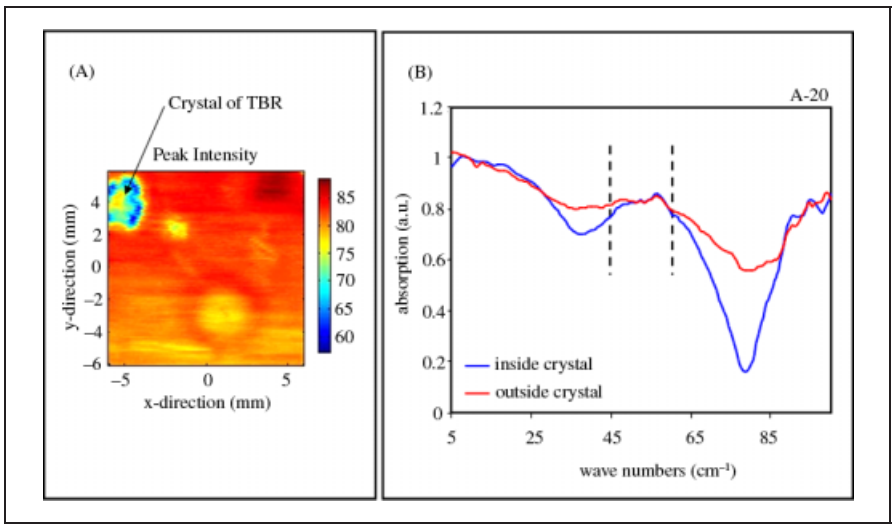


Fig. 3:
THz image of TBR crystal (A) and Fourier-transformed waveforms of pixels inside and outside of the crystals (B), obtained from A-20. The aggregation of TBR crystals which the arrow points to was clearly identified (A). It should be possible to observe the characteristic spectrum of TBR (from 45 cm^{-1} to 60 cm^{-1}) from both pixels located inside and outside of the crystal, but etaloning effects are again dominating the spectra

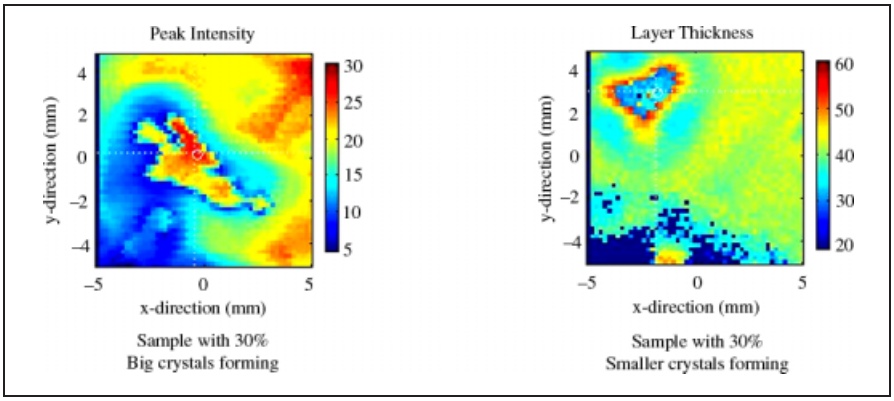


Fig. 4:
THz image of TBR crystals in matrix obtained using TPI 1000. Several sizes of TBR crystals were detected in the scanned area (the longer diameters: 0.5 mm to 3 mm, the shorter diameters: 0.1 mm to 0.2 mm)

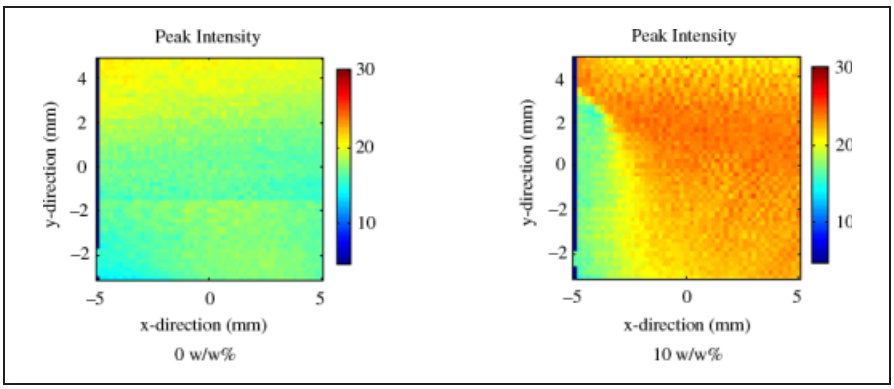


Fig. 5:
THz images of model tapes (0 and 10 w/w% TBR). Although there should be many small white crystals in R-10, only some were detected in the scanned area. In cases where the white crystals cannot be observed, the crystals might be smaller than the spatial resolution (100 μm) of TPI. Further studies need to be carried out to investigate differences in the samples

2.3. Size of crystals and spatial resolution of TPI

Fig. 4 shows the THz image obtained from the model tape (30 w/w% TBR, an acrylic matrix, A-30). Both model tapes were obtained from the same batch. Several sizes (short: 0.1 mm–0.2 mm, long: 0.5 mm–3 mm) of crystals were observed in these images.

