European Journal of Pharmaceutics and Biopharmaceutics 145 (2019) 35–41

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Determining the effect of photodegradation on film coated nifedipine tablets with terahertz based coating thickness measurements

Noritaka Odani[b], Shikhar Mohan[a,c], Eiji Kato[d], Hanzhou Feng[a,c], Yi Li[a,c], Md. Nayeem Hossain[a,c], James K. Drennen III[a,c], Carl A. Anderson[a,c,*]

[a] Duquesne Center for Pharmaceutical Technology, Duquesne University, Pittsburgh, PA 15282, United States
[b] Manufacturing Technology Department, Towa Pharmaceutical CO., LTD, Ichiban-cho, Kadoma, Osaka 571-0033, Japan
[c] Duquesne University Graduate School for Pharmaceutical Sciences, Pittsburgh, PA 15282, United States
[d] New Concept Product Initiative, Advantest Corporation, Sendai 989-3124, Japan

ARTICLE INFO

Keywords:
Terahertz spectroscopy
Process analytical technology
Photostability
Tablet coating

ABSTRACT

Film coating of nifedipine tablets is commonly performed to reduce photo-degradation. The coating thickness of these tablets is a primary dictating factor of photo-stability. Terahertz spectroscopy enables accurate measurement of coating thickness. This study identifies a method to determine an end-point of a photo-protective coating process by using coating thickness measurements from terahertz time of flight spectroscopy (THz-TOF). For this method, nifedipine tablets, at different coating thicknesses, were placed in a photostability chamber. The illumination conditions of the coated tablets were adjusted based on the time duration of these tablets inside the chamber. A multiple linear regression model was developed with the coating thickness estimates from THz-TOF and illumination conditions information to predict the amount of drug remaining after photo-degradation (percent label claim). The prediction error of this model was 1.03% label claim in the range of 88.4–100.6% label claim. According to this model, acceptable levels of photo-protection in illumination conditions of up to approximately 700,000 lx hours was achieved at the end of the coating process (approximately 50 μm coating thickness) performed in this study. These results suggest THz-TOF as a viable process analytical technology tool for process understanding and end-point determination of a photo-protective coating process.

1. Introduction

Tablet coating is an important unit operation in the manufacturing of solid oral dosage forms. Multiple applications exist for coating tablets; one such reason is to improve product stability. An example includes film coating of nifedipine tablets. Nifedipine is a calcium-channel blocker that is used to treat hypertension. A critical concern with nifedipine tablets is that it undergoes oxidation when exposed to light [1–3]. Specifically, a 40 W lamp causes 65% of nifedipine to convert to its degradant in approximately 300 min [1]. Applying light protective film coating layer onto the nifedipine tablets has shown to reduce photo-degradation [4].

Previous research has shown the importance of coating formulation and thickness on the stability performance of nifedipine tablets [4]. Increasing the concentration of the opacifer and the coating thickness reduces light penetration. However, increasing opacifier content to a high level inhibits desired film formation [4]. Therefore, optimizing coating thickness in the presence of small percentage of opacifier is a more feasible option to achieve an appropriate level of light protection. As a result, coating thickness and uniformity are considered critical quality attributes (CQA) of the coating process for enhancing photo-stability [3,4].

With FDA's initiative on quality by design (QbD), it is important to monitor and control the CQAs of the coating process to improve the final product quality [5]. Process analytical technology tools (PAT) such as near infrared (NIR) [6–14] and Raman [15–17] spectroscopy have been previously reported for this purpose as spectral information are generally collected rapidly and non-destructively with limited sample preparation from a film coating process [18]. Both NIR and Raman spectroscopy are complimentary vibrational techniques which provide quantitative information of the chemical components. For tablet coating, the tablet core and polymer from the coating formulation each tend to have a specific NIR and/or Raman signal. Therefore, the disappearance of the tablet core information along with the appearance of the polymer information in NIR and Raman spectra with increasing coating amount has been related to coating thickness and weight gain

* Corresponding author at: Duquesne Center for Pharmaceutical Technology, Duquesne University, Pittsburgh, PA 15282, United States.
E-mail address: andersonca@duq.edu (C.A. Anderson).

https://doi.org/10.1016/j.ejpb.2019.09.024
Received 3 May 2019; Received in revised form 2 August 2019; Accepted 26 September 2019
Available online 27 September 2019
0939-6411/

[14–16,18]. However, both these spectroscopic techniques are indirect, therefore, requiring a reference technique during method development. In addition, the method development typically involves application of chemometric techniques for generation of multivariate models relating the reference coating thickness measurements with the NIR/Raman spectra.

Alternatively, terahertz time of flight spectroscopy (THz-TOF) and optical coherence tomography (OCT) are potential PAT tools for measuring tablet coating thickness directly and without requiring extensive chemometrics during method development [19–30]. Specifically, OCT and THz-TOF measures the scattered light and specular refraction corresponding to refractive index changes respectively, to locate interfaces present in a coated tablet system. The two primary interfaces of interest for coating thickness measurements are the interface between the tablet surface and environmental air and the interface between the film coating layer and tablet core. Both THz-TOF and OCT determines the distance between these two interfaces to estimate coating thickness. The shorter wavelength (approximately 840 nm) utilized by OCT compared to THz-TOF (approximately 0.1–1 mm) allows for coating thickness measurements of as low as 15 μm [22,31,32]. However, for thicker coatings, OCT measurements decrease in accuracy owing potentially to significant scattering from tablet matrix and dust generation. In contrast, terahertz spectroscopic measurements are less susceptible to scattering concerns since the terahertz radiation is in the far-infrared region of the electromagnetic spectrum (approximately 300 GHz–3 THz or 10–100 cm^{-1}). This low frequency radiation allows for increased measurement accuracy at higher coating thicknesses. However, at thin coating thickness measurements, the specular reflection of the terahertz pulse from the interface of the film coating and tablet core becomes indistinguishable from the reflected pulse of the tablets surface owing to the longer wavelength. Therefore, THz-TOF has a reported lower limit of approximately 30–40 μm for coating thickness [21].

