International Journal of Pharmaceutics 382 (2009) 1–6

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

# Sustained release dosage forms dissolution behavior prediction: A study of matrix tablets using NIR spectroscopy

Simin Hassannejad Tabasi[a,c], Vikas Moolchandani[a], Raafat Fahmy[b], Stephen W. Hoag[a,*]

[a] School of Pharmacy, University of Maryland, 20 N. Pine Street, Baltimore, MD 21201, United States
[b] Office of New Animal Drug Evaluation, FDA, Rockville, MD 20855, United States
[c] Research and Development, Perrigo Company, Allegan, MI 49010, United States

ARTICLE INFO

*Article history:*
Received 16 March 2009
Received in revised form 23 July 2009
Accepted 25 July 2009
Available online 4 August 2009

*Keywords:*
NIR spectroscopy
Dissolution prediction
Drug release prediction
Matrix formulation
Multivariate calibration
Chemometrics

ABSTRACT

The objective of this study was to predict dissolution behavior of sustained release theophylline matrix tablets using near infrared (NIR) diffuse reflectance spectroscopy and multivariate calibration models. Eudragit NE 30D was used as a granulation binder to prepare theophylline sustained release tablets. A total of 117 tablets from 5 batches containing different proportions of Eudragit NE 30D were scanned using a NIR spectrometer. The release characteristics of the tablets were investigated in the acetate buffer for 4 h. The percentage release at 1, 2, 3 and 4 h was used to build the PLS calibration models. The Mahalanobis distance in principal component space and the 2nd derivative transformation were used for sample selection prior to building a four 4-factor partial least square (PLS) calibration models for predicting 1, 2, 3 and 4 h release rates. For $PLS_{1\,h}$, the standard error of calibration (SEC), and standard error of prediction (SEP) were 2.8 and 3.4%. For $PLS_{2\,h}$, the SEC and SEP were 2.7 and 3.5%. For $PLS_{3\,h}$, the SEC and SEP were 2.6 and 3.5% and for $PLS_{4\,h}$, the SEC and SEP were 3.0 and 3.5%, respectively. For the first time, NIR spectroscopy was successfully applied to predict drug release in the matrix tablets by correlating dissolution profile of each batch to its corresponding Eudragit NE 30D variation in tablet composition.


## 1. Introduction

Currently dissolution is the key method for evaluating solid oral dosage form release, consistency, similarity and is the only method that can have some degree of relevance to *in vivo* therapeutic efficacy. However, dissolution testing involves a series of time-consuming analytical tasks, which requires following labor-intensive protocols such as instrument calibration, media preparation, sample collection, data collection and drug assay.

Many factors may affect dissolution tests and results; these factors can originate from the drug product variability or the inherent variability associated with dissolution methodology. Each of these factors can lead to variability in test procedures and outcomes, leaving uncertainties about a product's quality. Examples of variability sources that cause inconsistency in dissolution results include API, excipient type, tablet surface and hardness, instrumentation, methods for sample withdrawal and analysis as well as others. Additionally, inconsistencies related to media buffer, dissolution apparatus and in-process test run may affect dissolution tests and results. Buffer media factors such as buffer pH and temperature, hydrodynamic flow inside vessel and variation in aeration of media can lead to variability in dissolution results. The factors related to dissolution apparatus such as differences in speed and height of paddle, shaft centering and wobbling, and vibration of equipment may potentially cause biased results. Coning, off-center placement of dosage form, and sticking of tablets on the vessels are some of the in-process test errors that may cause variability in dissolution results. During this study, dissolution methodology was consistent for all testing.

In contrast, the dissolution profile can also be assessed using rapid nondestructive spectroscopic tools such as near infrared spectroscopy (NIRS) in combination with multivariate statistical methods. NIRS is a technique that measures the reflectance and/or transmittance of near infrared light and with the aid of chemometric methods, the amount of drug release from solid dosage form can be predicted.

The ability of NIRS to predict the drug dissolution profile of sustained release film coated tablets, and the effect of film coat thickness and film coat uniformity on both drug dissolution rate and NIR spectra have been studied by several workers (Frickel and Reich, 2000; Kirsch and Drennen, 1995, 1996; Reich and Frickel, 1999, 2000; Tabasi et al., 2008a,b). In a recent study, Tabasi et al. (2008a) developed multivariate NIR calibrations to predict the full dissolution profile of sustained release coated tablets containing varying amounts of Eudragit® RL and RS 30D with acceptable SEC and SEP. In another study, Tabasi et al. (2008b) developed a PLS cal-

* Corresponding author. Tel.: +1 410 706 6865; fax: +1 410 706 0346.
*E-mail address:* shoag@rx.umaryland.edu (S.W. Hoag).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.07.029

ibration model to predict drug release after 250 min dissolution for tablets coated with a blend of Eudragit® polymers that were cured at 40 °C for 2, 4, 8, 24 and 48 h. Freitas et al. (2005) studied the correlation between dissolution results and NIR diffuse reflectance spectra of a series of clonazepam tablet formulations. The percent dissolution for each sample under various dissolution pH's were correlated to the NIR spectra of tablets from each batch using the partial least squares (PLS) regression algorithm. Donoso and Ghaly (2004) used NIRS in combination with linear and higher order regression models and partial least squares to determine the relationship between the dissolution profile data and NIR spectra for a series of theophylline tablets with the same composition but compacted at different compressional forces. They compared laboratory dissolution profiles to NIR diffuse reflectance data and found that a decrease in the amount of API dissolution produced an increase in NIR absorbance. Blanco et al. (2006a,b) developed PLS calibration models to determine the percentage of API dissolved at a given time by using tablets pressed at variable pressures and spanning a wide range of dissolution profiles. In a recent study, Otsuka et al. (2007) used both transmittance and diffused reflectance NIRS with chemoinformetrics to develop multivariate regression models that predicted the change in dissolution properties for indomethacin tablets pressed under varying compression pressures.

