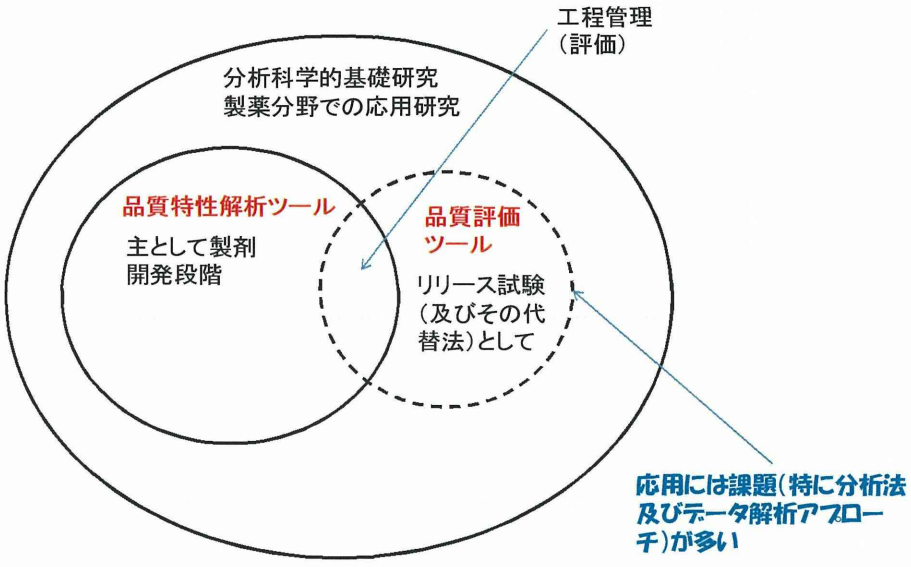
製薬分野での分析技術のポテンシャルと応用



41

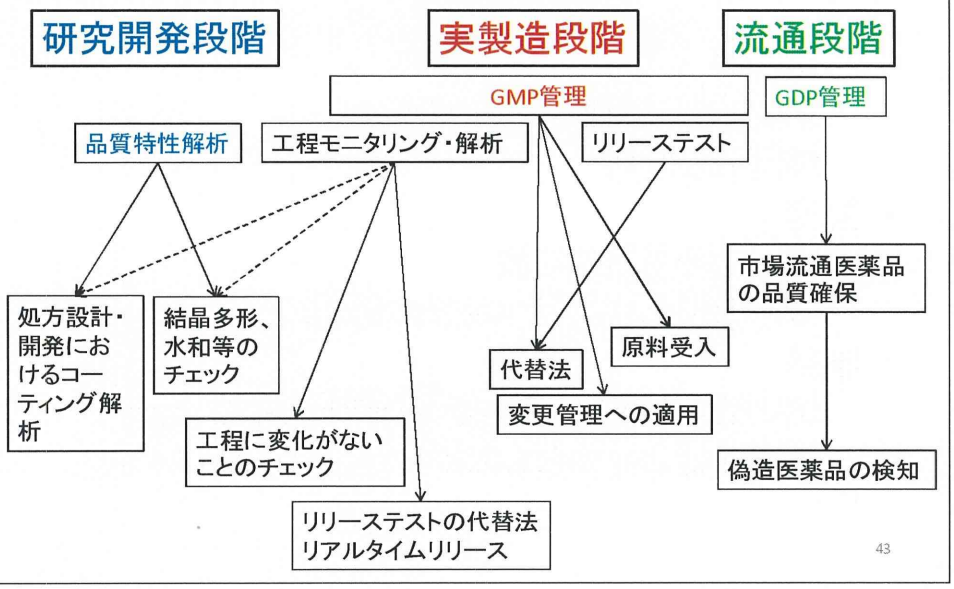
品質評価ツールとして導入する際の課題

- 医薬品の品質特性解析ツールとして規格・基準の確認、評価に関連した分析を行う場合、どのような適格性評価が必要となるか？

⇒日本薬局方（医薬品に関する基準書）や日米欧医薬品品質規制調和会議（ICH）で提唱される分析法のバリデーションが要求される

42

各ステージにおけるFIR/THz法への期待
---導入の一例---



43

分析法のタイプと評価すべき分析能パラメータ

	確認試験	純度試験		定量法など
		定量試験	限度試験	
真度	−	+	−	+
精度				
併行精度	−	+	−	+
室内再現精度	−	+*	−	+*
特異性	+	+	+	+
検出限界	−	−**	+	−
定量限界	−	+	−	−
直線性	−	+	−	+
範囲	−	+	−	+

- *: 室間再現精度を評価するときは，室内再現精度の評価は必要ない
- **: 必要なときもある

44

日本薬局方に準じた分析法バリデーションの評価とデータの信頼性確保（分析能パラメータと要求事項）

- 特異性：
  目的成分に特徴的なシグナル
  帰属の必要性
- 真度：
  測定値の偏りの程度
  対照分析法を基準(NIR法の場合）
- 精度：
  繰り返し分析の一連の測定値が一致する程度
  対照分析法と比較した相対誤差（NIR法の場合）