In this study, THz-TOF was selected to perform at-line coating thickness measurements of nifedipine coated tablets owing to its direct and relatively accurate measurement capability in the approximate coating thickness range of 30–50 μm. Coating thickness measurements using PAT for pan coating process has shown to be essential in ensuring final product quality. For example, the coating thickness measured by terahertz spectroscopy was shown to have strong correlation to dissolution parameters of sustained-released coated tablets [33–37]. However, to the authors knowledge there have been no studies using any PAT based coating thickness models in film coating process for understanding photostability. In this study, coating thickness estimates from THz-TOF were used to indicate percent label claim of coated nifedipine tablets after controlled photo-degradation. A multiple linear regression model was generated with the coating thickness and the illumination condition of the photostability chamber as the primary independent variables and drug amount as the dependent variable. This model was used to generate at-line predictions of the extent of photo-degradation at multiple illumination conditions using primarily coating thickness measurements. An appropriate end-point of the film coating process was established based on the desired photostability of the final drug product.

2. Materials and methods

2.1. Core tablet

Film coated nifedipine tablets were manufactured for this study. The core tablet formulation consisted of 10 wt% nifedipine, 70.8 wt% hydroxylpropyl cellulose (HPC-L, Nisso America Inc., New York, NY), 18.6 wt% ethylcellulose (NF, Spectrum Chemical Manufacturing Corp., New Brunswick), and 0.6 wt% magnesium stearate (Fisher Scientific, PA, USA). The manufacturing process involved first granulating nifedipine, HPC-L, and ethylcellulose with fluid bed granulation system (Glatt, Binzen, Germany) and then sieving using a comil (Quadro Comil Overdriven 197, Ontario, Canada) with a mesh size of 0.61 mm. The granulated material was then blended with magnesium stearate by using a bin blender. Tableting of the blended powder was performed on a 38-station tablet press (HT-AP-38, Elizabeth-Hata International, Inc. PA, USA) tooled with two sets of flat faced beveled edge 9.5 mm punches (3/16 in.). Fill depth and punch distance on the press were adjusted to maintain tablet weight and crushing force of approximately 350 mg and 9000 ponds.

2.2. Coating solution

The coating composition consisted of 4 wt% hypromellose (HPMC; Pharmacoat 606, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan), 2.4 wt% titanium dioxide (TiO_2; USP, Spectrum chemical, New Brunswick, NJ), 0.8 wt% Talc (powder USP, Spectrum chemical, New Brunswick, NJ) and 0.8 wt% polyethylene glycol 6000 (PEG 6000; Alfa Aesar, Haverhill, MA). Talc and TiO_2 were dispersed while HPMC and PEG 6000 were dissolved in 92 wt% water.

2.3. Tablet coating process

Coating was performed in an HCT-48 pan coater (Freund Co., Ltd., Tokyo, Japan). The pre-heating and spraying phase of coating were performed in the pan coater. Drying and cooling, however, were performed outside the pan coater by taking samples and placing them in a desiccator containing magnesium chloride at room temperature for humidity control of approximately 35 %RH. The parameters set for the pre-heating phase were 80 °C target inlet air temperature and 10 RPM pan speed. For the spraying phase, the spray rate was 17 g/min, and the rotation speed was adjusted to 15 RPM.

2.4. Photostability conditions

Tablets were placed in an in-house built photostability chamber to assess the light protective ability of the coating for nifedipine tablets. In accordance with the International Conference on Harmonisation (ICH) guidelines [38], a D65 light source was used. Each tablet was placed on a 24-well plate, which allowed the top side and the lateral band of the tablet to be exposed to the light. The 24-well plate was placed in a desiccator containing saturated magnesium chloride solution to control the relative humidity to approximately 35 %RH in room temperature. The desiccator, containing a flat transparent plexiglass lid, was then placed inside the photostability chamber. The light intensity inside the desiccator was measured to be approximately 3800 lx with a digital illuminance meter. The effect of light intensity on the tablets was studied by adjusting the duration of time the tablets were placed inside the photostability chamber.

2.5. Drug assay

The coated tablets underwent ultraviolet–visible (UV–VIS) analysis (Hewlett Packard 8453 UV–Visible Spectrophotometer, Agilent Technologies, Santa Clara, CA) to determine percent label claim of nifedipine after photo-degradation. The UV–VIS spectrum of nifedipine shows major absorbance peaks at approximately 206 nm, 236 nm and 350 nm. However, these regions overlap with the degradant peak. Therefore, absorbance at 380 nm was used to generate a univariate model (calibration curve) between absorbance and percent label claim of nifedipine due to minimal effect of degradant at this nifedipine absorbance. To further improve the linearity of the calibration curve the absorbance at 380 nm was subtracted by absorbance at 500 nm to correct for baseline.

The calibration curve was based on absorbance and concentration information from sixteen prepared solutions. The preparation method of these solutions involved weighing sixteen different amounts of

nifedipine powder in the range of 19.6–56.2 mg. Each weighed nifedipine powder was placed in individual 100 mL volumetric flasks and dissolved with 70 mL of 90% methanol. Sonication on the volumetric flasks was performed for 20 min to facilitate in the dissolving process. The dilution of the sample in the 100 mL volumetric flask was then completed by adding approximately 30 mL of 90% methanol. Sonication was performed again for 10 min on the solution to allow for complete dissolution of the sample. Another dilution step was performed by taking 5 mL of each solution and placing it in individual 50 mL volumetric flasks in which approximately 45 mL of 90% methanol was added. This final dilution step produced nifedipine concentrations within the approximate absorbance range of 0.2–0.7 at 380 nm wavelength. A univariate model was generated between baseline corrected absorbance and percent label claim. The percent label claim was calculated by taking the individually weighed amount of nifedipine and dividing by the expected amount of nifedipine (35 mg) in the manufactured tablet. The calibration curve resulted in a R^2 of 0.9967 and an intercept statistically including zero within 95% confidence interval.

The UV–VIS calibration curve was used to predict percent label claim of test solution made from photo-degraded tablets. Similar methodology was used in preparation of these test solutions as compared with the calibration solutions. The only difference involved filtering the test solution with 45 µm pore sized filter before UV–VIS measurement to remove undissolved excipients. Content uniformity of un-coated tablet was also confirmed by this method. The average percent label claim and relative standard deviation of 10 uncoated and non-degraded tablets was 98.9% (34.63 mg) and 0.9%, respectively, resulting in a relative error of approximately 0.91%.