Eudragit® NE 30D is widely used as a coating agent and sometimes as a granulating agent in controlled release matrix tablets (Langer, 1990; Rhine et al., 2006). Due to the pharmaceutical importance of the methacrylate copolymers as sustained release polymers, developing methods that can predict the complete dissolution profile of intact tablets would be time and cost effective, and to date no such studies have been performed. Thus, the objective of this study is to explore further the application of NIR spectroscopy to predict dissolution profiles of sustained release matrix tablet formulations containing Eudragit® NE 30D. In this work, we will continue our efforts to apply NIRS as a novel approach for determining the full dissolution profile for sustained release matrix solid dosage forms. A goal of this study is to develop a better understanding of critical quality attributes and product performance, which can justify the use of surrogate tests or support real time release in lieu of end-product dissolution testing. This study presents multivariate models for the prediction of theophylline tablet dissolution based on the composition of the Eudragit® NE 30D in the tablet matrix.

## 2. Materials and methods

### 2.1. Materials

Theophylline anhydrous (lot# SV0618) and 99.5% pure, magnesium stearate, N.F (lot# OX0283) were obtained from Spectrum Laboratory Products, New Brunswick, NJ. Lactose monohydrate, spray dried (Supertab, lot# 71010004), Microcrystalline cellulose (Avicel PH 102, lot# P204814355) and Croscarmellose sodium (AcDiSol, lot# TN04814211) were supplied by FMC Biopolymer, Newark, DE. Glacial acetic acid (lot# 109088) and Sodium hydroxide (lot# S0899) were obtained from Sigma Chemical Co. St Louis, MO. Sodium acetate trihydrate (lot# 3460-05) was obtained from Mallinckrodt Baker Inc., Phillipsburg, NJ. Methacrylic acid copolymer (Eudragit NE 30D, lot# B041212067) was generously donated by Rohm Pharma Polymers, Piscataway, NJ.

### 2.2. Methods

#### 2.2.1. Matrix tablet formulation preparation

Five batches, 0.6 kg each, were made by blending theophylline, Avicel PH 102, and lactose monohydrate in a twin-shell blender (Patterson-Kelley Co., East Stroudsburg, PA) for 10 min. Later, these five batches were subjected to high shear wet granulation process using Cuisinart DLC-X Plus Food Processor. Eudragit NE 30D dispersion was used as granulating agent and its amount was varied from 0 to 20% (w/w) (Table 1). The wet mass was forced through a number 14 sieve to produce wet granules which were dried in a forced air oven at 60 °C till the granules had a moisture content between 1.3 and 1.5%. The dried granules were sieved through number 45 mesh. To the sieved granules 2.5% (w/w) of AcDiSol® was added and blended for 5 min. Mg stearate (0.5%, w/w) was added to this blend and mixed for an additional 2 min. For compression, a single station of a Stokes B2 rotary tablet press was used; the press fitted with an instrumented eyebolt and 11.1 mm flat face tooling. The compression force for all batches was 3860 ± 110 N and all tablets weighed 400 ± 5 mg. All batches had breaking force of 83 ± 10.8 N except for theophylline-NE 30D 5% which had a breaking force of 57 ± 10 N. Tablet weight, thickness, diameter, and crushing strength were consistent in all batches and these measurements were conducted at room temperature. All tablets selected for this study were cured overnight at 50 °C and then subjected to NIR spectrometry followed by dissolution testing. The formulations ingredients and Eudragit NE 30D contents are summarized in Table 1.

**Table 1**
Formulation composition of all theophylline-NE 30D batches used in calibration development.

| Ingredients (g) | Theophylline-NE 30D | | | | |
|---|---|---|---|---|---|
| | NE-0% | NE-5% | NE-10% | NE-15% | NE-20% |
| Theophylline | 200 | 200 | 200 | 200 | 200 |
| Eudragit NE 30D | 0 | 30 | 60 | 90 | 120 |
| Lactose monohydrate | 247 | 217 | 187 | 157 | 127 |
| MCC PH 101 | 135 | 135 | 135 | 135 | 135 |
| Croscarmellose Na | 15 | 15 | 15 | 15 | 15 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 |
| Total (g) | 600 | 600 | 600 | 600 | 600 |

#### 2.2.2. Dissolution study

All dissolution studies for theophylline matrix tablets were carried out in 900 mL 0.075 M acetate buffer at pH 3.95 ± 0.05 using a fully automated USP apparatus II dissolution system (VK 7000, Vankel, Edison, NJ) at 37 ± 0.5 °C and 50 rpm. The samples were withdrawn using a peristaltic pump (Rainin instrument Inc., Woburn, MA) at 10 min intervals and the drug release was assayed by UV spectroscopy (UV 160U, Shimatzu Corp. Colombia, MD) at 270 nm for 4 h. At the end of dissolution process, tablets were crushed using stainless steel rod and the solution was stirred at 250 rpm for 20 min to assess the infinity release. The infinity release was used to calculate the percentage drug release for each sample at every time point.