45

分析法バリデーションの評価結果がもつ役割

1．評価者が自身で設定した分析法が適格であることを判断する材料

2．審査・査察等で設定されている分析法が適確であることを判断する材料

申請時の規格及び試験方法に設定する際には分析法の妥当性を示す資料として提出

⇒ 客観的に妥当性が判断できることが必要

46

遠赤外／テラヘルツ波技術への期待と今後の課題

品質特性解析ツール

結晶多形
水和物の識別
コーティング等層の解析
化学結合・相互作用等解析

他分析法との比較の必要がある場合あり

規格・基準の設定に向けた適用の場合には分光学的なバックグラウンドを示す必要あり？

品質評価ツール

定性・定量分析（リリーステスト）

工程内管理（品質評価）

審査・査察の対象の可能性
標準化（標準的導入アプローチ）研究

スペクトルの解釈の重要性

47

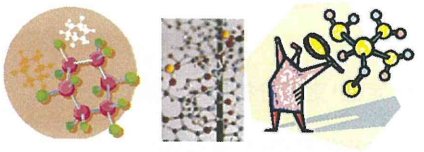
医薬品の品質評価ツールとして...

- ●定性的適用
  - スペクトルの解釈： 帰属について（特異性の確保）
  - 再現性の高いサンプル処理（標準的アプローチ）
  - スペクトルライブラリーの活用
- ●定量的適用
  - 標準的スペクトル解析技術の提案

48

テラヘルツ波技術への期待
（研究の目標）

分光計測



製剤の品質特性解析
品質評価ツール
化学結合等の解析

工程管理

製錠工程・コーティング工程評価
分光計測技術・イメージング技術

既存の分光分析技術では検知できなかった分光（物理・化学）情報の獲得
医薬品品質解析・工程評価ツールとしての可能性を検計・提案
医薬品評価技術としての標準化

49

ご清聴有難うございました

50

日本薬学会第132年会発表要旨

高速透過含量測定と分光分析バリデーションアプローチ

坂本知昭[1]、藤巻康人[2]、小金井誠司[2]、村山広大[3]、小宮山誠[3]、香取典子[1]、檜山行雄[1]、奥田晴宏[1]
[1]国立医薬品食品衛生研、[2]都産業技術研究セ、[3]横河電機センシング研

【緒言】近赤外分光（NIRS）法は、特に固形製剤のインライン工程評価ツールとして導入が試みられてきた分析法の１つである。しかしながら、含量測定など特に透過による定量評価に用いる分光情報を適切に得るためには 1 錠当たりの測定時間が長く、工程における検体解析数は限定される。そこで著者らは解析検体数の増加による精密な定量予測効果を得ることを目的として、錠剤の超高速透過測定法の工程評価ツールとしての導入研究を行っている。本年会では、実用化に向けて適確な NIR 分光情報に基づいて定量評価を行っていることを検証するためのバリデーションアプローチについて検討したので報告する。

【実験】装置は横河電機株式会社製 NIR 分光器を用いた。測定範囲は 930 nm～1736 nm、波数分解能は 1 nm、積算回数（平均化回数）は 10 回に設定した。リファレンスには拡散透過板として、2 mm の PTFE 板を用いた。検体は直径 8 mm の錠剤を用意し、錠剤の全分光情報を標準データとして、モデル工程において得られる分光情報との関連性を比較検討するために治具を作成した。

【結果及び考察】１錠当たりの測定時間は１秒間であった。適用したモデル錠剤では、1450 nm～1700 cmの範囲に特徴的な吸収が観察された。これらの範囲の吸収極大値について、治具を通して検出部に到達した透過光の吸光度を100%として、モデル工程における透過率と比較した。これらの詳細を本年会で報告する。

【謝辞】本研究は厚生労働科学研究費補助金医薬品・医療機器等レギュラトリーサイエンス総合研究推進事業（H23-医薬-一般-010）の一部として行ったものである。錠剤試料を提供頂いた株式会社パウレック長門氏及び細野氏に深謝する。

添付資料１１　国内学会発表要旨４
日本薬学会第132年会口頭発表資料

高速透過含量測定と分光分析バリデーションアプローチ

坂本知昭[1]、○藤巻康人[2]、小金井誠司[2]、村山広大[3]、
小宮山誠[3]、香取典子[1]、檜山行雄[1]、奥田晴宏[1]
[1]国立衛研、[2]都産技研セ、[3]横河電機センシング研

