TERAHERTZ SPECTROSCOPY AND IMAGING STUDY FOR QUALITY EVALUATION OF GENERIC DRUGS I. CIPROFLOXACIN HYDROCHLORIDE TABLETS

Tomoaki Sakamoto[1], Alessia Portieri[2], Daisuke Sasakura[3], Tomoyuki Matsubara[3], Tsuyoshi Miura[3], Philip F. Taday[2], Donald D. Arnone[2], Toru Kawanishi[1], Yukio Hiyama[1]
[1]National Institute of Health Sciences Japan [2]TeraView Limited United Kingdom [3]Bruker Optics K.K. Japan
tsakamot@nihs.go.jp

Objective
In this work terahertz pulsed spectroscopy (TPS) and imaging (TPI) has been used for quality evaluation of generic drugs. Tablets of Ciprofloxacin hydrochloride (CPFX.HCl), which is one of the effective drugs for anthrax infection, were selected. Tablets from the innovator's and four kinds of generic tablets were measured for acquiring unique THz spectra as well as imaging information.
Experimental
CPFX.HCl, commercially available, was used as the standard substance to identify the API in tablets. Tablets were crushed and polyethylene pellets were pressed together with the resulting powdered tablets. These were measured using the TPS Spectra 1000 system (TeraView Ltd., Cambridge, UK) and THz spectra were obtained. The Imaga 2000 system (TeraView Ltd., Cambridge, UK) was also used to acquire THz images of the intact tablets.
Result and discussions
Unique spectral features between 35cm-1 and 90cm-1 were observed in the spectra from the five kinds of tablets in the spectroscopic measurments. These features are deriving predominantly from the API, CPFX.HCl, as the same features are present when comparing with the API substance alone. The characteristic peaks were observed at 30cm-1, 40cm-1, 80cm-1, 85cm-1.
THz images of the intact tablets were also acquired. When analyzing the images of the tablets it was possible to distinguish between the innovator's tablet from the generic tablets as the generic tablets all showed features of in homogeneity and added layers in the coating that that might be due to different processing methods, un-uniformity of particle size. The B-scan image specifically show for each tablet that different profiles such as coating thickness and added layers inside the tablets were formed by different compression methods. These results show that the TPS and/or TPI are applicable to discriminate generic tablets from each other as well as from the innovator's tablet and that the technology is useful to evaluate the quality of generic drugs and to compare the brand drugs. Furthermore, characteristic THz spectra provide the possibility to screen counterfeit drugs from that of the legal product.

テラヘルツ波で医薬品を評価する

テラヘルツ(THz)領域の電磁波は，人体への影響が少なく半透過的であることから，様々な分野での応用が実用化されつつある。特に製薬及び化学分野では結晶形の違いの識別に加え，医薬品源薬や不法薬物において特徴的な波形が観察されることから新たな分析法として注目されている。本研究では，光学活性化合物の識別について光学異性体を含むアミノ酸であるロイシンの結晶作製条件の違いによる試料を用いて検討したところ，結晶構造の違いでテラヘルツスペクトルが変化することを確認した。今後は，光学純度の測定や，医薬品の安定性などの品質評価への応用が期待される。

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テラヘルツ波を用いた医薬品評価技術の開発に関する研究　I.

（国立衛研薬品部・東北大院工[1]・首都大研究戦略セ[2]）○坂本知昭・田邉匡生[1]・佐々木哲朗[2]・小山　裕[1]・西澤潤一[2]・川西　徹・檜山行雄［連絡者：坂本知昭，電話03-3700-1141，E-mail：tsakamot@nihs.go.jp］

テラヘルツ(THz)波領域(100GHz-10THz，3cm^{-1}-333cm^{-1})の電磁波は，人体への影響は少なく，半透過的であることから，空港等での危険物や爆発物の検知などのセキュリティー分野や体組織中の腫瘍などを映像化するT-ray可視化技術への応用など医療分野において実用化されつつある．製薬・化学分野においては，水素結合などの弱い分子間エネルギーや結晶格子のフォノン振動などを検出する特性を利用した結晶形の変化の識別や，医薬品原薬や不法薬物などの特徴的な波形の検出が報告されており，指紋的波形を用いた定性・定量分析への応用が期待されている．しかしながら，スペクトルの解釈など未知の部分も多く，分析手法の確立に向けて検討課題が積み重なっている．本研究は薬効にも影響する光学活性化合物の識別性について検討したものである．THz波によるラセミ化合物の識別は可能であるが，個々の光学異性体の識別手法は具体的には実現されていない．そこでアミノ酸であるロイシンの結晶作製条件に起因するTHz波形の違いに着目し，光学異性体を含む結晶構造の識別を試みた．図ではL体，D体50%ずつの混合試料と混晶試料（再結晶）のTHzスペクトル(167cm^{-1}-33cm^{-1}(1Hz-5Hz))を示したが，再結晶試料では混合試料と比べて吸収の幅が狭くなり，吸収極小ピークが低波数側にシフトしていることが観察され，混晶形成による結晶構造の違いがスペクトルのシフトと関連することが示唆された．更に光学純度を定量的に測定できる可能性も示唆された．以上の成果は，THz波による光学純度測定への可能性を示すとともに，有効性，安全性など光学活性医薬品の品質評価へのTHz波の適用可能性を示すものであった．