#### 2.2.3. NIR spectroscopy and multivariate analysis

A rapid content analyzer (RCA) DS model 6500 NIR spectrometer (Foss NIRSystems Inc., Laurel, MD) was used for all NIR scans. The rapid content analyzer (RCA) DS was operated in diffuse reflectance mode. Instrument operation and data analysis for calibration construction were performed using Vision™ 3.2 software. To ensure measurement accuracy, performance testing was carried out every month to verify instrument noise level, NIR and visible gain, internal wavelength performance (wavelength position) and precision (repeatability). Wavelength linearization was performed daily, to maintain correct wavelength registration, using an internal wavelength standard. In addition, the ceramic reference was scanned at the beginning of each day, and this scan was repeated after every 20–30 scans.

The data collection method was set to full range (400–2500 nm). Samples and references scans were an average of 32 scans at 2 nm intervals. All tablets in this study were scanned on both faces and the averaged spectra of the two faces were used for final analy-

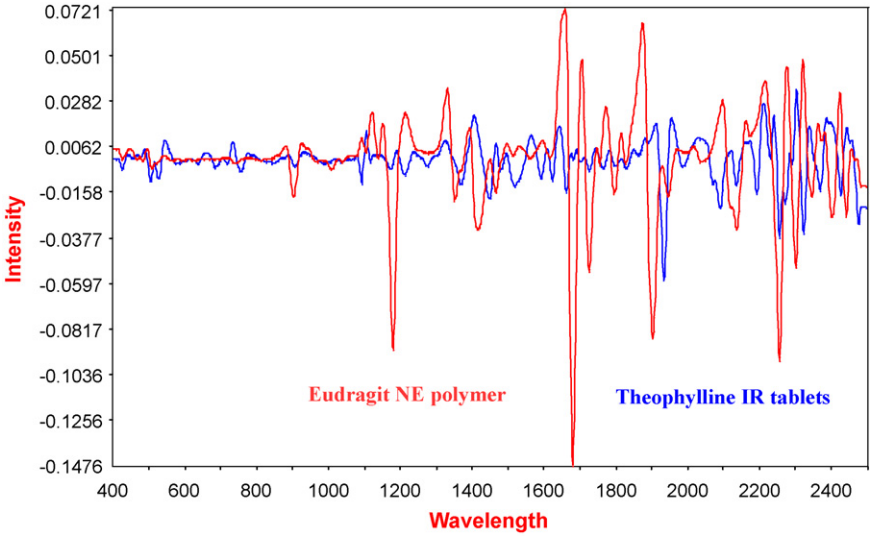


**Fig. 1.** 2nd D spectra of theophylline and Eudragit NE 30D.

sis. Matlab 7.0.4 (The MathWorks Inc., Natick, MA) equipped with PLS toolbox (Eigenvector Research Inc., Wenatchee, WA) package was used for principal component analysis (PCA). Prior to calibration development, PCA was carried out to study the relationship among the variables in the sample sets. A total of 117 theophylline matrix tablets from 5 batches containing different proportions of Eudragit NE 30D (0, 5, 10, 15 and 20%) were randomly chosen and scanned on both faces using NIR spectroscopy and then subjected to dissolution test. The two face average spectra and dissolution test values for each tablet were used to develop the calibration regressions. Spectra for all the multivariate analysis and calibration development were mathematically pretreated by combinations of median centering, Savitzky–Golay (SG, 7 data points, 2nd D, convolution polynomial: quadratic), Savitzyk-Golay, 2nd D (2nd D: segment size = 10 nm, gap size = 0.0 nm), standard normal variate (SNV), and detrend (polynomial degree 1). The percentage release at 1, 2, 3 and 4 h were taken as the reference values to build the PLS calibrations using 1150–2200 nm NIR regions. Calibrations were generated by using laboratory tablets alone. Such samples, which spanned a range of Eudragit NE 30D contents were pressed at similar breaking forces and analyzed individually by NIRS. Calibration models were developed using partial least squares (PLS) algorithm.

To build the calibration regression models, samples were divided into calibration, validation and prediction sets. Cross-validation with a segment size of four was used to validate the calibrations models. Cross-validation was done in rotation of 4 times (depends on the segment size) to plot prediction residual error-sum squares (PRESS). Usually, the first minimum in PRESS plot was used to determine the optimum number of factors with the best prediction of the cross-validation samples. Calibration and validation sets were mathematically transformed and the optimum preprocessing method was established based upon the methods, that achieved the overall lowest standard error of calibration (SEC), cross-validation (SECV) and prediction (SEP).