2.6. Terahertz imaging

Tablets were sampled from the coating process at specified time points and analyzed with THz-TOF for assessment of coating thickness. The coated tablet face that was scanned was marked by applying a small drop of coating solution for identification purposes. The coated tablets were positioned in the photostability chamber such that the marked face of the tablet was exposed to the light. According to this tablet positioning, it is expected that the drug degradation begins to occur at the marked face of the tablet. Therefore, the measurement of coating thickness at the marked face more appropriately represents the degree of photo-protection.

Terahertz images of coated tablets were acquired by using TAS7500IM (Advantest, Tokyo, Japan). The spatial resolution of the images was set to 0.2 mm. At each pixel, 128 time domain waveforms were collected in reflection mode and averaged to produce a final pixel waveform. A flat metal mirror was used to acquire a reference waveform. These waveforms include information of reflected pulses which occur when the incident pulse encounters a change in refractive index. The first reflected pulse is due to the refractive index change between the air and solid surface of the coated tablet or metal mirror. The second reflected pulse in a coated tablet sample is expected to be from the incident pulse encountering the tablet core. Assuming the incident angle is perpendicular to the tablet surface, the time delay (Δt) between the second pulse (core surface) and first pulse (coated tablet surface) is directly related to the coating thickness by Eq. (1). In this Equation, 'c' is the speed of light and 'n' is the refractive index of the film coating layer. The refractive index of the film was measured separately by casting a thin film with appropriately characterized thickness to be approximately 2.06 with terahertz instrument in transmission setup. The time delay was calculated by first shifting the waveforms allowing the first pulse maximum of sample and reference to correspond to 0 picosecond time point. Then, all waveforms were normalized to the first peak maximum value of the reference waveform. Subtraction of the normalized sample and reference waveforms was performed, and the time point at the minima of the resulting vector was determined to be the time delay.

$$CT = \frac{c\Delta t}{2n} \quad (1)$$

At the edge of the tablet, the reflection of the terahertz pulse is expected to be influenced by the curvature, so the thickness data was extracted from a 5.2 mm square from the center of the tablet excluding the area of the marking. The average coating thickness from the approximate 674 pixels of this area were used as the final coating thickness value.

2.7. Experimental design

A design of experiment (DOE) was used to build a model to predict the amount of nifedipine remaining after photo-degradation with the coating thickness and light illumination information. In this DOE, five levels of light illumination conditions (10,000, 50,000, 120,000, 200,000, and 300,000 lx hours) were used. The center point illumination condition of 120,000 lx hours corresponds to approximate light intensity of maximum sunlight. The increment of light exposure time was increased after 120,000 lx hours until the drug content was considered out of specification (< 10% label claim) [39] at minimum coating thickness level. The DOE also included coating variation by sampling tablets at six different coating time points of 40, 60, 80, 100, 120, and 140 min. Fig. 1 shows each design point and their corresponding combination of coating time and light illumination condition. Three tablets were obtained at each design point. The dataset was split into calibration and test set highlighted respectively in Fig. 1. At all the

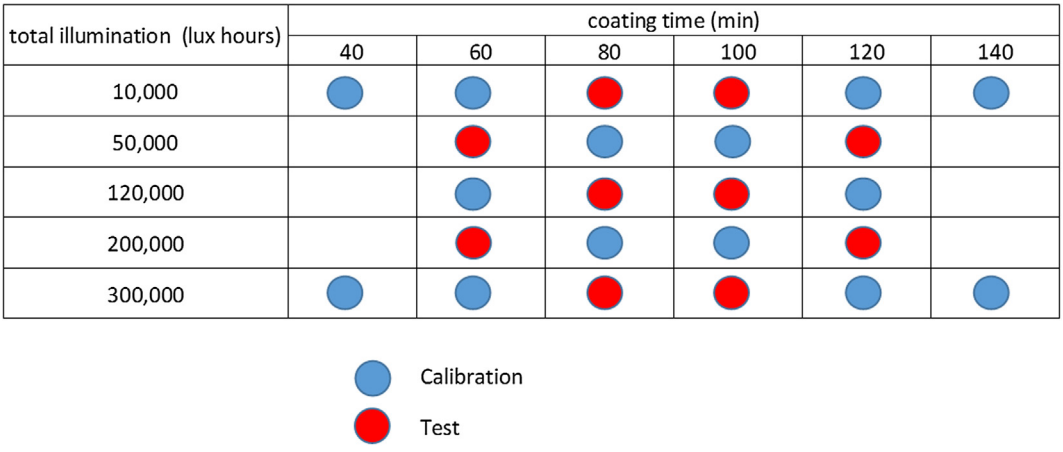

Fig. 1. Design of experiment.

