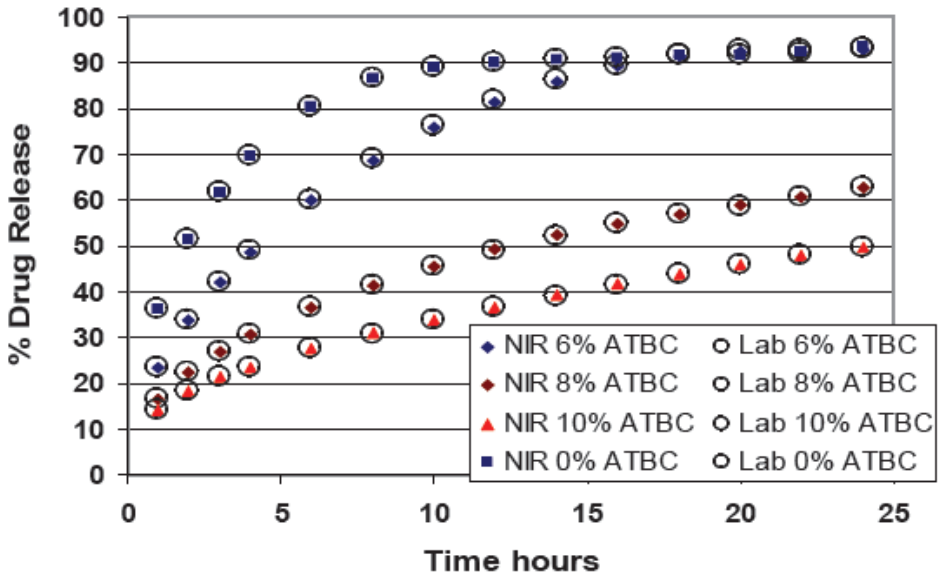
Near-Infrared Spectroscopy Application Note NIR–17

NIR prediction of solid dosage form dissolution profile



This Application Note shows that NIR prediction of the dissolution profile of intact tablets provides a fast and accurate means of nondestructively assessing tablets that is in step with the FDA Process Analytical Technology (PAT) initiatives. The data shows promising results that could reduce laboratory workload in dissolution testing.

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Method description

Introduction

Dissolution testing is used in solid dosage form manufacturing to determine the rate of dissolution of the active pharmaceutical ingredient (API) into solvents that simulate the digestive tract fluids. There are several dissolution testing apparatuses described in the US Pharmacopoeia. The general design has 6 to 9 temperature controlled 900 ml vessels that contain the buffered solvent and a stirring device. The tablet is dropped in at time zero and the concentration of the API in the dissolution medium is periodically monitored by an appropriate analytical technique such as UV spectrophotometry. A dissolution profile is plotted with percentage of drug released versus time.

Solid dosage forms designed for sustained release require dissolution testing of a duration equivalent to the designated release time. Sustained release tablets that release the API over a 24 hour period have many therapeutic advantages. However, they require 24 hours of dissolution testing which ties up laboratory equipment and personnel. Only an extremely small sampling of the batch can be dissolution tested.

Near-infrared spectroscopy (NIRS) is an analytical technique based on absorption measured in the near-infrared region of the electromagnetic spectrum that is between the visible and the mid-infrared. The fundamental absorption bands of functional groups occur in the mid-infrared and are very strong and usually KBr pellets, mulls or dilutions are required to bring the absorbances within the linear range of the mid-IR detector. The overtone absorptions of these fundamental bands occur in the near infrared (NIR) spectral region and allow direct measurement without sample preparation due to the relative weakness of absorption. The OH, CH, NH and SH bonds have the strongest overtone absorbances in the NIR region.

Near Infrared (NIR) has been evaluated by numerous investigators for predicting dissolution profiles in the spirit of QbD and PAT "to verify product quality and release it for subsequent processing without delay"[1, 2].

Experimental

In this study, propranolol tablets were formulated with ethylcellulose as the sustained release polymer. Different levels of acetyltributyl citrate (ATBC) were used as plasticizer. Tablets with 0%, 6%, 8%, and 10% ATBC levels were formulated and compressed. Dissolution testing was performed on each formulation and the average dissolution profile was plotted for each formulation (Figure 1).