To ensure the correctness of the calibration models, their statistical parameters were carefully examined. In this study, the following criteria were used before accepting any calibration as a best-fit model. Generally, the SEP should not be greater than 1.3 × SEC, indicating the error has not increased considerably on testing the prediction set. Generally, the slope adjustment to fit the calibration line should be 1 (i.e., no change) and standard error of the slope gives an estimate of error on the line. If it was not 1 (slope adjustment $\neq$ 1), then to test the skewness of the slope, the absolute value of slope was subtracted from 1 and compared the value to the slope adjustment error. The error bigger than the difference from 1 (i.e. |slope adjustment − 1| < |slope adjustment error|), indicates insignificant slope adjustment, otherwise (|slope adjustment − 1| > |slope adjustment error|), the line is skewed.

The bias also should be zero when comparing the results. If it was not zero, then the bias should be compared to the standard error of the bias. The bias was insignificant when the standard error of bias was bigger than the bias itself (i.e. |bias| < standard error of

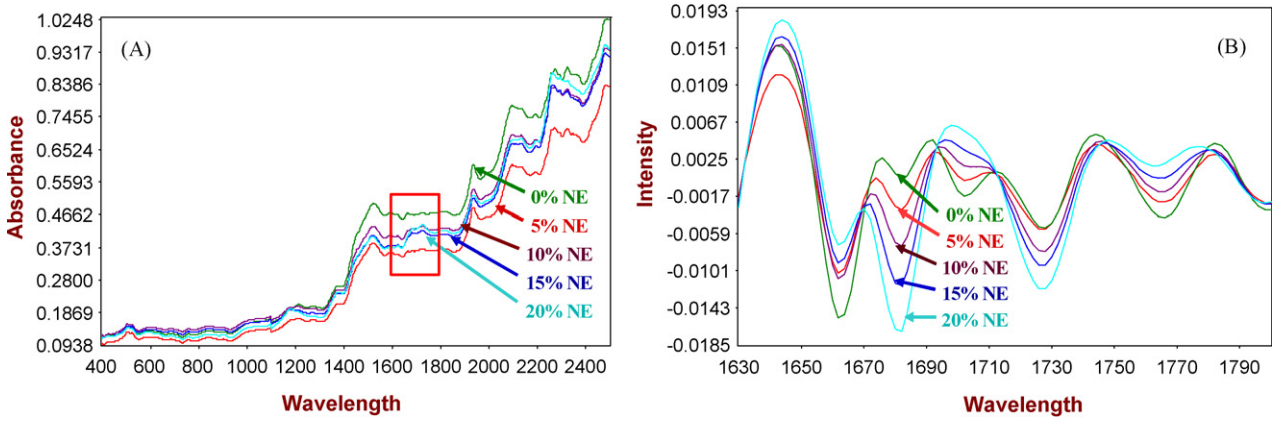


**Fig. 2.** Overlaid raw (A) and 2nd D (B, magnified) spectra of theophylline tablets containing 0, 5, 10, 15, and 20% Eudragit NE 30D.

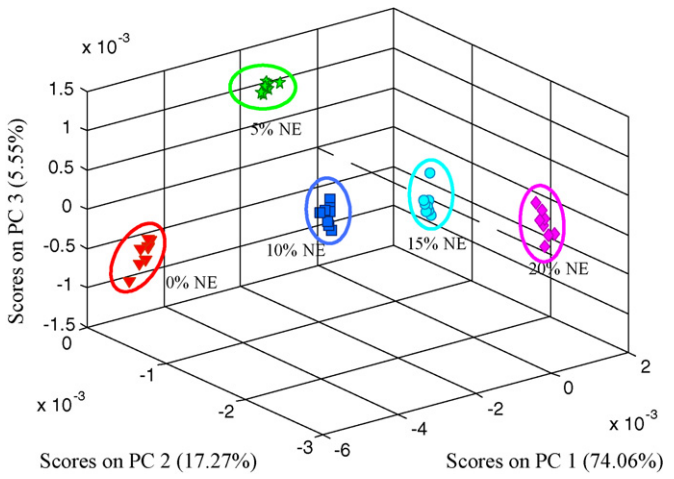


**Fig. 3.** Principal component and score plot of first, second and third PCs for tablets containing varying amounts of Eudragit NE 30D.

the bias). Usually, bias in the prediction set should not be greater than 0.6 × SEC, otherwise presence of systematic error between the calibration and prediction set should be tested. In this study all calibration were tested for bias and slope adjustment to ensure development of the best-fit calibration regressions.

## 3. Results and discussion

### 3.1. Feasibility study

The superimposed raw NIR spectra over the 2nd D spectra of polymer matrix and theophylline tablets (containing 0% NE 30D) indicate regions of non-interference between the polymer and theophylline tablet peaks (Fig. 1). The polymer absorbance at 1600–1700 nm and 2200–2400 nm corresponds to CH–CH first overtone and combination bands, respectively. Fig. 2A shows that raw spectra provide little information regarding the relationship between tablet spectra and its NE 30D content in the range from 0 to 20%, i.e., there is no rank order with respect to NE 30D content. However, the 2nd D spectra of the same tablets (Fig. 2B) shows a direct rank order correlation between the spectra and NE 30D content, in other words, the increase in polymer content correlated with the 2nd derivative of the raw spectrum. In our study, this correlation was most observable in the CH–CH first overtone and combination regions. Thus, the relationship between dissolution performance and polymer content could be investigated by utilizing the absorbance in the 1600–1700 nm NIR regions.