1

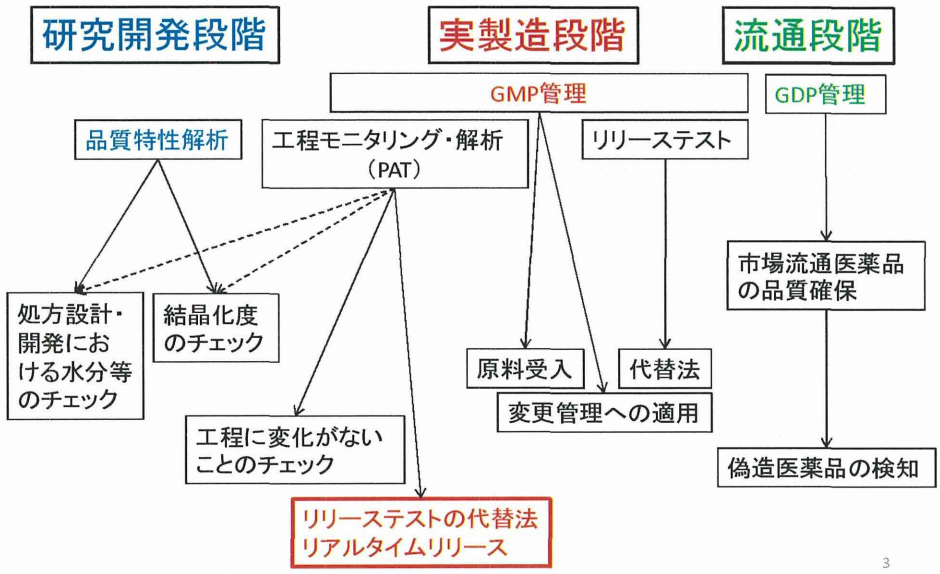
はじめに

- PAT更にはRTRTの概念の達成に向けた、分析技術の工程内への導入（NIRなど分光分析が中心）
- 具体的な実生産段階への取り込みでは審査及びGMP管理上の課題が生じる可能性
- 分析法の導入形態を考慮し、客観的な分析導入適格性の評価アプローチが必要

⇒ 分析法バリデーションの導入の際の考え方及び透過測定による含量評価法導入の際の具体的評価アプローチ事例の一部を本年会で紹介

2

NIRS法の品質評価ツールとしての期待（導入の一例）



3

研究対象としたNIR法の導入形態

- 透過測定による工程中の含量測定

（導入のメリット）

：錠剤中の全分光情報の取得

（導入の際の問題点）

①測定時間の問題

②適用波数範囲が限定的

⇒ 高速測定が可能な分光器の導入

4

研究内容

●NIR分光器（横河電機製P-NIRS017）

測定範囲： 10700 cm^{-1} - 7500 cm^{-1}

波数分解能： 8 cm^{-1}

積算回数（平均化回数）： 10回または1回

スペクトル前処理： SNV処理

●モデル錠剤

アセトアミノフェン	10 w/w%
乳糖一水和物	57 w/w%
コーンスターチ	30 w/w%
HPC-L	2 w/w%
ステアリン酸Mg	1 w/w%

●分析に際しての留意点

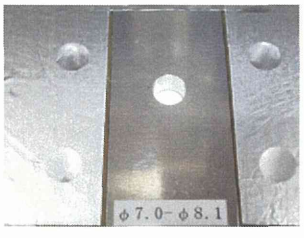
①基準分光情報の取得（工程内で得られる定量性能評価のための基準分光情報）： 治具の作製