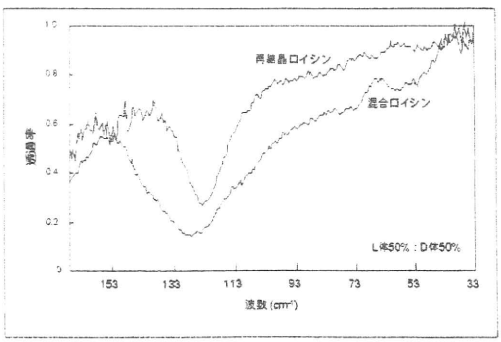

図　L体とD体のロイシン(50%:50%)における混合試料と再結晶試料のテラヘルツスペクトル

Development of quality evaluation method for pharmaceuticals using terahertz wave - terahertz spectral features in re-crystallization DL mixture of amino acids and applicability for an optical purity analysis-

Tomoaki Sakamoto[1], Tadao Tanabe[2], Tetsuo Sasaki[3], Yutaka Oyama[2], Junichi Nishizawa[3], Toru Kawanishi[1], Yukio Hiyama[1]
[1]Division of Drugs, National Institute of Health Sciences
[2]Graduate School of Engineering, Tohoku University
[3]Center for Priority Area, Tokyo Metropolitan University
tsakamot@nihs.go.jp

Purpose Authors have studied about quality evaluation techniques of pharmaceuticals using terahertz (THz) spectroscopy and imaging. As one of our activities for study on applicability of THz wave for pharmaceutical analysis, amino acids were used to examine distinguishability of chiral isomers by THz wave. Although the distinction between racemate and enantiomer using THz spectroscopy could be developed, identification of each enantiomer has not been realized. The purpose of this study is not only to develop quantitative methods for an optical purity of chiral pharmaceuticals but also to provide concerning spectroscopic understanding of THz wave region.

Experimental All measurements of THz spectra were performed by a GaP THz signal generator system equipped with room temperature operated pyroelectric detectors. Re-crystallized D, L-leucine and their mixtures with several levels of concentration ratio were obtained from water. These spectra of samples were measured at the wave numbers range of between 33cm^{-1} (1 THz) and 167cm^{-1} (5 THz).

Results and discussion Re-crystallized D, L-leucine mixtures appeared the characteristic THz spectral features, and the half width of peaks tended to be narrow compared with those of mixture of them. The peak tops were sifted to lower wave numbers (by 2.5 cm^{-1}- 3.5 cm^{-1}) (Fig. 1). It was suggested that this phenomenon was caused by the change of crystal structure due to re-crystallization of D, L mixtures. Furthermore, the difference of spectral features of THz spectra of re-crystallized D- and L-leucines between 133 cm^{-1} (4 THz) and 190 cm^{-1} (6 THz) was observed (Fig. 2). Then, relatively good correlation between the ratios of the optical isomer and the THz transmittance (%) was also observed. Although further study should be needed to explain detail of this phenomenon, possibility of optical purity measurement is shown in this study. In this symposium, authors will present applicability of THz spectroscopy for purity estimation of optical isomers based on differences of spectral features obtained from several re-crystallization condition of D, L- leucine mixture.

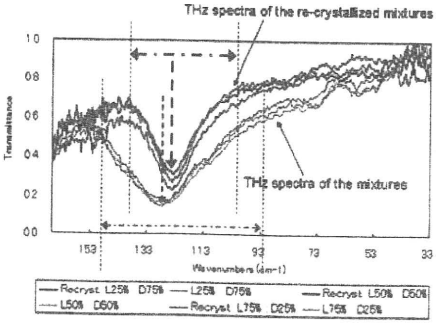

Fig. 1 THz spectra of D,L-leucine mixtures and their re-crystallization mixtures

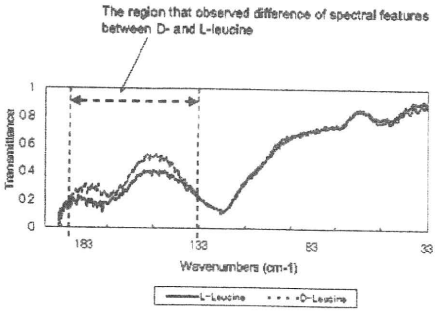

Fig. 2 THz spectra of re-crystallized D- and L-leucine

P01B

Qualitative Investigation of Tulobuterol Transdermal (TDDS) Tapes using Near Infrared Spectroscopy and Imaging