### 3.2. Principal component analysis (PCA)

To model drug release, eight tablets were randomly selected from each theophylline batch NE 30D and subjected to PCA analysis. The initial preprocessing included median centering and SG. The 3D PCA score plot shown in Fig. 3 offers more information about the formulation effects. Fig. 3 shows the first and second PC in a score plot for the five levels of NE 30D content in all batches. The first PC captured 74.06% of variability in the sample set. The 1st, 2nd and 3rd PCs captured 17.27 and 5.55% of variability in the sample set, respectively. All batches were differentiated along the first PC based on their NE 30D content.

Close examination of the loadings showed that the PC1 loadings (Fig. 4A) approximately resembled to Eudragit NE 30D (Fig. 4I) and the PC2 loadings (Fig. 4B) approximately resembled to lactose spectra (Fig. 4II). The PC3 loadings (Fig. 4C) were correlated to the whole tablet absorbance (Fig. 4III). Tablet breaking force testing showed that all theophylline-NE 30D tablets had an average of 83 N except for theophylline-NE 30D 5%, which had an average of 57 N breaking force. Close examination of PC3 in Fig. 3 shows that only theophylline-NE 30D 5% has a shift along PC3, accounting for 5.55% variability, which indicates a correlation between PC3 and tablet breaking force. The PC3 loading's likeness to the whole tablet spectra supports this assumption.

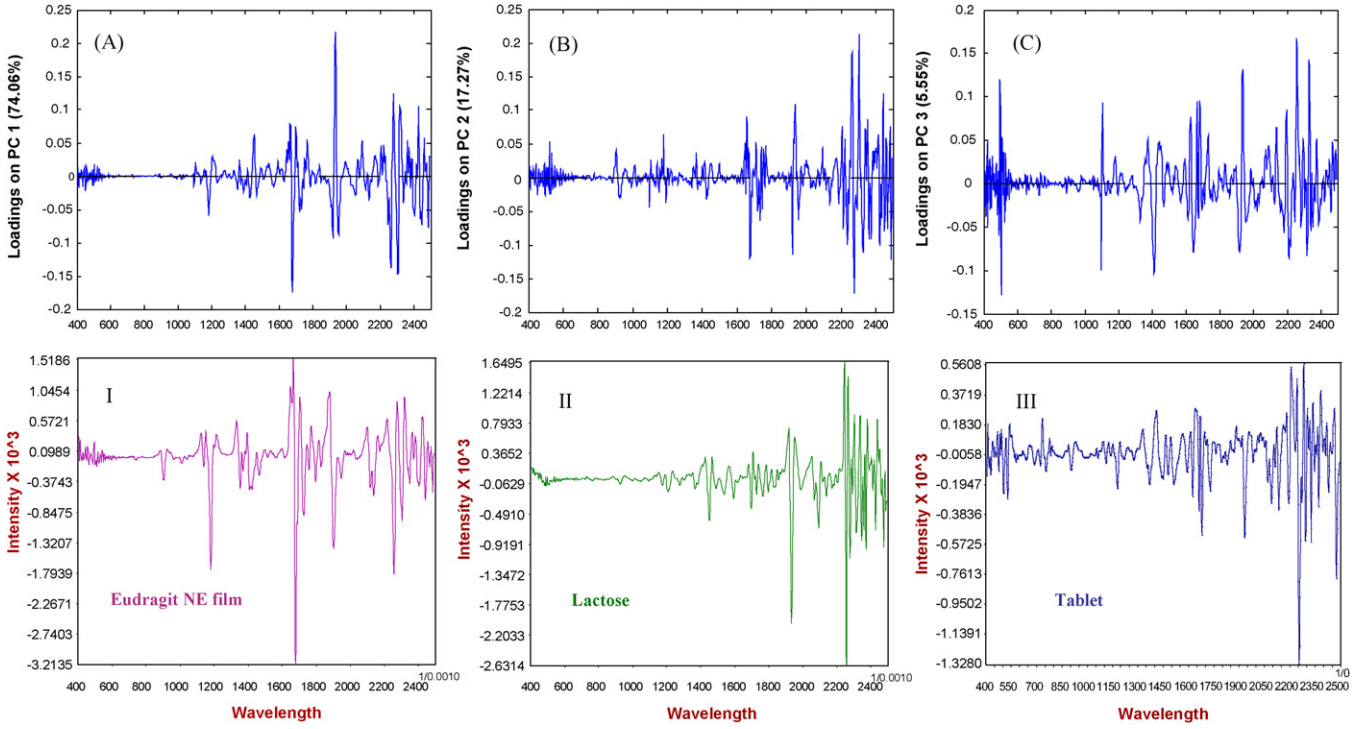


**Fig. 4.** PCA loadings and related spectra for dissolution study: (A) PC1 loading; (B) PC2 loading; (C) PC3 loading; (I) Eudragit NE 30D spectra; (II) lactose spectra; (III) tablet spectra. Same mathematical pretreatments were used to develop PCA and to transform raw spectra of Eudragit NE 30D, lactose and whole tablet.