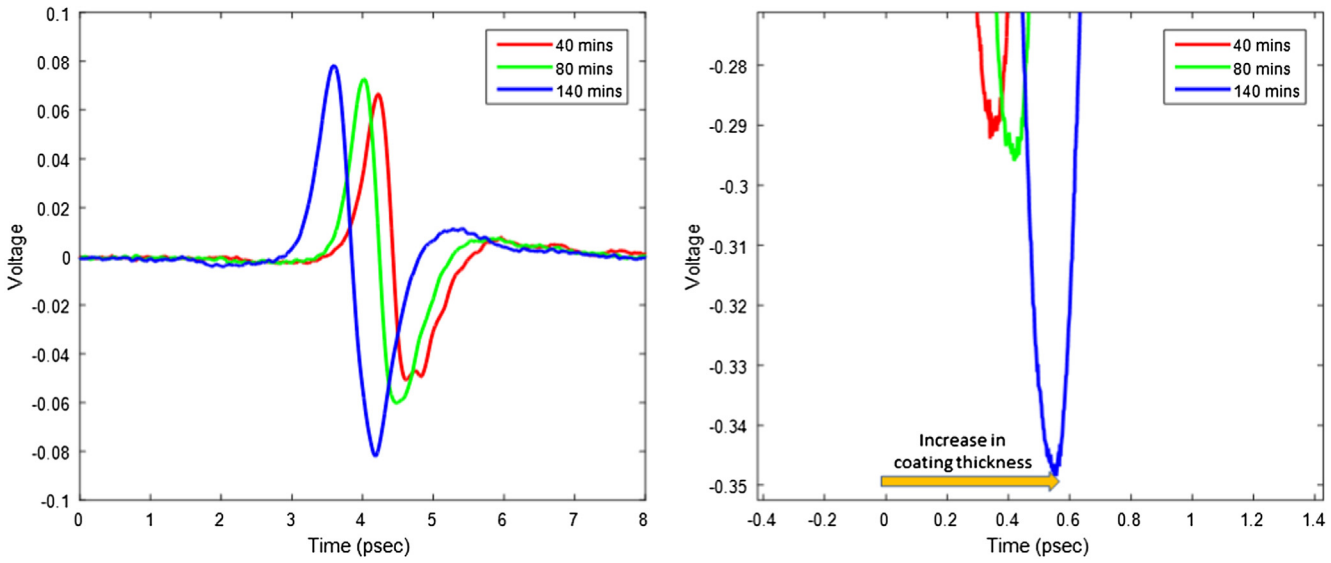

Fig. 2. Raw (a) and shifted (b) time domain waveforms of coated tablets.

design points, coating thickness estimates from THz-TOF were obtained. A multiple linear regression (MLR) model was then developed with the calibration set using coating thickness estimate, illumination condition, and interaction term as independent variables and percent label claim of nifedipine after photo-degradation as the dependent variable. The test set was used to evaluate the model performance. In addition to this test set, another three set of tablets coated for 40 and 140 min were obtained and placed in light exposure of 1.2 million lx hours. The model was extrapolated to 1.2 million lx hours as a preliminary model accuracy assessment at the ICH guideline [38] suggested light exposure amount. Significance testing of each independent variable was performed with JMP pro 10. All models were developed using MATLAB software (Version R2016b, Mathworks Inc., MA, USA) and PLS_Toolbox (Version 821, Eigen-vector Research Inc., WA, USA).

3. Results and discussion

In this study, THz-TOF was used as an analytical technique to assess the film layer thickness of coated tablets. Fig. 2a shows time domain signal of a tablet sampled at 40 min, 80 min, and 140 min coating times. The first positive peak in the time domain is associated with the reflected terahertz pulse from the coated tablet surface. The tablet sample position is standardized based on the tablet face on the opposite side of the detector. Therefore, tablets with thicker coating layer are closer to the detector as compared to tablets with less coating layer. This is a primary reason why the terahertz signal is seen to reach the detector at an earlier time for the more coated tablet than the less coated tablet in Fig. 2a. This tablet position effect was addressed by shifting all the time domain waveforms until the first maximum peak corresponded to zero picoseconds. The subsequent peaks in the time domain waveform after the shift are associated with any further refractive index changes encountered by the terahertz pulse. The next major refractive index difference is at the coating layer and tablet core interface. A tablet with a thicker coating results in a longer time delay of the reflected terahertz pulse. This was seen in Fig. 2b in which the tablet with thicker coating showed the peak minima at a higher time compared to the tablets with less coating thickness. This time delay was used to calculate coating thickness according to Eq. (1). Fig. 3a shows a terahertz image of a tablet coated for 80 min. This image is color coded in terms of the calculated coating thickness estimates. The mean coating thickness of the red boxed area was used as the final coating thickness estimate for each tablet. For this tablet, the coating thickness estimate was approximately 37 μm as seen from the respective coating thickness distribution (Fig. 3b). The intra-tablet standard deviation of coating thickness was approximately 3 μm at 80 min coating time. Similar intra-tablet coating thickness standard deviations were observed at each sampling time point.

The coating thickness increased over spraying time. This was indicated by changes in pixel color of imaged tablets between sampled time points in Fig. 4. The increase in mean coating thickness of all tablets at each sampling point is seen in Fig. 5. The standard deviation range of inter-tablet coating thickness estimate at each coating time sampling point ranged between 1.27 and 4.34 μm. Potential reasons for inter-tablet coating thickness variation at specified time points include variation in core tablet dimensions and low drying capacity. The range of coating thickness observed from the sampling points varied between approximately 30 to 50 μm.

The coating thickness measured from THz-TOF was validated with optical microscopy to ensure measurement accuracy in the observed coating thickness. An additional placebo coating batch was produced, and a tablet was sampled at the same coating time design points. The thickness of these tablets was measured first with terahertz and then with optical microscope. For optical microscopy measurements, tablets were sliced in half and then placed under the microscope to obtain image as seen in Fig. 3c. In this image, the tablet core and film coating layer are identifiable. Five manual measurements of the coating thickness were made on the microscope image. The average of these measurements at different coating time points were compared with average coating thickness estimates from terahertz. According to Fig. 3d, these two measurements techniques are very well correlated with a correlation coefficient of approximately 0.99 and intercept containing zero within 95% confidence interval. These results suggest that THz-TOF measures coating thickness accurately in the range of 30–50 μm for this specific coating process. Similar accuracy is expected for nifedipine coating tablets as the coating thickness measurements is dependent on a significance change in refractive index between the tablet core and the film coating which exists for both the placebo and active coated tablet systems.