Tomoaki Sakamoto,[1] Daisuke Sasakura,[2] Yasunori Takada,[3] Kazunosuke Aida,[3] Yasuto Fujimaki,[4] Tomoyuki Matsubara,[2] Tsuyoshi Miura,[2] Takaaki Terahara,[3] Toru Kawanishi[1] and Yukio Hiyama[1]

[1]Division of Drugs, National Institute of Health Sciences, Tokyo 158-8501, Japan, E-mail: tsakamot@nihs.go.jp

[2]Bruker Optics K.K., Tokyo 110-0016, Japan

[3]TDDS Laboratory, Hisamitsu Pharmaceutical Inc., Tsukuba 305-0856, Japan

[4]Tokyo Metropolitan Industrial Technology Research Institute, Tokyo 125-0062, Japan

Abstract

The objective of this work is to develop an evaluation method for crystallization of tulobuterol (TBR) in transdermal pharmaceuticals using near infrared spectroscopy (NIRS) and near infrared imaging (NIRI). The unique absorption, the first overtone of secondary amine was used for detection of TBR crystals in the matrix. More than 30 days of the duration process was needed to complete the crystallization of TBR in tulobuterol transdermal (TDDS) model tapes. A time-course distribution analysis of TBR crystals in the matrix was conducted using NIRI.

Keywords: tulobuterol, transdermal tape, TDDS, crystallization

Introduction

An evaluation method for crystallization of tulobuterol (TBR) in transdermal pharmaceuticals using near infrared spectroscopy (NIRS) and near infrared imaging (NIRI) has been developed. TBR exists as crystal form in matrices to control its release rate from matrices into skin, because it has highly skin penetration. Although crystallization of TBR is very important for quality control of TBR Tapes, confirmation of TBR crystals in products is not possible by a commonly used release testing. Therefore, the end point of the crystallization manufacturing process depends on information obtained from the development stage of product. In this symposium, authors will present not only the development of NIRS/NIRI analysis for evaluation of crystallization process of TBR but also the comparison study of TBR distribution and microscopic investigation between the brand and generic products.

Materials and methods

Sample

Model tapes were prepared by the tulobuterol transdermal (TDDS) Laboratory, Hisamitsu Pharmaceutical Co., Inc. (Tsukuba, Japan). Model tapes that contained 0 % w/w (R-0, placebo), and 10 % w/w (R-10) of TBR in a rubber matrix that consisted of polyisobutylene, polybutene, and lipocyclic petroleum resin, were prepared for this study. Small white crystals were seen in all areas of the matrix in the R-10 sample. TBR and other matrix adhesive solution ingredients were mixed and thoroughly stirred. The mixture was extended on a liner and residual solvents were removed by drying. The matrix was adjusted to a constant thickness (approximately 50 μm) and pasted onto a supporting board. A polyethylene terephthalate (PET) film was selected for the liner and the supporting board of the model tapes. Then, the sample was cut to a size of 36 mm diameter. TBR crystals in the model tapes were generated by leaving the sample to stand.

Brand and generic products were purchased from commercial source.

Spectral acquisition

The Fourier transform (FT)-NIR spectrometer model MPA (Bruker Optics, Ettlingen, Germany) was used for spectral acquisition and to make macroscopic (spatial resolution: 3 mm) NIR chemical maps. The VERTEX 70 with the infrared microscope model HYPERION 2000 (Bruker Optics, Ettlingen, Germany) was used for acquiring NIR chemical images. Resolution, scan numbers were 2 cm^{-1}, 64 scans for the MPA, 16 cm^{-1}, 32 scans for the VERTEX70, respectively. Measurement range of both analyses was 8000 cm^{-1} to 4000 cm^{-1}. In case of macroscopic NIR chemical maps, resolution and scan numbers were set at 4 cm^{-1} and 64 scans, respectively.

Data analysis

Data analysis was performed with OPUS 6.5 software (Bruker Optics, Ettlingen, Germany). The unique peak at 6450 cm^{-1} based on crystallization and its integrated values were used to detect TBR crystals and to make chemical images. Relative intensities (%) of TBR absorptions were calculated for estimating of crystallization rate of TBR.