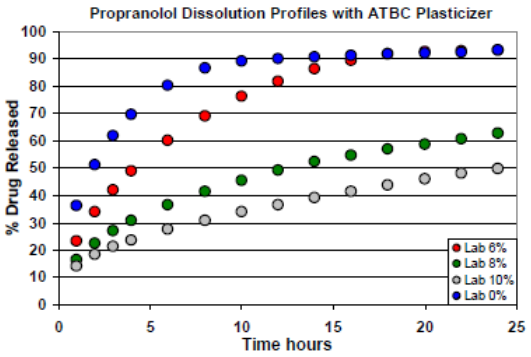

Fig. 1. Dissolution profiles of tablets formulated with varying concentrations of ATBC

The seven batches of tablets with 20% Propranolol per tablet and varying levels of ATBC, were formulated and compressed on an Elizabeth-Hata tablet press (HT-AP 18 SS-U/I rotary tablet press, Elizabeth Hata International, Inc., North Huntingdon, PA).

The NIR instrument used in the study was the NIRS XDS MasterLab which was capable of automatically measuring multiple tablets after they are positioned in a special tray (Figure 2). In the inset, a tablet tray is to the left, and to the right is the NIST traceable standards tray for photometric and wavelength accuracy and precision. The tray used for this study had 31 pockets machined to the diameter of tablets under test. The 31 tablets were scanned in less than ten minutes, taking a reference spectrum before scanning each set of ten tablets. Spectra were collected in the transmission mode from 800 to 1650 nm with 0.5 nm data intervals and 32 scans were co-added to produce a single spectrum.

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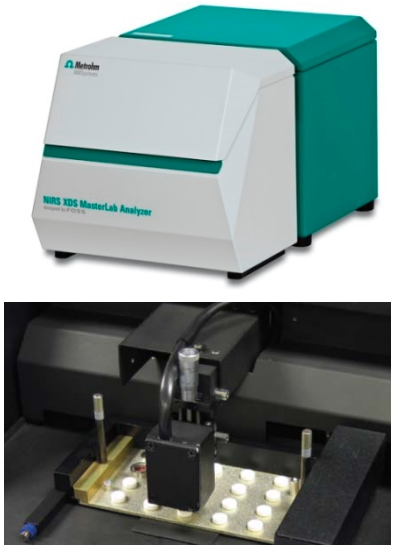

Fig. 2. Tablets in the NIRS MasterLab in transmission mode

Results and discussion

Figure 3 shows the second derivative of the calibration set spectra. The baseline was normalized and the spectral features were enhanced so that the "fanning out" of the absorbance bands occurs[3]. Smoothing was done on the derivative with a segment of 10 and a gap of 0. Standard normal variate pretreatment was applied to further reduce scattering.

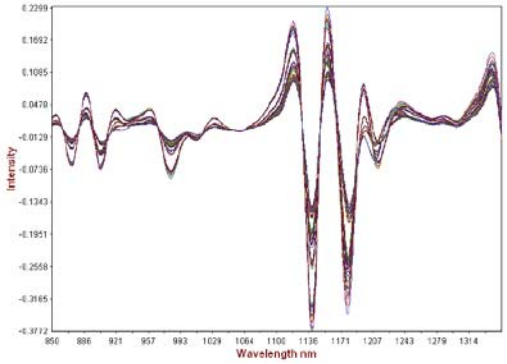

Fig. 3. Second derivative math pretreatment of calibration spectra showing analytical range

Partial least squares (PLS) regression was used to develop the prediction models. Fourteen PLS1 models were developed for the ATBC plasticizer for hours: 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 to predict the dissolution profiles. PLS uses principal component analysis and is a variation of principle component regression (PCR)[1]. The maximum number of principal components or factors was determined by the Vision® software supplied with the instrument by determining where the predicted residual error sum of squares (PRESS) reaches a minimum. The chosen model used only 7 of these factors, thus trading decreased error for robustness.