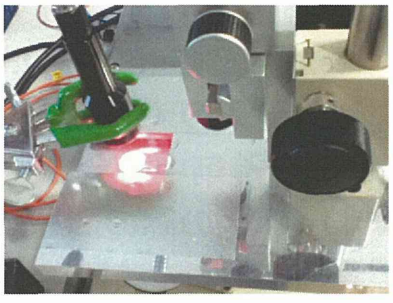
②客観性の高いデータ評価アプローチの確立

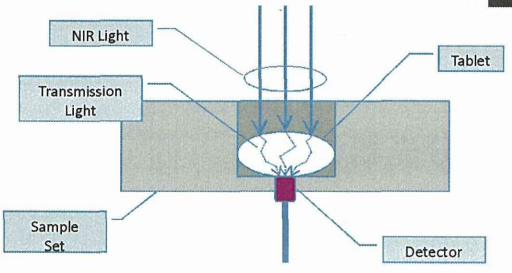
5

作製した治具

基準透過スペクトルデータの取得に向けて







6

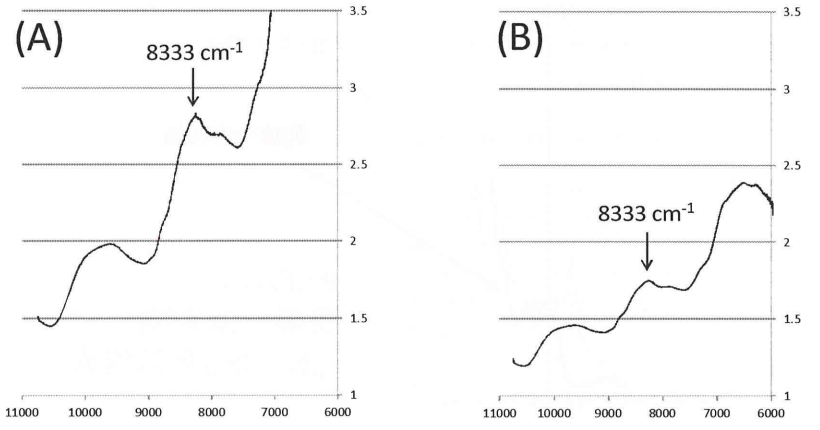


図　錠剤のNIR透過原スペクトル
（A: 治具あり（基準スペクトル）、B: 治具なし）

7

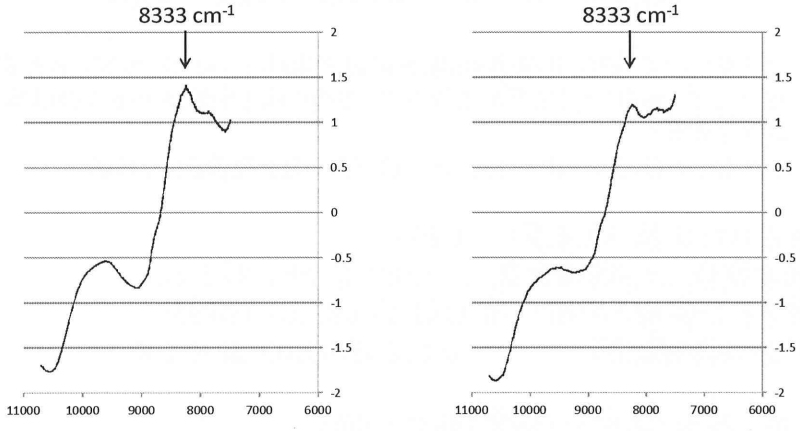


図　錠剤のNIR透過SNVスペクトル
（A: 治具あり（基準スペクトル）、B: 治具なし）

8

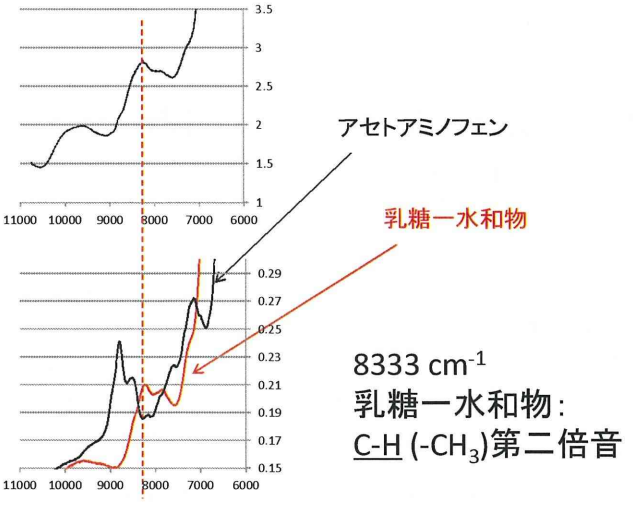


図　錠剤及び標準物質の透過スペクトル
（上段: 錠剤、下段: 標準物質）

9

透過NIR法における真度・精度の検討

- 治具を用いて測定した透過NIR吸光度の平均値（n=30）を“合意された真値”として、治具なし（モデル工程測定）で得られた吸光度との差の信頼区間を評価
- 治具なしで得た吸光度（8333 cm^{-1}）のばらつきを精度として評価

合意された真値（吸光度）:　1.299
工程測定値（SNV後吸光度）:　1.084 ≦ Abs. ≦ 1.211
合意された真値との差:　-0.2149 ≦ Dif. ≦ -0.0883
差の90%信頼区間:　-0.162 ≦ 90%CI ≦ -0.130

繰り返し精度（平均化（積算）回数10回）
基準原スペクトル（RSD、n=30）:　0.23 %（積算回数1回: 0.61%）
基準SNVスペクトル（RSD、n=30）: 0.64 %（積算回数1回: 1.97%）
工程原スペクトル（RSD、n=15）: 28.84 %
工程SNV測定値（RSD、n=15）:　3.28 %

10

想定する工程測定時間における精度

同一錠剤、繰返し回数30、積算回数1回、測定時間約1秒（治具なし）

原吸光度　：　0.45 %（RSD)

SNV吸光度：　1.50 %（RSD）

工程中の錠剤連続測定におけるばらつき

●錠剤設置回数6回、積算回数10回、治具なし

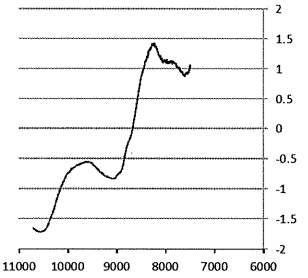
原スペクトル（RSD、n=1）：　27.82 %

SNV測定値（RSD、n=1）：　4.53 %

●錠剤設置回数6回、積算回数1回、治具なし

原スペクトル（RSD、n=1）：　20.40%

SNVスペクトル（RSD、n=1）：　3.24%



積算回数1回の測定条件で得られたスペクトル（SNV処理後）

11

まとめ

- 工程内に導入する分光器から得られる分光情報を的確に把握するために、基準スペクトルの設定が有用であるものと思われた。
- 全分光情報を得るための治具を用いることにより、“合意された真値”を設定することができ、導入装置がもつ真度を推定することが可能であった。
- 具体的な主薬成分の定量性に関する評価では、主薬成分由来の吸収または計量化学データを用いる必要があると思われるが、今後の検討対象とする。
- 導入しようとする分析・解析条件における評価結果は、精度と含量規格との整合性を確認する際に有用であり、また客観的な判断基準を与えることに貢献すると考えられる。