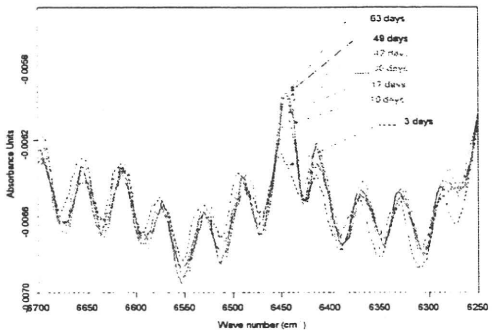

Figure 1. Time-course of the unique near infrared absorbance of tulobuterol (TBS) crystals in tulobuterol transdermal (TDDS) model tapes.

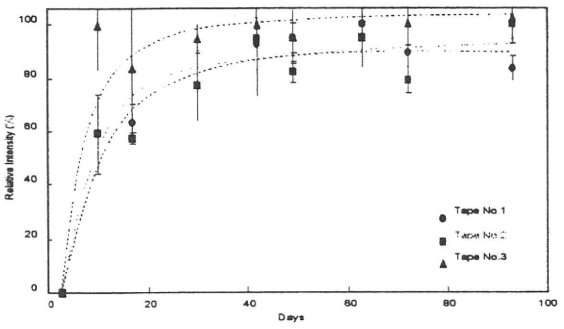

Figure 2. Day-relative peak intensity correlation of tulobuterol (TBS) crystallization.

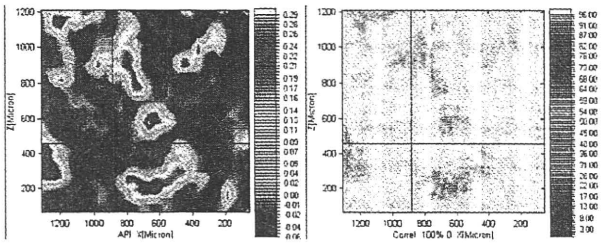

Figure 3. Near infrared chemical image (Left) and microphotograph (Right) of tulobuterol (TBS) crystals in tulobuterol transdermal (TDDS) model tapes.

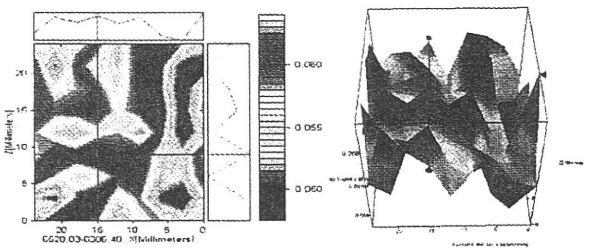

Figure 4. Typical macroscopic near infrared map and three dimensional (3D) map of tulobuterol (TBS) crystals in commercial tape.

Results and discussion

Detecting the unique peak against crystallization provided distribution information of TBR crystals in matrix (Figure 1). Estimation of the end point of crystallization of TBR in the model tapes was possible by observing time-course changes of the crystal distribution (Figure 2). Moreover, the growth of bulk of TBR crystals was traceable chemically using the microscopic NIR chemical imaging technique (Figure 3). The other hands, a macroscopic NIR chemical mapping by measuring 15 x 15 mm area, which can cover the most of a commercial tape area, could provide rough distribution information of crystals in commercial tapes quickly. The macroscopic maps obtained from several commercial tapes which were made from one batch showed un-uniformly distribution of TBR crystals in each tape (Figure 4). This result suggests the bulks of TBR crystal were generated irregularly in the matrices. Moreover, this method was applied to detect TBR crystals in 7 kinds of generic tapes. No any unique peak which shows an existence of crystals were observed in all generic tapes prescribed by different way to control release rate compared with the brand product. This approach was also applicable to confirm TBR crystal in commercial tapes.

Conclusion

This approach with a combination of the three methods would be useful for not only an end point estimation of crystallization of an active drug in the manufacturing process development stage but also an identification of crystals of an active drug in products. Moreover, NIR chemical images used by the characteristic peak of crystallization of an active drug can be used for analysis of a mechanism of crystallization of chemicals in polymer. Furthermore, a macroscopic NIR chemical mapping provides information of rough distribution of TBR crystals in comparatively wide-area with short analytical time. For example, this rapid macroscopic mapping technique would be used to determine crystalline uniformity of the tapes. This innovative and non-destructive quality evaluation method using NIRS/NIRI or macroscopic mapping techniques will contribute to build unique and/or robust quality system for development and manufacturing of TDDS pharmaceuticals.

Acknowledgement

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