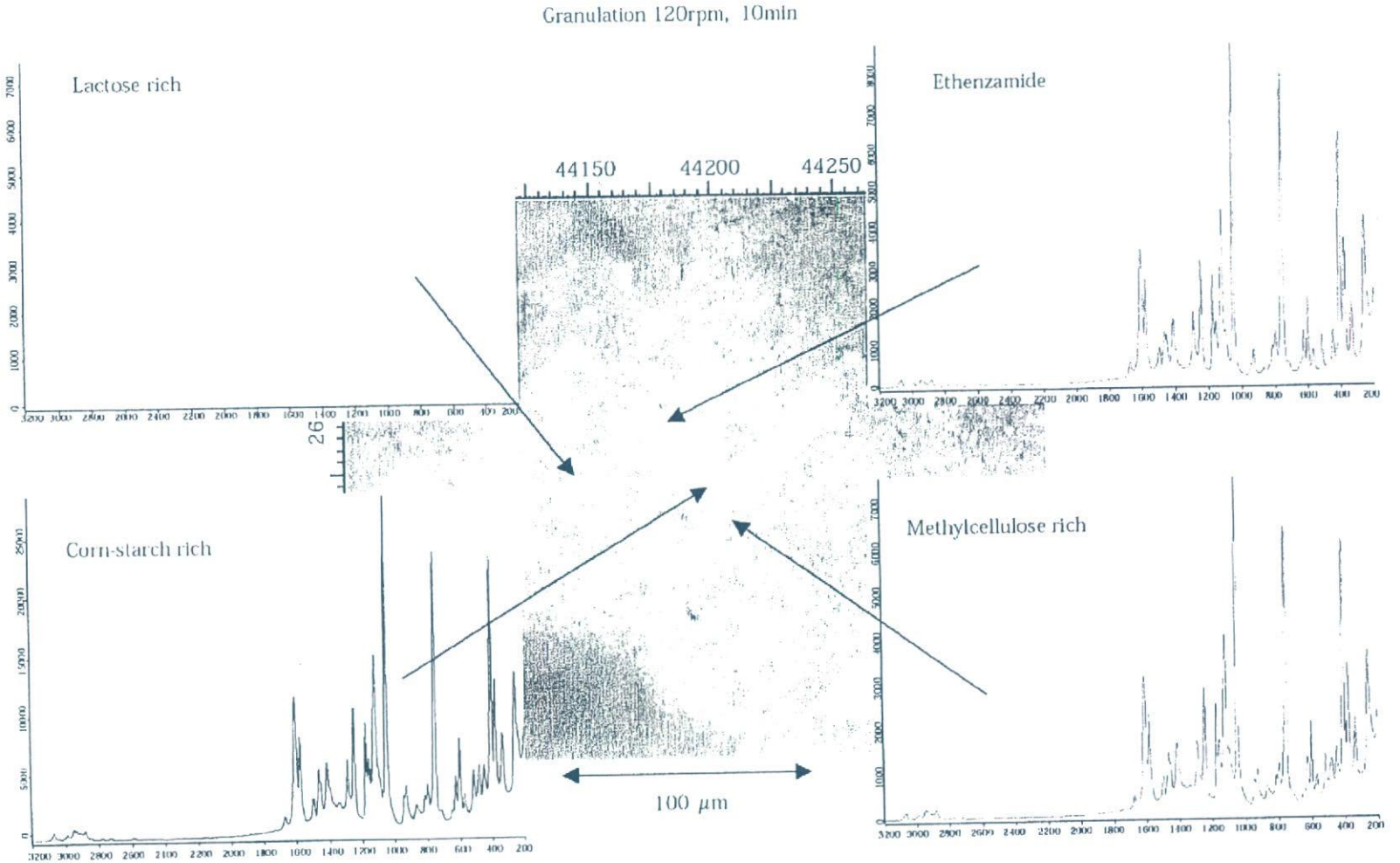

図 13　高速撹拌造粒（120r.p.m，10 分間）により得られた顆粒表面における各成分の光学顕微写真とラマンスペクトル

※カラーの図は巻頭ページ参照

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Detection of Tulobuterol Crystal in Transdermal Tapes using Terahertz Pulsed Spectroscopy and Imaging