12

謝辞

本研究は厚生労働科学研究費補助金医薬品・医療機器等レギュラトリーサイエンス総合研究推進事業（H23-医薬-一般-010）の一部として行ったものである。

錠剤試料をご提供頂いた株式会社パウレック長門様及び細野様に深謝致します。

13

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
T. Sakamoto, K. Nakayama, A. Portieri, D. Arnone, D. Sasakura, P. Taday, A. Zeitler, T. Kawanishi, Y. Hiyama	Time-course analysis of tablet film-coating using terahertz pulsed imaging	Proceeding of 36th International Conference on Infrared, Millimeter and Terahertz Waves		1-2	2011
Tomoaki Sakamoto, Alessia Portieri, Donald D. Arnone, Philip F. Taday, Toru Kawanishi, Yukio Hiyama	Coating and density distribution analysis of commercial ciprofloxacin hydrochloride monohydrate tablets by terahertz pulsed spectroscopy and imaging	J Pharm Innov	7	87-93	2012

Vibrational spectroscopic analysis of theophylline in a pharmaceutical granulation process using near-, mid- and far-infrared/terahertz spectroscopy

Tomoaki Sakamoto*, Tetsuo Sasaki**, Jun-ichi Nishizawa**, Noriko Katori*, Yukio Hiyama*, and Haruhiro Okuda*
* Division of Drugs, National Institute of Health Sciences, Tokyo 158-8501, Japan
** Semiconductor Research Institute, Sophia University, Tokyo, Japan
Email: tsakamot@nihs.go.jp

Abstract— **Vibrational spectroscopic analysis of theophylline in a wet granulation process was performed. An anhydride was converted to a monohydrate during the granulation and a dehydration of monohydrate progressed during the drying process. A C-N stretching would be affected by an interaction between theophylline and a binder under a wet granulation process.**

I. Introduction and Background

A granulation process is often introduced to a pharmaceutical manufacturing process to improve a mobility of materials in a process and/or a compression property of tableting. A granulation process usually consists of two steps. One is to make homogeneous granules of ingredients by spraying of a binder aqueous solution and the other is a drying process of wet granules. Theophylline tablet which is used for asthma contains an anhydride form of theophylline as an active pharmaceutical ingredient (API). It is known that theophylline anhydride will be converted to its monohydrate form under high humidity condition. This phenomenon would be cause of delay of a dissolution rate of API from tablet. Therefore, theophylline may be affected during a wet granulation process physicochemically. We obtained different spectral data on C-H combination region derived from theophylline between the mixture (under dry condition) and the dried granules. We expect that a functional group (-N(CH3)-CO-) in theophylline chemical structure may form inter-molecular hydrogen bonding with a binder during a granulation process under wet condition. Near-infrared (NIR), mid-infrared (MIR), and far-infrared (FIR)/terahertz (THz) spectroscopy were used to scrutinize vibrational spectral changes of theophylline in a granulation and a drying process. Furthermore, we investigated pseudo-polymorphism conversion of theophylline (TP) during a wet granulation and drying processes.

II. Experimental

A. Granulation process and theophylline granules

A share granulation process was used in this study. To the mixture of 10 g of theophylline anhydride and 1.2 g of HPC add 4 ml of water during the granulation. Wet granules were dried under decompressed circumstance at room temperature, or were dried by dry air under ambient atmosphere at room temperature or 70 °C.

B. Analytical condition

For NIR or MIR measurement, MPA Fourier-transform NIR spectrometer (Bruker Optik GmbH, Ettlingen, Germany) or FT/IR-6300 Fourier-transform IR spectrometer (JASCO, Tokyo, Japan) was used. For FIR/THz measurement, a Gallium-Phosphorus (GaP) THz signal generator system equipped with a pyroelectric DTGS detector was used. This THz generator system was developed and constructed by Nishizawa et al [1,2]. The measurement range, resolution and scan number were set at 12500 cm^{-1} to 4000 cm^{-1}, 2 cm^{-1} and 128, for a NIR measurement, 4000 cm^{-1} to 400 cm^{-1}, 1 cm^{-1} and 64 for a MIR measurement, respectively. For THz measurement, a spectrum was obtained from 1 THz (33 cm^{-1}) to 5 THz (167 cm^{-1}) at 15 GHz measurement steps. NIR spectra or MIR spectra were obtained by diffuse-reflectance or attenuated total reflectance (ATR) mode, respectively. For THz transmittance measurement, the jig (attachment) was made to obtain a suitable spectrum of the granules, and the granules with the particle size which was below 100 μm were used.