The resulting model for hour 1.0 had an R^2 value of 0.9972 and a standard error of calibration (SEC) of 0.3165. The standard error of prediction (SEP) was 0.416 for the chosen samples. The one-left-out cross validation demonstrated good predictability with a standard error of cross validation (SECV) of 0.4221. Figure 4 shows the NIR predicted percent drug (Propranolol) released versus the actual drug dissolution results for the hour 1.0 calibration set (left hand plot). One tablet was left out of the calibration set at each level for prediction model validation as seen in the right hand plot. Figure 5 and Figure 6 similarly show the NIR predictions of the calibration set and validation set, respectively, versus the laboratory results for 12 hours and 24 hours. Figure 7 shows the Propranolol release from tablets compressed with varying concentrations of ATBC as plasticizer and superimposed NIR predictions.

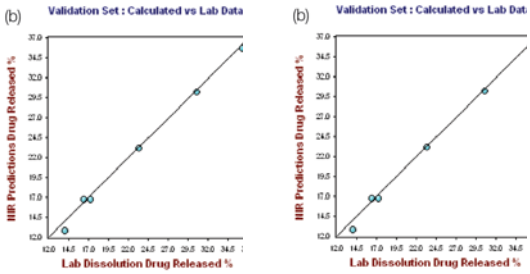

Fig. 4. Hour 1, no. of Factor = 7, R^2 = 0.9972, SECV = 0.4221

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Method description

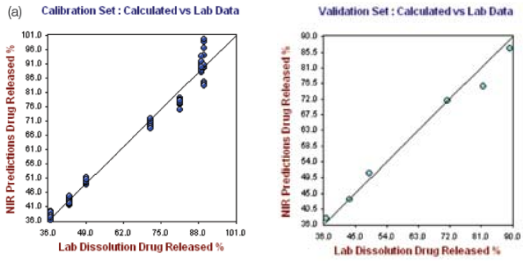

Fig. 5. Hour 12, No. of Factor = 7, R^2 = 0.9787, CrossVal= 3.4791

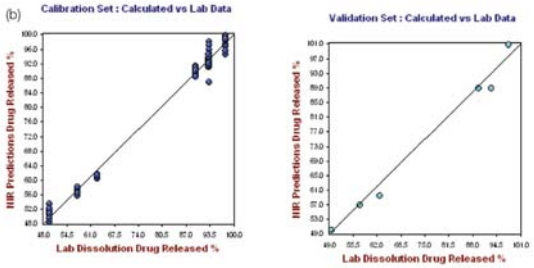

Fig. 6. Hour 24, no. of Factor = 7, R^2= 0.9919, SECV = 2.1249

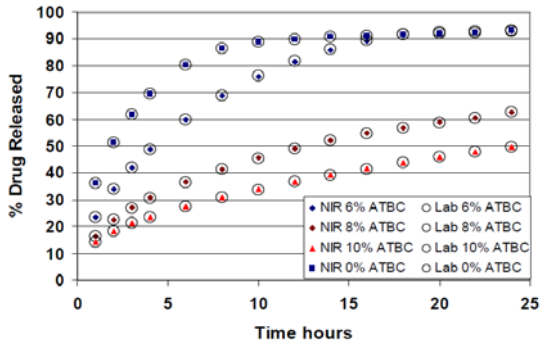

Fig. 7. Propranolol release from tablets compressed with varying concentrations of ATBC as plasticizer and superimposed NIR predictions

The Vision software supplied by Metrohm has a convenient routine analysis method that allows calculating dissolution automatically and produces a 21 CFR part 11 compliant report.

Conclusions

It can be concluded from this study that near infrared prediction of dissolution profiles of intact tablets provides a fast and accurate means of non-destructively assessing tablets that is in step with the FDA Process Analytical Technology (PAT) initiatives. The data showed promising results that could relieve laboratory workload from dissolution testing. Thirty one tablets could be analyzed in less than ten minutes. NIR was able to predict dissolution profiles for tablets with different levels of acetyltributyl citrate (ATBC) closely replicating the error of the lab method.

References

1) M. Blanco, et al., Non-destructive dissolution testing by NIR spectroscopy, Sept 2007, Vol. 18, No.6.

2) R. Fahmy, Quality by Design: Application of NIR Spectroscopy for Formulation Development of Sustained Release Dosage Forms, Presentation, FDA Center of Veterinary Medicine/University of Maryland.

3) R. A. Mattes, et al., Near-Infrared Assay and Content Uniformity of Tablets, Pharmaceutical Technology, 4, 2007.

4) R. Kramer, Chemometric Techniques for Quantitative Analysis, Marcel Dekker, 1998

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