After obtaining coating thickness measurements from THz-TOF, the sampled tablets were stored in a photostability chamber. Fig. 6 shows the trends relating coating thickness measurements to percent label claim of nifedipine after photo-degradation. These trends are color coded according to illumination amount. At 10,000 lx hours, there is little to no photo-degradation occurring as the percent label remains between 98 and 100% at most coating times and coating thicknesses. Photo-degradation is more significantly observed at 50,000 lx hours

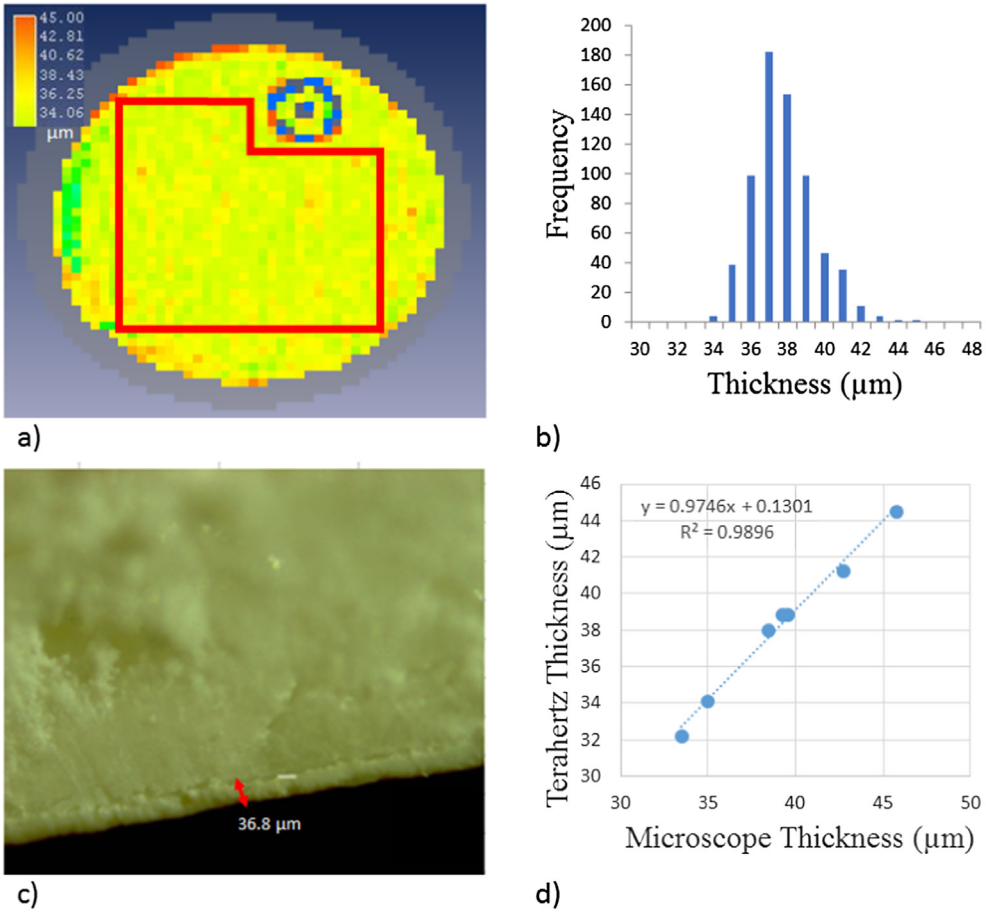

Fig. 3. Terahertz thickness (a) and optical microscopy (c) image of tablet coated for 80 min. The distribution of terahertz coating thickness estimates associated with this tablet at all relevant pixels (b). Terahertz thickness measurement versus microscope thickness measurement (d).

and greater. The highest photo-degradation occurs at 40 min coating or approximately 31 µm coating thickness and 300,000 lx hours illumination. A multiple linear regression model was developed to relate terahertz coating thickness estimate and illumination amount to % label claim after photo-degradation. An interaction term was also included in the model due to potential non-linearity between coating thickness estimates and % label claim at higher illumination conditions.

The significance of the independent variables was assessed with a *t*-test after autoscaling the independent variables and mean centering the dependent variable. The independent variables that were tested with this method were terahertz coating thickness estimates (Thickness), illumination condition (Lux), and the interaction between Thickness and Lux. The results are shown in Table 1. The p-values for all the variables are very low and under $\alpha = 0.05$ all the variables are

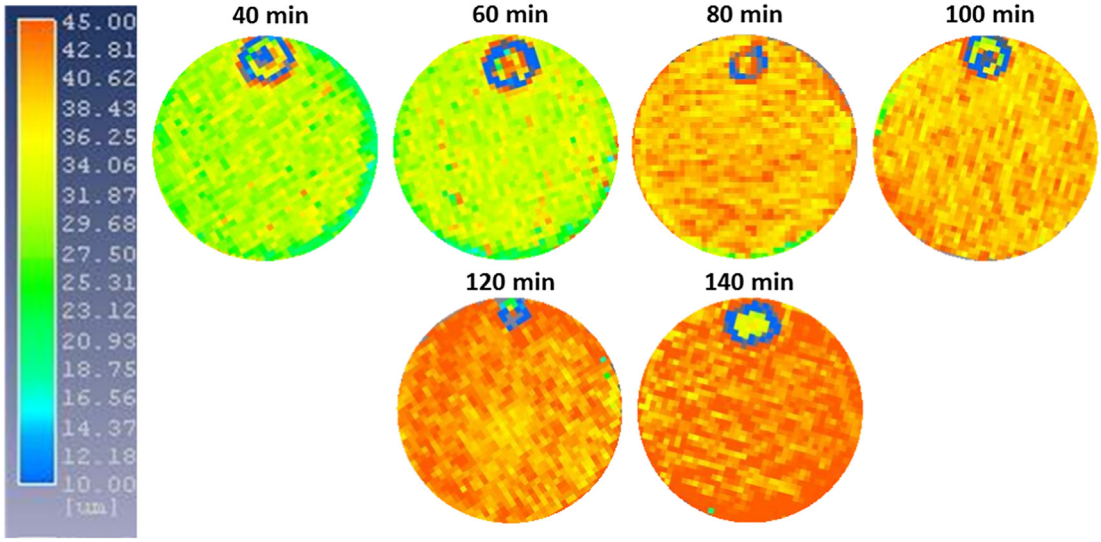

Fig. 4. Terahertz based thickness images of coating tablets.

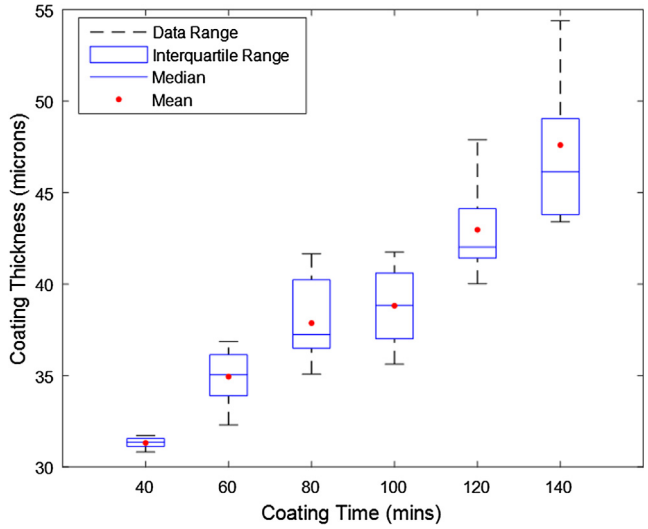

Fig. 5. Terahertz coating thickness versus coating time.