III. Results

In the NIR spectrum, a significant difference of a spectral feature at 4300 cm^{-1} which was included in C-H combination region was observed. In the ATR-MIR spectrum obtained from the mixture of theophylline and HPC under dry condition or from the dried granules made by a wet granulation, an absorption at 1048 cm^{-1} (C-N stretching of N-CH_3 derived from theophylline) disappeared in the spectrum obtained from the dried granules. Moreover, the absorption at 1700 cm^{-1}

(C=O stretching) also disappeared on the spectrum obtained from the dried granules. This observation suggests that an inter-molecular hydrogen bonding between theophylline (C=O) and HPC might occur under a wet condition. We predict that formation of inter-molecular hydrogen bonding of C=O affects C-H combination derived from an adjacent functional group "N-CH_3". In the THz spectrum obtained from theophylline granules before drying, one of two major absorptions of theophylline anhydride at 0.95 THz disappeared. The waveform which has single absorption at 1.5 THz in the frequency range below 2 THz showed same waveform pattern as theophylline monohydrate. In case of the drying process under decompressed circumstance, the intensity of the absorption at 1.5 THz which is observed on the waveforms obtained from both forms decreased gradually with the passage of time, and disappeared at 240 min after the drying process was started (Fig. 1).

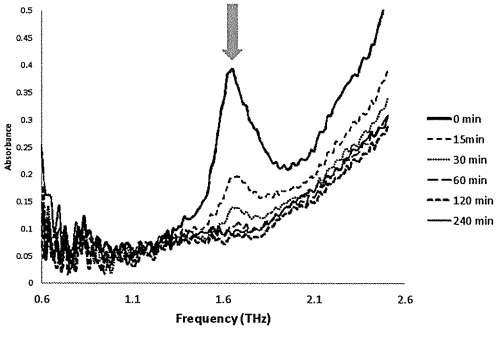


Fig. 1 Time-course change of THz spectra of theophylline granules (theophylline + HPC) under decompressed circumstance at room temperature

The absorption at 0.95 THz had not appeared through the drying process under ambient atmosphere at room temperature. However, in case the temperature was set at 70 °C, the absorption was already observed at 15 min after the drying process was started (Fig. 2).

This phenomenon indicates that temperature is the factor to convert its pseudo-polymorphism from monohydrate form to anhydride form. In case of decompressed circumstance, the absorption at 1.5 THz disappeared gradually with the passage of time. We guess this observation would be based on conversion from monohydrate form to amorphous form during a dehydration process. These results suggest that HPC would affect pseudo-polymorphism conversion and a dehydration of theophylline during a wet granulation.

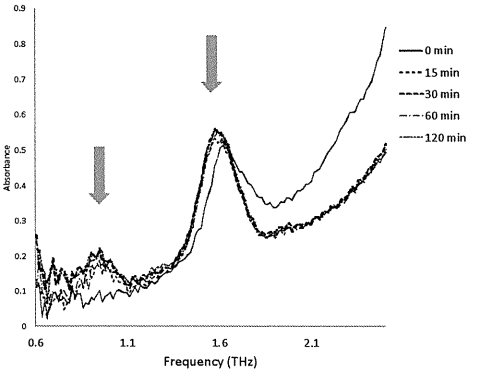


Fig. 2 Time-course change of THz spectra of theophylline granules (theophylline + HPC) under an ambient atmosphere at 70 ºC

IV. Conclusion

Terahertz spectroscopy is useful not only to scrutinize pseudo-polymorphism of theophylline but also to study contribution of a binder during a wet granulation process. Furthermore, an integrative spectroscopic analysis using NIR, MIR and FIR/THz electromagnetic wave would contribute for understanding of a pharmaceutical manufacturing process and for performing efficient quality control of pharmaceutical products.

Acknowledgment

This study was supported in part by a research grant from the Ministry of Health, Labour and Welfare of Japan (H23-iyaku-ippan-010) and a research grant (KHB1005) for Research on Health Sciences Focusing on Drug Innovation from Japan Health Science Foundation.

References

[1] T. Tanabe, K. Suto, J. Nishizawa, K. Saito, T. Kimura, Tunable terahertz wave generation in the 3- to 7-THz region from GaP, Appl. Physics letters, 83, 237-239 (2003)

[2] T. Tanabe, J. Nishizawa, K. Suto, Y. Watanabe, T. Sasaki, Y. Oyama, Terahertz wave generation from GaP with continuous wave and pulse pumping in the 1-1.2μm region, Materials Transactions, 48, 980-983 (2007)