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Abstract— **Applicability of the terahertz pulsed spectroscopy (TPS) and the terahertz pulsed imaging (TPI) to detect tulobuterol (TBR) crystal in transdermal tape has been investigated. The TBR crystal was identified by comparison between spectrum of tapes and TBR reference standard. The TBR crystal in patch matrix was successfully detected by the TPS and TPI. These results indicate that the TPS and TPI are applicable to identify an active substance in patch matrix for quality control.**

I. Introduction

Tulobuterol (TBR) transdermal tapes are used to cure bronchial asthma as a bronchodilator (β_2-blocker). TBR is one of the most suitable compounds for systemic transdermal formulation because it has very high permeability into keratin layer. The release rate of TBR from the matrix is controlled by the formation of crystals of TBR. For this reason, the chemical state of TBR in matrix is an important factor to assure the quality of this tape. Recently, the THz technology has been applied in pharmaceutical industrial field. Optical-delay analysis using THz pulse is also possible to measure the thickness of the layer of a sample that has multi-layers structure by using the time delay of THz pulse. These advantages of this technology have been applied to acquire depth chemical image of layers in the multilayer tablets, and to measure a coating film thickness in coated tablets. This study deals with an applicability of the THz spectroscopy (TPS) and imaging (TPI) for detection of TBR crystals in transdermal tapes.

II. Procedure

The model tapes that contain 0w/w% (placebo, A-0), 10w/w% (A-10), 20w/w% (A-20) or 30w/w% (A-30) of TBR were prepared. The TPI 1000 system (TeraView Ltd., Cambridge, UK) has been used for the measurements. Terahertz maps were obtained by raster scanning the terahertz beam across the sample, which was mounted at the focus position. The scanned area which corresponds to 120 x 120 pixels at 100μm of spatial resolution was 12mm x 12mm. The total measurement time was approximately 30 min.

III. Results and Discussion

A. THz pulsed spectrum of TBR obtained from TPS instrument

Fourier-transformed THz waveform of TBR tablet was observed compared with that of the polyethylene reference (Fig. 1). It seemed that unique absorbance range, from 35cm^{-1} to 70cm^{-1}, is available to detect TBR absorbance from total waveform of tapes specifically.

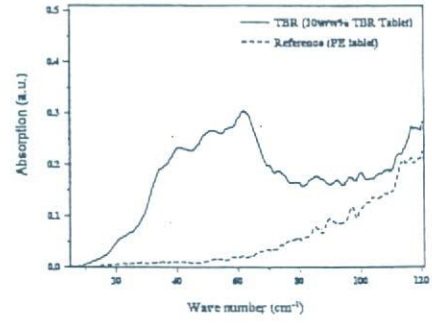

Fig. 1 Typical Fourier-transformed THz waveforms of the TBR tablet (solid line) and the PE tablet (reference, broken line)

B. Fourier transformed spectrum of placebo model tape and TBR model tape

The THz pulsed waveforms obtained from the A-0 and A-20 are shown in Fig. 2. The absorbance that would be specific waveform of TBR from 45cm^{-1} to 70cm^{-1} was observed from waveform of sample.

C. Detectability of TBR in crystal area and outside crystal area in matrix

The THz image of A-20 in 12mm x 12mm of area is shown in Fig. 3 (A). The aggregation of TBR crystal that is pointed by arrow in matrix was clearly identified. Fig. 3 (B) shows the waveforms obtained from model tapes. The characteristic

absorption of TBR that was shown inside range between two broken lines, from 45cm^{-1} to 60cm^{-1} was detected from the pixels that were located not only inside crystal but also outside crystal. This observation suggested that the TBR also existed at the outside of crystal in matrix.