The THz images obtained from the placebo tape (a rubber matrix, R-0) and the model tape (10 w/w% TBR, rubber matrix, R-10) are shown in Fig. 5. The image on the right side was obtained from R-10. Although small white crystals can be observed through a liner or a supporting board, no image of the lumps was observed in the THz image. This suggested that the sizes of the TBR crystals were smaller than the spatial resolution of TPI (approximately 100 μm). According to our study using Microscopic Laser Raman Spectroscopy/Mapping, the size of the TBR crystals was estimated to be from 6 μm to 40 μm (Sakamoto et al. 2006, 2007).

2.4. Depth image of crystals in TDDS tape

The THz image of A-30 and its depth image are shown in Fig. 6. The thickness of the lump of crystals in the matrix increased. The refractive index of the THz pulse was shifted due to the edges of the lumps of TBR crystals. This suggested that a comparatively big shift of a refractive index provides a definite image.

In conclusion, it was shown that THz spectroscopy/imaging technology was useful for detecting lumps of crystals of an active drug in transdermal tapes. THz spectroscopy/imaging can provide unique physical (and/or certain kinds of chemical) information compared with near infrared and/or mid infrared spectroscopy/imaging. In particular, obtaining a depth image from a pharmaceutical sample would be very useful for gaining an in-depth understanding of the quality of pharmaceuticals.

Although approximately 100 μm of spatial resolution in the THz pulsed image would hinder the detection of min-

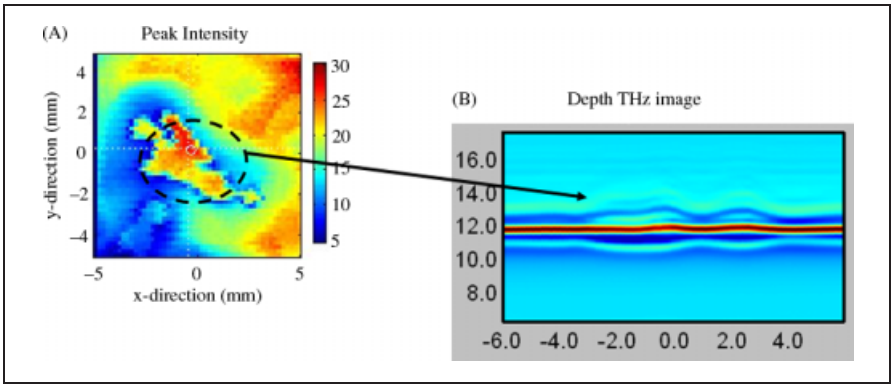


Fig. 6:
THz image of TBR crystal and depth THz image of matrix (A). The depth THz image in the scanned area where the crystal is observed shows the change in the thickness of the tape that can be seen (B)

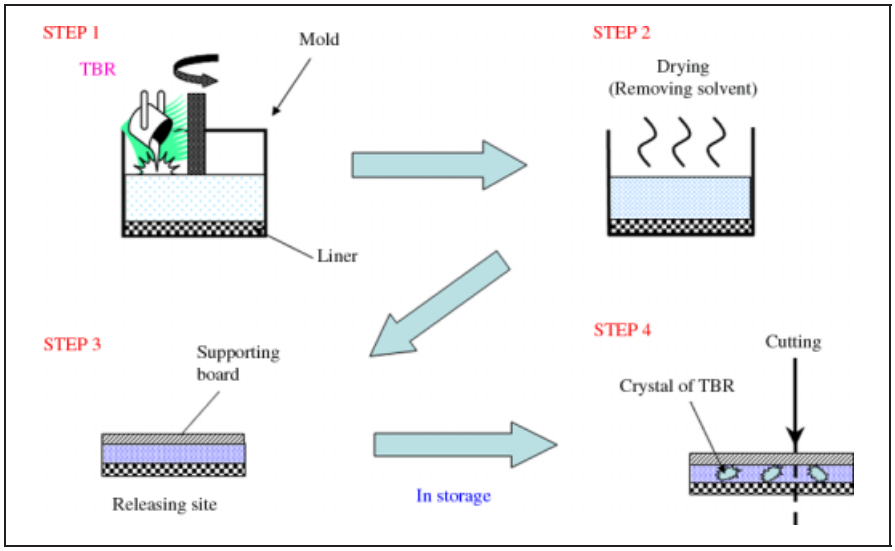


Fig. 7:
Flowchart showing preparation of model tapes. Residual solvents were removed by heating, and the mold was used to produce a sheet of model tape with a constant thickness and area

ute particles that are smaller than the spatial resolution, a reflective index of the THz pulsed wave may provide other useful information. Moreover, it would be able to detect problems caused by the manufacturing process, such as mixing of air bubbles and heterogeneity of active substances in the matrix. Therefore, this technology would be useful as an analytical tool not only for pharmaceutical quality control, but also for process control in pharmaceutical manufacturing.