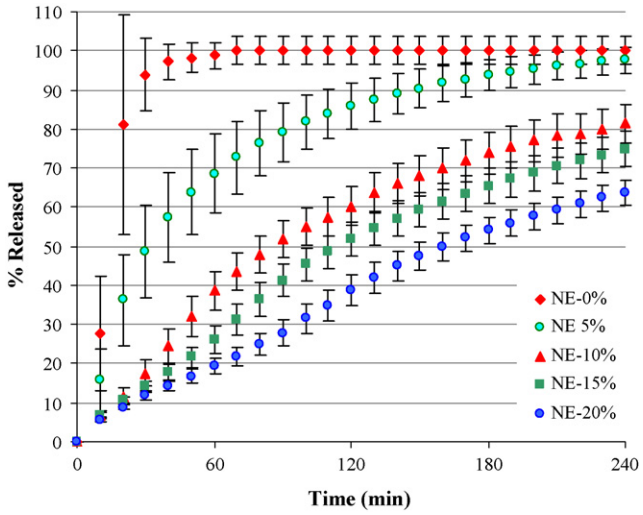


**Fig. 5.** Dissolution profile for theophylline batches containing varying amount of Eudragit NE 30D polymers.

**Table 2**
Average % drug release after 1, 2, 3 and 4 h for theophylline tablets used for calibration development.

| Time (h) | Drug release (%) | | | | |
|---|---|---|---|---|---|
| | NE-0% | NE-5% | NE-10% | NE-15% | NE-20% |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 98.7 ± 3.5 | 68.6 ± 10.2 | 38.6 ± 4.9 | 26.0 ± 3.5 | 19.4 ± 2.0 |
| 2 | 100.0 ± 3.5 | 85.8 ± 6.0 | 60.3 ± 4.9 | 51.9 ± 4.3 | 38.7 ± 4.0 |
| 3 | 100.0 ± 3.5 | 93.7 ± 4.1 | 73.8 ± 5.3 | 65.5 ± 4.6 | 54.1 ± 3.4 |
| 4 | 100.0 ± 3.57 | 97.6 ± 3.3 | 81.4 ± 5.0 | 74.9 ± 4.6 | 63.8 ± 3.3 |

### 3.3. Calibration development and prediction

The dissolution profile for all formulations is shown in Fig. 5. The mean percentage drug releases at 1, 2, 3 and 4 h are summarized in Table 2. The calibration sample set contained both immediate (NE 30D 0%) and sustained release (NE 30D 5, 10, 15, and 20%) tablets, which expanded calibration range to 100% release. Approximately, 117 tablets from 5 batches with variation in Eudragit NE 30D composition were used to build the PLS calibrations. To predict the dissolution profile, four PLS calibrations denoted as $PLS_{(1\,h)}$, $PLS_{(2\,h)}$, $PLS_{(3\,h)}$ and $PLS_{(4\,h)}$ corresponding to 1, 2, 3 and 4 h release were built. For all calibrations in the sample selection step, the Mahalanobis distance in principal component space (threshold 0.95) and 2nd derivative transformation were used. In this process, calibration and internal validation sets contained 56 and 19 samples, respectively. All four PLS calibrations for dissolution were developed using detrend, SNV and 2nd D transformation in the 1150–2200 nm NIR region; four factors were used in the final model.

This treatment for $PLS_{1\,h}$ resulted in a calibration with SEC, SECV and $R^2$ equal to 2.83%, 3.1% and 0.992, respectively (Table 3). During the prediction step, the calibration predictability was tested using 30 samples. The prediction step gave SEP and correlation coefficient of 3.38% and 0.991, respectively (Table 3). The linearity of the calibration was tested when bias and slope were compared with their standard errors (1.16 and 0.026). Application of bias and slope adjustment reduced the SEP insignificantly (3.18%). Fig. 6A and I illustrates calibration and prediction regressions for this model.

The same treatment was applied for $PLS_{(2\,h)}$, and the SEC, SECV and $R^2$ were 2.67, 2.80% and 0.988, respectively (Table 3). The calibration was subjected to prediction using 34 samples, giving SEP and correlation coefficient of 3.48% and 0.986, respectively (Fig. 6B and II). Application of slope and bias adjustment did not significantly reduce the SEP (3.33%). The third calibration, $PLS_{(3\,h)}$ was developed and the SEC, SECV and $R^2$ were 2.58%, 2.75% and 0.982, respectively. In prediction process using 37 samples (Fig. 6C and III), the SEP and correlation coefficient were 3.46% and 0.982, respectively (Table 3).

The forth and final model, $PLS_{(4\,h)}$, gave SEC, SECV and $R^2$ of 3.02%, 3.23% and 0.960, respectively (Fig. 6D and IV). When the calibration was subjected to 42 samples for prediction process, SEP and correlation coefficient were, 3.54% and 0.971, respectively (Table 3). Both bias and slop adjustment for PLS 2, 3 and 4 h were compared to their standard errors to confirm linearity of the models. Application of both bias and slope adjustments did not change prediction performance for $PLS_{(2\,h)}$, $PLS_{(3\,h)}$ and $PLS_{(4\,h)}$ significantly (see Table 3).