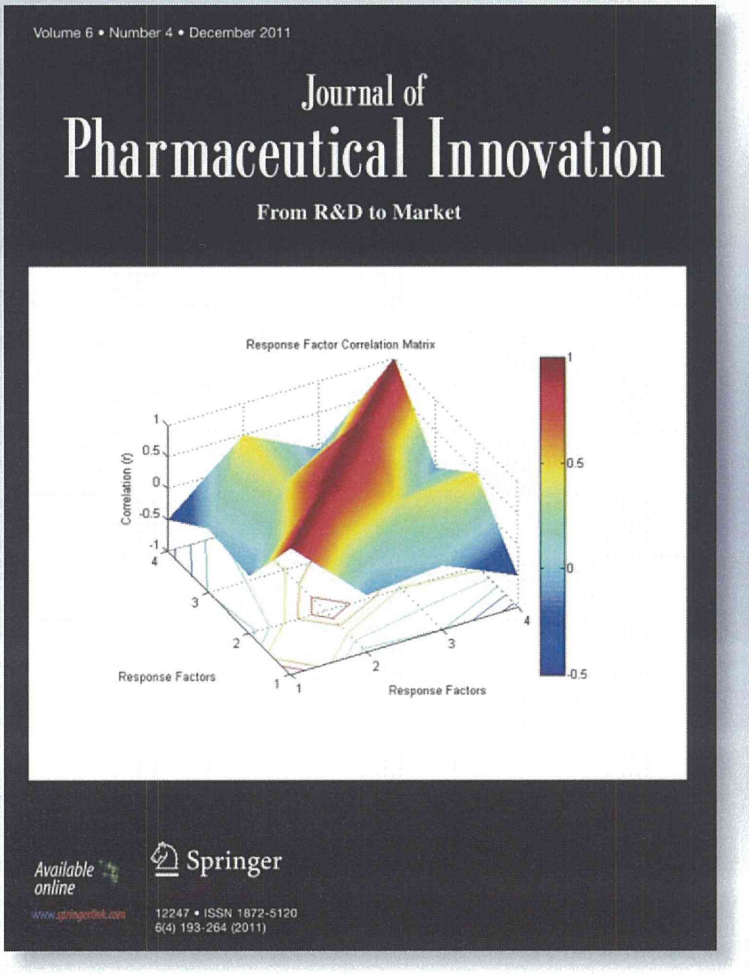
Coating and Density Distribution Analysis of Commercial Ciprofloxacin Hydrochloride Monohydrate Tablets by Terahertz Pulsed Spectroscopy and Imaging

Tomoaki Sakamoto, Alessia Portieri, Donald D. Arnone, Philip F. Taday, Toru Kawanishi & Yukio Hiyama

Journal of Pharmaceutical Innovation
From R&D to Market

ISSN 1872-5120
Volume 7
Number 2

J Pharm Innov (2012) 7:87-93
DOI 10.1007/s12247-012-9130-1



Springer

J Pharm Innov (2012) 7:87–93
DOI 10.1007/s12247-012-9130-1

RESEARCH ARTICLE

Coating and Density Distribution Analysis of Commercial Ciprofloxacin Hydrochloride Monohydrate Tablets by Terahertz Pulsed Spectroscopy and Imaging

Tomoaki Sakamoto · Alessia Portieri · Donald D. Arnone · Philip F. Taday · Toru Kawanishi · Yukio Hiyama

Published online: 25 May 2012

Abstract Terahertz pulsed spectroscopy was used to qualitatively detect ciprofloxacin hydrochloride monohydrate (CPFX·HCl·H_2O) in tablets, and terahertz pulsed imaging (TPI) was used to scrutinize not only the coating state but also the density distribution of tablets produced by several manufacturers. TPI was also used to evaluate distinguishability among these tablets. The same waveform, which is a unique terahertz absorption spectrum derived from pure CPFX·HCl·H_2O, was observed in all of the crushed tablets and in pure CPFX·HCl·H_2O. TPI can provide information about the physical states of coated tablets. Information about the uniformity of parameters such as a coating thickness and density can be obtained. In this study, the authors investigated the coating thickness distributions of film-coated CPFX·HCl·H_2O from four different manufacturers. Unique terahertz images of the density distributions in these commercial tablets were obtained. Moreover, B-scan (depth) images show the status of the coating layer in each tablet and the density map inside the tablets. These features would reflect differences resulting from different tablet-manufacturing processes.

Keywords Terahertz pulsed spectroscopy · Terahertz pulsed imaging · Coating · Density distribution · Tablet · Imaging methods · Ciprofloxacin

T. Sakamoto (✉) · T. Kawanishi · Y. Hiyama
Division of Drugs, National Institute of Health Sciences, Tokyo 158-8501, Japan
e-mail: tsakamot@nihs.go.jp

A. Portieri · D. D. Arnone · P. F. Taday
TeraView Ltd., Cambridge CB4 0WS, UK

Introduction

The electro-magnetic wave on terahertz region is generally defined from 0.1 THz to 10 THz (3.3 to 333 cm^{-1}). This electro-magnetic region has also been known as a far-infrared wave region. But, an irradiated light energy from a typical far-infrared spectrometer equipped with a high-pressure mercury lamp will drop at a frequency below 1 THz drastically. Recent development of laser devices and semi-conductors has allowed us to use coherent terahertz wave with lower frequency. In a terahertz region, vibrational information about weak intermolecular energy such as crystal lattice, hydrogen bonding, and van der Waals force can be detected [1–6]. This leads to applications in the pharmaceutical and chemical industries such as the detection of polymorphs [2, 7–13]. A number of authors have shown that unique terahertz spectra can be obtained for active pharmaceutical ingredients (APIs), illegal drugs, and explosives [7, 9, 12]. The assignment of spectroscopic bands in this region of the spectrum remain challenging due to the complicated properties of crystalline materials, but a number of groups are having some success. Comparative studies between hydrates and their anhydrides have been reported by Kogermann et al. [14] and others [15, 16]. These authors have also investigated the thermodynamics of phase transformation following dehydration.