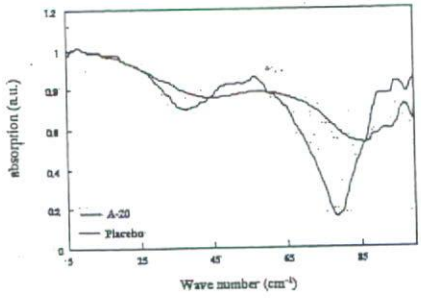

Fig. 2 Typical Fourier-transformed THz waveforms of the model tape (A-20, blue line) and the placebo model tape (A-0, red line)

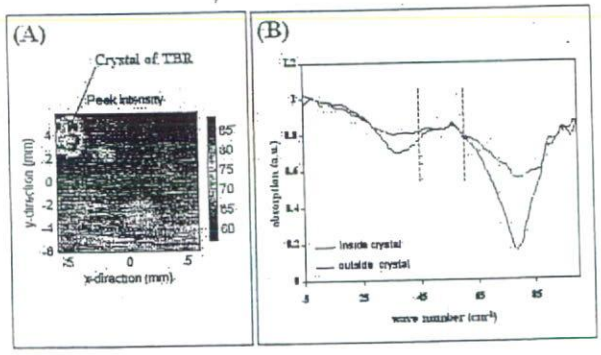

Fig. 3 Typical THz image and Fourier-transformed THz waveforms of the model tape (Blue line: inside crystal, Red line: outside crystal)

D. *Crystal size of TBR in matrix*

The THz image obtained from the A-30 is shown in Fig. 4. Several sizes of TBR crystal lump were observed in two scanned areas. The size of observed crystals was from 0.5mm to 3mm in longer diameters and from 0.1mm to 0.2mm in shorter diameters.

E. *Detection of TBR crystal using refractive index*

Despite the THz image of the TBR crystal was clearly identified in the acrylic matrix, it was difficult to detect the unique absorption of TBR was observed (Fig. 5 (A), (B)). This phenomenon was presumably because characteristic waveform of TBR became broad by oscillation generated when measuring a sample using quartz. The depth THz imaging in the area where the crystal was observed showed the change in thickness of the tape in the sight (Fig. 5 (C)). This result suggests that the change in the thickness of the tape by the existence of the crystal is detected by refracting the terahertz pulsed laser light from this on the edge of the crystal. Therefore the crystal of TBR in matrix could be detected as the image by the contrast of the refractive index.

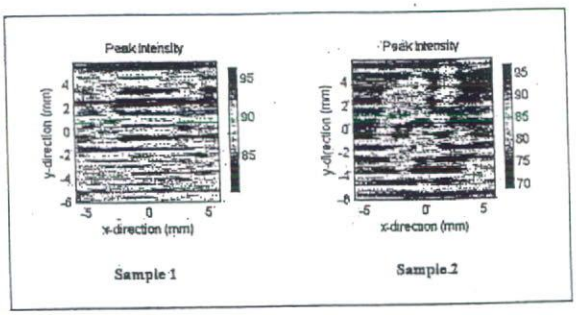

Fig. 4 The THz pulsed images obtained from the A-30s

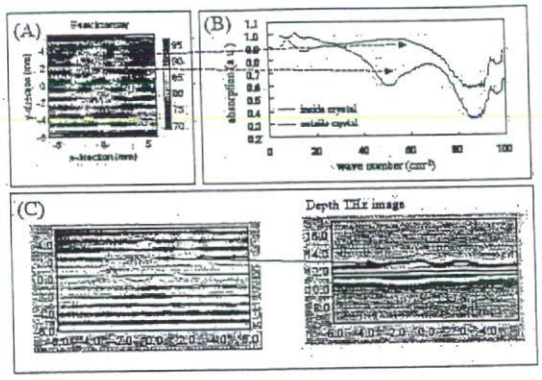

Fig. 5 The THz pulsed images (A), the Fourier-transformed waveforms (B) and the depth THz image obtained from the A-30

IV. Conclusions

It was shown that the TPI and TPS technology was useful for the detection of the crystal of an active substance in transdermal tapes. A depth image that could be obtained from pharmaceutical sample would be very useful to understand quality of pharmaceuticals profoundly. Although approximately 100μm of spatial resolution in the THz pulsed image would be hinder to detect minute particles that are smaller than the spatial resolution, reflective index of the THz pulsed wave may provide other useful information. This technology has good advantage as an analytical tool for not only pharmaceutical quality analysis but also process control in pharmaceutical manufacturing.

Acknowledgement

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