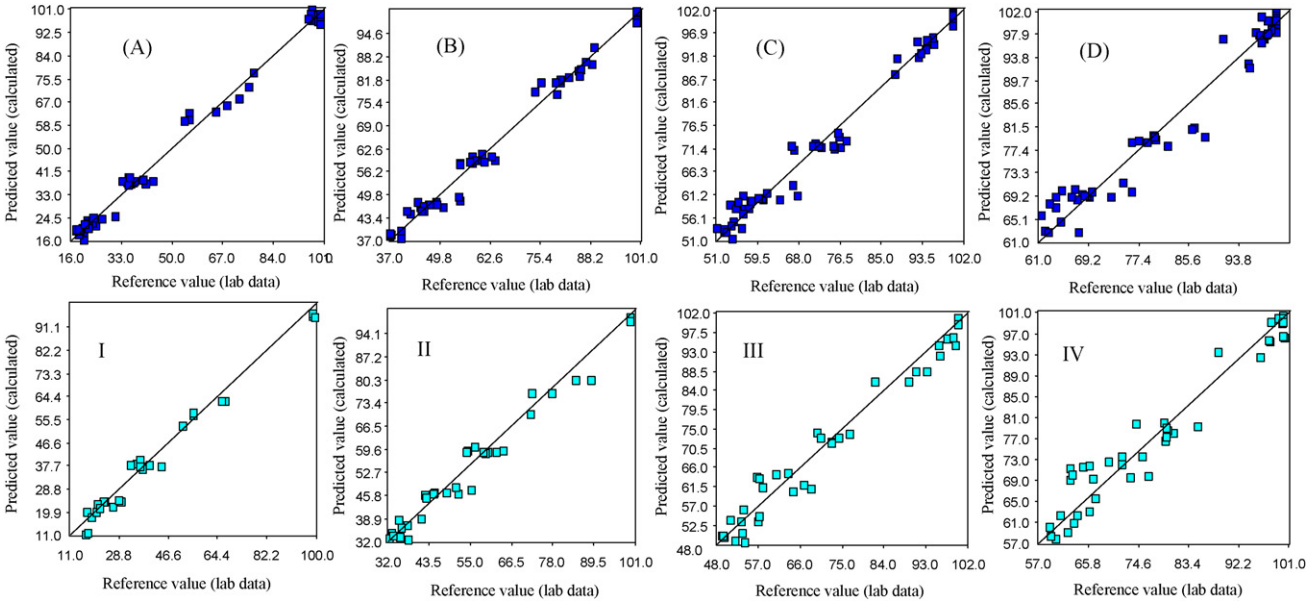


**Fig. 6.** PLS calibrations and validation regressions for drug release (%) from the tablets containing varying amount of Eudragit NE 30D polymers. Calibration for drug release (%) at 1 (A), 2 (B), 3 (C) and 4 (D) hours and PLS prediction regressions for drug release (%) at 1 (I), 2 (II), 3 (III) and 4 (IV) hours from theophylline tablets containing varying amount of Eudragit NE 30D polymers.

**Table 3**
Dissolution profile prediction summary for the PLS calibration models. SEP possible: SEP after slope and bias adjustment.

| PLS calibrations | SEC (%) | SECV (%) | $R^2$ | SEP (%) | Correlation | Slope Adj. | Slope Adj. SD | Bias Adj. | Bias Adj. SD | SEP[a] possible |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 h | 2.83 | 3.10 | 0.9915 | 3.38 | 0.991 | 1.015 | 0.026 | 0.519 | 1.163 | 3.18 |
| 2 h | 2.67 | 2.80 | 0.9881 | 3.48 | 0.986 | 1.027 | 0.031 | −0.593 | 1.810 | 3.33 |
| 3 h | 2.58 | 2.75 | 0.9816 | 3.46 | 0.982 | 1.013 | 0.033 | −0.218 | 2.386 | 3.37 |
| 4 h | 3.02 | 3.23 | 0.9604 | 3.54 | 0.971 | 1.021 | 0.040 | −1.584 | 3.216 | 3.53 |

[a] SEP after bias and slope adjustment.

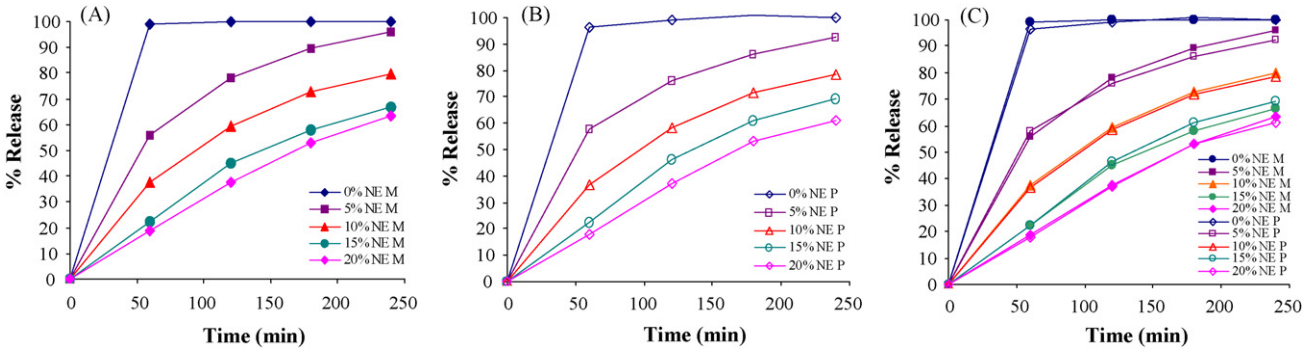


**Fig. 7.** Measured (A), predicted (B) and overlaid (C) dissolution profile for randomly selected samples from various theophylline-NE 30D formulations. M: measured; P: predicted.