Table: Prepared model transdermal tapes in this study

TBR level	Acrylic matrix	Rubber matrix
0 w/w% (Placebo)	A-0	R-0
10 w/w%	–	R-10
20 w/w%	A-20	–
30 w/w%	A-30	–

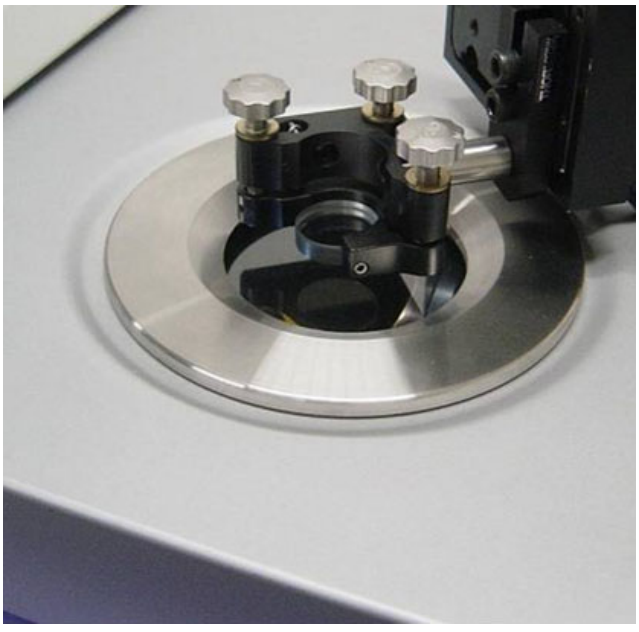


Fig. 8: Photograph of the metallic arm used when measuring the sample with a reference mirror

3. Experimental

3.1. Materials

TBR (purity $> 99.0\%$) and model tapes were supplied by Hisamitsu Pharmaceutical Co Inc (Tokyo, Japan). Polyethylene (PE) powder of particle size < 80 µm was supplied by Induchem.

3.2. Model tapes

The model tapes were prepared by TDDS Laboratory, Hisamitsu Pharmaceutical Co Inc (Tsukuba, Japan). In order to identify crystals of TBR in the matrix, two kinds of matrices, rubber and acrylic matrices, were prepared. The flowchart for preparing the model tapes is shown in Fig. 7. TBR and other ingredients of the adhesive solutions were stirred in the mold adequately. The mixture was extended on the liner and residual solvents were removed by drying. When the thickness of the matrix (the adhesive layer) became a constant (approximately 50 µm thickness), a supporting board was pasted on the matrix after removing the mold. A polyethylene terephthalate (PET) film was selected as a liner and as a supporting board, for both the model and the placebo tape. And then these tapes cut to a size of 36 mm diameter. TBR crystals in model tapes were generated by leaving the tapes to crystallize for some time.
The model tape that contained 0 w/w% (R-0, placebo), 5 w/w% (R-5) or 10 w/w% (R-10) of TBR in a rubber matrix consisted of polyisobutylene, polybutene and lipocyclic petroleum resin. Small white crystals were seen in all areas of the matrix in the A-10 through a liner or a supporting board. The model tape that contained 0 w/w% (A-0, placebo), 20 w/w% (A-20) or 30 w/w% (A-30) of TBR in an acrylic matrix consisted of acryl adhesion polymer and isopropyl myristate. On the A-30 samples, small white crystals were seen in all areas of the matrices. A higher TBR concentration was needed to generate the crystals in the acrylic matrix compared with the rubber matrix because of the solubility of TBR. The prepared model tapes are shown in the Table.

3.3. Apparatus and measurements

3.3.1. Transmittance measurement of tablet by TPS

In order to identify a THz spectrum of TBR, a pellet containing approximately 10 w/w% of TBR was prepared by compressing at 2 t for 3 min with a press machine. The pellet was measured using a TPS 1000 spectrometer (TeraView Limited, Cambridge, UK). Each sample was measured covering the spectral range from 120 cm^{-1} to 2 cm^{-1} at 1.5 cm^{-1} of spectral resolution. Spectra were obtained averaging 1800 scans.

3.3.2. Transmittance-reflectance measurements of tapes by TPI

A reference mirror was first measured, and then the samples were mounted to the mirror and adjusted horizontally against the measurement window of the TPI Imaga^{TM} 1000 instrument (Fig. 8); subsequently, THz radiation was focused onto the samples to gain maximum sensitivity. Placebo tapes were used as a background for all measurements.
A TPI imaging system, TPI Imaga 1000 (TeraView Ltd., Cambridge, UK), was used for the reflectance measurement, which was operated in the rapid scan mode. Terahertz images were obtained by raster scanning the terahertz beam across the sample, which was mounted at the focus position. The scanned area was 12 mm × 12 mm, which corresponds to 120 pixels × 120 pixels at 100 µm spatial resolution. The total measurement time was approximately 30 min.

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