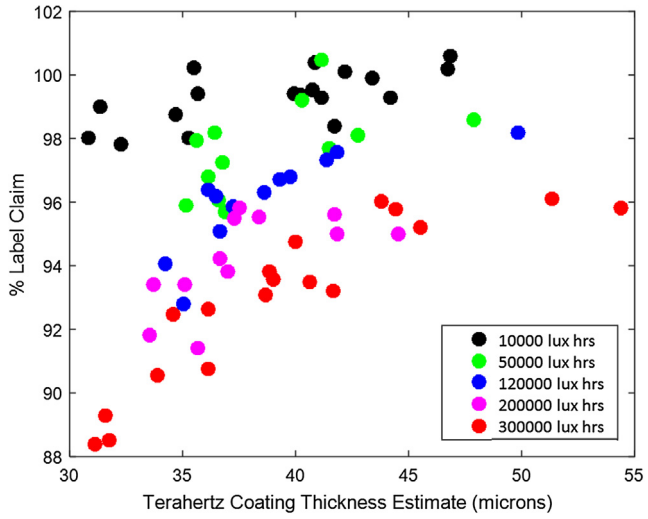

Fig. 6. Photo-degradation results versus terahertz thickness measurements.

Table 1
Significance of each parameter in the MLR model.

Parameter	Estimate	Standard Error	t Ratio	Prob > [t]
Intercept	−1.25E−14	0.18	0.00	1.0000
Lux	−6.12	1.15	−5.31	< 0.0001
Thickness	0.83	0.31	2.65	0.0118
Lux * Thickness	3.48	1.20	2.90	0.0061

significant. The interaction term is potentially required to account for the different degradation and coating thickness trends at different illumination conditions. For example, at the lowest illumination conditions there is little to no photo-degradation occurring at all coating thicknesses. However, at the highest illumination conditions there is potential non-linear increase of photo-degradation with increase in coating thickness (Fig. 5).

A multiple linear regression (MLR) model was developed with the three significant variables. The results of the model are found in Fig. 7 and the regression coefficients are shown in Table 1. The model was developed with only the calibration design points as seen in Fig. 1. The model performance was assessed by cross-validation and predicting on a separate test set. The cross-validation technique used was a venetian blind with six data splits and one sample per blind. The calibration,

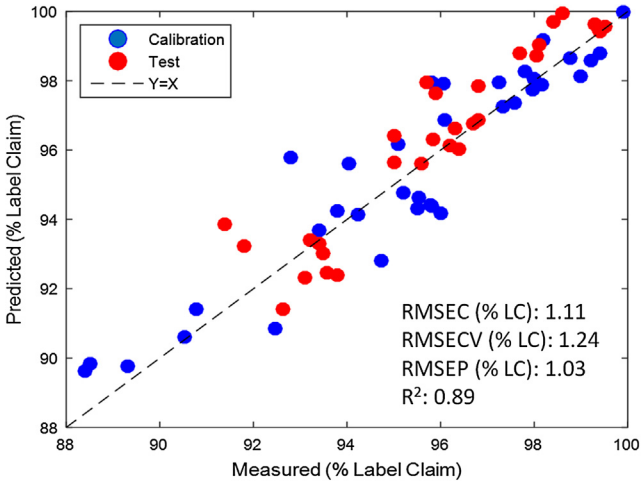

Fig. 7. Measured versus predicted photo-degradation results.

cross-validation, and prediction error of the MLR model was 1.11, 1.24, and 1.03% label claim respectively in the range of 88.4–100.6% label claim of nifedipine. This prediction error relative to the range of % label claim was below 10%. The model can be potentially improved with a lower intra-tablet coating thickness variation in addition to using non-linear modeling methods. However, this study shows that with only the coating thickness information of coated nifedipine tablets, the photo-degradation results can be predicted for different illumination conditions.

The original calibration conditions did not include the ICH guideline [38] suggested illumination of 1.2 million lx hours. Specifically, a nifedipine tablets must maintain 90% of its potency after being subjected to this illumination condition [39]. A set of tablets (40 min, or approximately 32 μm and 140 min, or approximately 48 μm) was subjected to these conditions to assess the utility of the model past the range of the original calibration model. The average extrapolated model prediction for the illumination condition of 1.2 million lx hours of a 32 μm and a 48 μm coated sample were 64.7 and 80.6% label claim, respectively. The measured photo-degradation results were 69.3 and 78.7% label claim. The prediction error for all the extrapolated results was 3.82% label claim. These results suggest that additional coating is required to achieve minimum stability performance at 1.2 million lux hours. At the highest coating thickness the percent label claim at 1.2 million lx hours is predicted to be 80.6% label claim. To achieve a minimum of 90% label claim the coating thickness needs to be approximately 58 um according to the generated MLR model. Fig. 8 shows the % label claim predictions associated with different illumination conditions at the highest coating thickness achieved in this study,

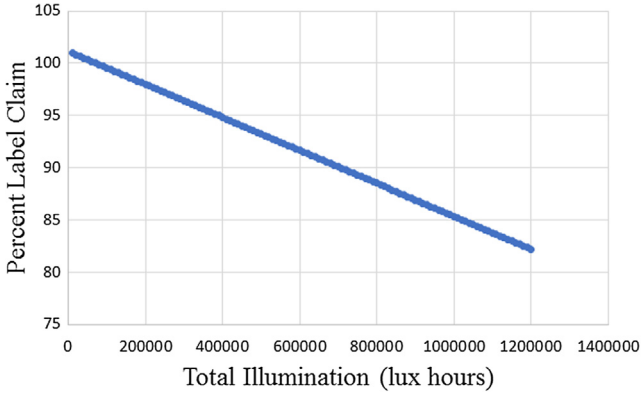

Fig. 8. Estimated percent label claim using illumination conditions in the range of 0–1,200,000 lx hours and constant coating thickness of 50 μm.

approximately 50 μm. The 50 μm coated tablet was stable up to 700,000 lx hours, falling short of the ICH recommended conditions. At-line measurements of coating thickness with THz-TOF during the coating of photo-labile tablets was used to determine the end-point and degree of photostability at various illumination conditions.