**Table 4**
Summary of measured and the predicted drug release (%) of selected individual samples from each theophylline-Eudragit NE 30D batches.

| Time (h) | Measured (reference data) drug release | | | | | Predicted (calculated data) drug release | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NE-0% | NE-5% | NE-10% | NE-15% | NE-20% | NE-0% | NE-5% | NE-10% | NE-15% | NE-20% |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 98.9 | 55.8 | 37.5 | 22.1 | 18.8 | 96.4 | 57.8 | 36.6 | 22.4 | 18 |
| 2 | 100 | 78.1 | 59.5 | 45.1 | 37.6 | 98.9 | 76.1 | 58.4 | 46.5 | 37 |
| 3 | 100 | 89.5 | 72.8 | 58.1 | 53.2 | 101 | 86 | 71.7 | 61.2 | 53.3 |
| 4 | 100 | 96.1 | 79.8 | 66.7 | 63.2 | 99.9 | 92.5 | 78.5 | 69.2 | 60.9 |

Comparing UV reference and NIR predicted values for release prediction using paired *t*-test ($\alpha = 0.05$) demonstrate insignificant deference between these two methods ($P > 0.073$, 0.13, 0.2 and 0.96 for PLSs 1, 2, 3 and 4 h, respectively). Fig. 7A–C demonstrates the measured, predicted and overlay profiles of selected individual samples from each Eudragit NE 30D composition level. The actual values are given in Table 4.

## 4. Conclusion

For the first time, this investigation successfully applied NIR spectroscopy to predict dissolution profile based on the composition of the Eudragit NE 30D in the matrix tablets. The results of this study clearly show that NIR spectroscopy along with multivariate modeling was able to successfully differentiate Eudragit NE 30D variations in tablet formulation and correlate dissolution profiles of each batch to its corresponding tablet composition. Using NIRS, dissolution results could be accurately predicted; without having to actually analyze the product. The results of this study expand the application NIRS in pharmaceutical dosage forms, sustained release products.

## References

Blanco, M., Alcala, M., Gonzalez, J.M., Torras, H., 2006a. A process analytical technology approach based on near infrared spectroscopy: tablet hardness, content uniformity, and dissolution test measurements of intact tablets. J. Pharm. Sci. 9, 2137–2144.

Blanco, M., Alcala, M., Gonzalez, J.M., Torras, H., 2006b. Determination of dissolution profiles in intact pharmaceutical tablets by NIR spectroscopy. PAT 3, 25–28.

Donoso, M., Ghaly, E.S., 2004. Prediction of drug dissolution from tablets using near-infrared diffuse reflectance spectroscopy as a nondestructive method. Pharm. Dev. Technol. 9, 247–263.

Freitas, M.P., Sabadin, A., Silva, L.M., Giannotti, F.M., Do Couto, D.A., Tonhi, E., Medeiros, R.S., Coco, G.L., Russo, V.F., Martins, J.A., 2005. Prediction of drug dissolution profiles from tablets using NIR diffuse reflectance spectroscopy: a rapid and nondestructive method. J. Pharm. Biomed. Anal. 39, 17–21.

Frickel, H., Reich, G., 2000. NIR spectroscopy of film-coated tablets-fast and nondestructive evaluation of film coat uniformity and drug release kinetics. Proc. Int. Symp. Control. Release Bioact. Mater. 27, 740–741.

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

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

Langer, R., 1990. New methods of drug delivery. Science 249, 1527–1533.

Otsuka, M., Tanabe, H., Osaki, K., Otsuka, K., Ozaki, Y., 2007. Chemoinformetrical evaluation of dissolution property of indomethacin tablets by near-infrared spectroscopy. J. Pharm. Sci. 96, 788–801.

Reich, G., Frickel, H., 1999. Use of transmission spectroscopy to determine physical and functional film coat properties on tablets. Proc. Int. Symp. Control. Release Bioact. Mater. 26, 905–906.

Reich, G., Frickel, H., NIR spectroscopy - A rapid method to evaluate gastroresistance and drug release kinetics of film-coated tablets. Proceedings of 3rd World Meeting APV/APGI, Berlin, 3/6 April 2000, pp. 627-628.

Rhine, W.D., Hsieh, D.S.T., Langer, R., 2006. Polymers for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics. J. Pharm. Sci. 69, 265–270.

Tabasi, S.H., Fahmy, R.M., Bensley, D., O'Brien, C., Hoag, S.W., 2008a. Quality by design. Part II. Application of NIR spectroscopy to monitor coating process for pharmaceutical coated product. J. Pharm. Sci. 97, 4052–4066.

Tabasi, S.H., Fahmy, R.M., Bensley, D., O'Brien, C., Hoag, S.W., 2008b. Quality by design. Part III. Study of curing process of sustained release polymer products using NIR spectroscopy. J. Pharm. Sci. 97, 4067–4086.