A time domain terahertz technology (terahertz pulsed technology) is non-destructive analytical tool for investigating pharmaceutical materials and products. This technique can provide two modes which are an imaging mode known as terahertz pulsed imaging (TPI) and a spectroscopic mode known as terahertz pulsed spectroscopy (TPS). Especially, TPI can produce images or maps which are obtained by detecting reflected pulses from each pixel on a tablet or

other dosage forms. Terahertz pulses are irradiated at each pixel on a tablet and penetrate, and echoes or reflections from layers are measured. Then, TPI also obtain depth information at each pixel. The detection time and intensity of reflected wave is affected by the refractive index of the sample. For a coated tablet, this time-of-flight technique makes detector distinguish different arriving time of terahertz pulse. The reflected pulses which are originated from the interface between coating layer and the surface of core tablet or another coating layer in the tablet are detected, and information of the time of flight is used not only to calculate the coating thickness but also to acquire 3D images of a coated tablet. Ho et al. [17–19] reported that not only the coating thickness but also the density of the coating can influence the quality performance of sustained-release film-coated tablets. The authors were able to use the intensity of the terahertz reflected pulse from a coating to model the changes in refraction of terahertz pulsed wave which is correlated with changes in density of coating [19–21]. Recently, we applied TPI to the nondestructive testing of a transdermal drug delivery system. These products have a crystal reservoir system inside a membrane that controls the release rate of an active ingredient from the matrix into the skin by forming crystals [22]. Thus, a terahertz pulse wave can penetrate comparatively deeply and provide physical and/or chemical information inside a solid pharmaceutical nondestructively. These advantages suggest that TPI would be applicable as a nondestructive analytical tool not only for process control but also for the quality analysis of commercial products.

In this paper, we compare the terahertz absorption spectra of pure API component with those contained within the solid dosage form. We also obtain terahertz images of four film-coated ciprofloxacin hydrochloride monohydrate ($CPFX{\cdot}HCl{\cdot}H_2O$) tablets. In this product, the coating has the very important role of protecting the API against degradation caused by light and/or humidity. The authors analyze the coating uniformity and the density of components inside tablets and evaluate the distinguishability among several kinds of commercial tablets that have the same clinical application.

Experimental

Materials

To obtain the terahertz absorption spectra of pure materials, $CPFX{\cdot}HCl{\cdot}H_2O$ was purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). This compound was used without any further purification. Polyethylene (particle size,<80 μm) used to prepare the sample pellets was purchased from Induchem AG (Volketswil, Switzerland).

$CPFX{\cdot}HCl{\cdot}H_2O$ tablets were obtained from five different commercial sources (Bayer Healthcare Co. Ltd. (Osaka, Japan), Sawai Pharmaceutical Co. Ltd. (Osaka, Japan), Nichi-iko Pharmaceutical Co. Ltd. (Toyama, Japan), Choseido Pharmaceutical Co. Ltd. (Tokushima, Japan) and J-Dolph Pharmaceutical Co. Ltd. (Shiga, Japan)).

All commercial tablets used in this study were a round shape and had a central band. The weight, diameter, and labeled amount were 305 to 310 mg, about 10 mm, and 232.8 mg (as hydrochloride salt monohydrate), respectively.

Instruments and Measurement Conditions

The terahertz pulsed spectra of the pure $CPFX{\cdot}HCl{\cdot}H_2O$ and the crushed commercial tablets were obtained using TPS Spectra 3000 terahertz spectrometer (TeraView Ltd., Cambridge, UK). Each sample was measured using a spectral range from 120 to 2 cm^{-1} and a spectral resolution of 1.5 cm^{-1}. A spectrum was obtained by averaging 1,800 scans and took 1 min. Measurements were obtained by transmittance mode in a dry nitrogen-purged sample compartment. Blackman–Harris term 3 was used as the apodization function. The data were collected using TPS spectra version 1.17.0 (TeraView Ltd.).

Discs were prepared by mixing the pure sample with polyethylene powder at a 10 % (*w/w*) concentration, and the two components were mixed well. Then, 400 mg of the mixture was pressed at 2 tons for 2 min to form a disc between 3 and 4 mm thick and with a diameter of 13 mm.

Whole tablets were crushed in a mortar. A portion of the powder equivalent to 10 % API was put into another mortar, up to 200 mg polyethylene powder was added per pellet, and the two were mixed together well. Then a pellet was prepared in the same manner as described above.

Terahertz images of tablets were obtained using the TPI imaga 2000 Coating Scan system (TeraView Ltd.). The operation of this system was well described by Zeitler et al. [11]. Images were acquired in a point-to-point mode with a step size of 100 μm. Three measurements of each tablet were taken, and the measurements together took about 30 min/tablet. Images were analyzed using TPI View version 2.3.10. No sample preparation was required.

Results and Discussion

Identification of $CPFX{\cdot}HCl{\cdot}H_2O$ in Tablets Using TPS

The terahertz absorption spectra of the crushed tablets are shown in Fig. 1. Tablets A, B, C, and D show similar spectral features while tablet E exhibits a different spectrum (especially lower wavenumber than 40 cm^{-1}). By comparing these spectra to the pure chemical species, we can see