4. Summary and conclusion

In this project nifedipine tablets were film coated to mitigate photo-degradation. Nifedipine tablets with different film coating thicknesses were placed in a photostability chamber. Coating thickness was estimated by using THz-TOF which was validated with optical microscopy measurements. The time of illumination on the coated nifedipine tablets was varied to study both the effect of coating thickness and illumination amount on photo-degradation. The coating thickness, illumination amount, and interaction between the coating thickness and illumination amount were all determined to be significant in determining photo-degradation.

A multiple linear regression model was generated with all the significant variables to predict the percent label of the drug after photo-degradation. The results showed that photo-degradation was appropriately predicted with coating thickness and illumination condition information. The prediction error for the model was approximately 1.03% label claim in the range of 88.4 to 100.6% label claim. This model was applied at-line to estimate the extent of the photo-protection of the drug product for end-point determination. The coated tablets at the end of the process (50 μm approximate coating thickness) in this study achieved appropriate levels of photostability (% label claim equal to or greater than 90%) at illumination conditions of 700,000 lx hours and lower.

References

[1] M. Shamsipur, B. Hemmateenejad, M. Akhond, K. Javidnia, R. Miri, A study of the photo-degradation kinetics of nifedipine by multivariate curve resolution analysis, J. Pharm. Biomed. Anal. 31 (5) (2003) 1013–1019.

[2] D. Desai, M. Abdelnasser, B. Rubitski, S. Varia, Photostabilization of uncoated tablets of sorivudine and nifedipine by incorporation of synthetic iron oxides, Int. J. Pharm. 103 (1) (1994) 69–76.

[3] R. Teraoka, Y. Matsuda, I. Sugimoto, Quantitative design for photostabilization of nifedipine by using titanium dioxide and/or tartrazine as colourants in model film coating systems, J. Pharm. Pharmacol. 41 (5) (1989) 293–297.

[4] S. Bechard, O. Quraishi, E. Kwong, Film coating: effect of titanium dioxide concentration and film thickness on the photostability of nifedipine, Int. J. Pharm. 87 (1–3) (1992) 133–139.

[5] Food, Administration D 2004. Guidance for industry, PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. http://www.fda gov/cder/guidance/published html.

[6] T. Ozawa, M. Yokoyama, T. Hosono, T. Nagato, K. Tahara, H. Takeuchi, A novel approach to monitor coating amount by short-wavelength near-infrared spectroscopy using a tracer with a long-chain hydrocarbyl group, Int. J. Pharm. 458 (1) (2013) 9–14.

[7] J.D. Kirsch, J.K. Drennen, Determination of film-coated tablet parameters by near-infrared spectroscopy, J. Pharm. Biomed. Anal. 13 (10) (1995) 1273–1281.

[8] B. Igne, H. Arai, J.K. Drennen, C.A. Anderson, Effect of sampling frequency for real-time tablet coating monitoring using near infrared spectroscopy, Appl. Spectrosc. 70 (9) (2016) 1476–1488.

[9] C. Gendre, M. Boiret, M. Genty, P. Chaminade, J.M. Pean, Real-time predictions of drug release and end point detection of a coating operation by in-line near infrared measurements, Int. J. Pharm. 421 (2) (2011) 237–243.

[10] J.D. Pérez-Ramos, W.P. Findlay, G. Peck, K.R. Morris, Quantitative analysis of film coating in a pan coater based on in-line sensor measurements, Aaps Pharmscitech 6 (1) (2005) E127–E136.

[11] C.-V. Möltgen, T. Puchert, J. Menezes, D. Lochmann, G. Reich, A novel in-line NIR spectroscopy application for the monitoring of tablet film coating in an industrial scale process, Talanta 92 (2012) 26–37.

[12] M. Andersson, M. Josefson, F.W. Langkilde, K.G. Wahlund, Monitoring of a film coating process for tablets using near infrared reflectance spectrometry, J. Pharm. Biomed. Anal. 20 (1) (1999) 27–37.

[13] J.D. Kirsch, J.K. Drennen, Near-infrared spectroscopic monitoring of the film coating process, Pharm. Res. 13 (2) (1996) 234–237.

[14] J.J. Moes, M.M. Ruijken, E. Gout, H.W. Frijlink, M.I. Ugwoke, Application of process analytical technology in tablet process development using NIR spectroscopy: blend uniformity, content uniformity and coating thickness measurements, Int. J. Pharm. 357 (1–2) (2008) 108–118.

[15] J.F. Kauffman, M. Dellibovi, C.R. Cunningham, Raman spectroscopy of coated pharmaceutical tablets and physical models for multivariate calibration to tablet coating thickness, J. Pharm. Biomed. Anal. 43 (1) (2007) 39–48.

[16] S. Romero-Torres, J.D. Perez-Ramos, K.R. Morris, E.R. Grant, Raman spectroscopy for tablet coating thickness quantification and coating characterization in the presence of strong fluorescent interference, J. Pharm. Biomed. Anal. 41 (3) (2006) 811–819.

[17] S. Romero-Torres, J.D. Perez-Ramos, K.R. Morris, E.R. Grant, Raman spectroscopic measurement of tablet-to-tablet coating variability, J. Pharm. Biomed. Anal. 38 (2) (2005) 270–274.

[18] C. Cahyadi, A.D. Karande, L.W. Chan, P.W. Heng, Comparative study of non-destructive methods to quantify thickness of tablet coatings, Int. J. Pharm. 398 (1–2) (2010) 39–49.

[19] H. Lin, R.K. May, M.J. Evans, S. Zhong, L.F. Gladden, Y. Shen, J.A. Zeitler, Impact of processing conditions on inter-tablet coating thickness variations measured by Terahertz in-line sensing, J. Pharm. Sci. 104 (8) (2015) 2513–2522.

[20] H. Lin, Y. Dong, Y. Shen, J. Axel Zeitler, Quantifying pharmaceutical film coating with optical coherence tomography and Terahertz pulsed imaging: an evaluation, J. Pharm. Sci. 104 (10) (2015) 3377–3385.

[21] R.K. May, M.J. Evans, S. Zhong, I. Warr, L.F. Gladden, Y. Shen, J.A. Zeitler, Terahertz in-line sensor for direct coating thickness measurement of individual tablets during film coating in real-time, J. Pharm. Sci. 100 (4) (2011) 1535–1544.

[22] H. Lin, Y. Dong, D. Markl, B.M. Williams, Y. Zheng, Y. Shen, J.A. Zeitler, Measurement of the intertablet coating uniformity of a pharmaceutical pan coating process with combined Terahertz and optical coherence tomography in-line sensing, J. Pharm. Sci. 106 (4) (2017) 1075–1084.

[23] R.P. Cogdill, R.N. Forcht, Y. Shen, P.F. Taday, J.R. Creekmore, C.A. Anderson, J.K. Drennen, Comparison of Terahertz pulse imaging and near-infrared spectroscopy for rapid, non-destructive analysis of tablet coating thickness and uniformity, J. Pharm. Innov. 2 (1–2) (2007) 29–36.

[24] W. Momose, H. Yoshino, Y. Katakawa, K. Yamashita, K. Imai, K. Sako, E. Kato, A. Irisawa, E. Yonemochi, K. Terada, Applying terahertz technology for non-destructive detection of crack initiation in a film-coated layer on a swelling tablet, Results Pharm. Sci. 2 (2012) 29–37.

[25] H. Lin, Y. Dong, C. Pei, B.M. Williams, D. Markl, Y. Zheng, J.A. Elliot, Y. Shen, J.A. Zeitler, Studying the pharmaceutical film coating process with Terahertz sensing, optical coherence tomography and numerical modelling, in: 2016 41st International Conference on IEEE, ed.: Infrared, Millimeter, and Terahertz waves (IRMMW-THz).

[26] L. Maurer, H. Leuenberger, Terahertz pulsed imaging and near infrared imaging to monitor the coating process of pharmaceutical tablets, Int. J. Pharm. 370 (1–2) (2009) 8–16.

[27] S. Zhong, Y.-C. Shen, L. Ho, R.K. May, J.A. Zeitler, M. Evans, P.F. Taday, M. Pepper, T. Rades, K.C. Gordon, R. Müller, P. Kleinebudde, Non-destructive quantification of pharmaceutical tablet coatings using terahertz pulsed imaging and optical coherence tomography, Opt. Lasers Eng. 49 (3) (2011) 361–365.

[28] M. Dohi, W. Momose, H. Yoshino, Y. Hara, K. Yamashita, T. Hakomori, S. Sato, K. Terada, Application of terahertz pulse imaging as PAT tool for non-destructive evaluation of film-coated tablets under different manufacturing conditions, J. Pharm. Biomed. Anal. 119 (2016) 104–113.

[29] J.A. Zeitler, Y. Shen, C. Baker, P.F. Taday, M. Pepper, T. Rades, Analysis of coating structures and interfaces in solid oral dosage forms by three dimensional terahertz pulsed imaging, J. Pharm. Sci. 96 (2) (2007) 330–340.

[30] I.S. Russe, D. Brock, K. Knop, P. Kleinebudde, J.A. Zeitler, Validation of Terahertz coating thickness measurements using X-ray microtomography, Mol. Pharm. 9 (12) (2012) 3551–3559.

[31] D. Markl, G. Hannesschläger, S. Sacher, M. Leitner, J.G. Khinast, Optical coherence tomography as a novel tool for in-line monitoring of a pharmaceutical film-coating process, Eur. J. Pharm. Sci. 55 (2014) 58–67.

[32] D. Markl, G. Hannesschläger, S. Sacher, M. Leitner, A. Buchsbaum, R. Pescod, T. Baele, J.G. Khinast, In-line monitoring of a pharmaceutical pan coating process by optical coherence tomography, J. Pharm. Sci. 104 (8) (2015) 2531–2540.

[33] L. Ho, R. Muller, M. Romer, K.C. Gordon, J. Heinamaki, P. Kleinebudde, M. Pepper, T. Rades, Y.C. Shen, C.J. Strachan, P.F. Taday, J.A. Zeitler, Analysis of sustained-release tablet film coats using terahertz pulsed imaging, J. Control Release 119 (3) (2007) 253–261.

[34] L. Ho, R. Muller, K.C. Gordon, P. Kleinebudde, M. Pepper, T. Rades, Y. Shen, P.F. Taday, J.A. Zeitler, Terahertz pulsed imaging as an analytical tool for sustained-release tablet film coating, Eur. J. Pharm. Biopharm. 71 (1) (2009) 117–123.

[35] J.A. Spencer, Z. Gao, T. Moore, L.F. Buhse, P.F. Taday, D.A. Newnham, Y. Shen, A. Portieri, A. Husain, Delayed release tablet dissolution related to coating thickness by terahertz pulsed image mapping, J. Pharm. Sci. 97 (4) (2008) 1543–1550.

[36] L. Ho, R. Muller, K.C. Gordon, P. Kleinebudde, M. Pepper, T. Rades, Y. Shen, P.F. Taday, J.A. Zeitler, Monitoring the film coating unit operation and predicting drug dissolution using terahertz pulsed imaging, J. Pharm.. Sci 98 (12) (2009) 4866–4876.

[37] L. Ho, R. Muller, K.C. Gordon, P. Kleinebudde, M. Pepper, T. Rades, Y. Shen, P.F. Taday, J.A. Zeitler, Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance, J. Control Release 127 (1) (2008) 79–87.

[38] Guideline I 1996, Q1B: Photostability Testing of New Drug Substances and Products, ICH Secretariat, Geneva, Switzerland.

[39] Pharmacopeia US 2017, Nifedipine Extended-Release Tablets, The United States Pharmacopeial Convention.