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Research Article

Spectrophotometric Prediction of the Dissolution Rate of Carbamazepine Tablets

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A near-infrared (IR) spectrophotometer, integrating optics, and parallel-vector supercomputer are employed to develop a mathematical model that predicts the dissolution rate of individual intact tablets from near-IR spectra (r^2 = 0.985). Each tablet can be analyzed nondestructively by the spectrophotometer in less than 1 min. The model permits hundreds of near-IR wavelengths to be used in the determination of dissolution rate, leading to increased accuracy.

KEY WORDS: intact tablets; dissolution rate; near-infrared (IR); moisture effects; degradation product.

INTRODUCTION

The use of near-infrared spectrophotometry to solve pharmaceutical problems is increasing, because of technological advances in near-infrared (IR) analytical instrumentation and computer software. Recent examples include the study of pharmaceutical raw materials (1), particle size (2), and moisture determination (3) and detection of tampering of intact capsules and tablets (4,5). The use of near-infrared spectrophotometry to determine a degradation product in individual intact aspirin tablets has been reported (6). In the aspirin work, single tablets were analyzed quickly and nondestructively, two advantages of the near-IR technique that are exploited in the following study of carbamazepine.

A recent study by FDA scientists and researchers at the University of Tennessee showed that carbamazepine tablets can lose a significant proportion of their effectiveness from exposure to humidity (7). The presence of moisture resulted in decreased dissolution of tablets both *in vivo* and *in vitro*. Several thousand of the 2 million epileptics in the United States take carbamazepine regularly to control seizures. Complaints by some patients of variability in effectiveness of the drug may be due to the effects of moisture, which can be acquired during storage in humid areas such as bathroom medicine cabinets (8). Variations in effectiveness may have serious consequences—seven seizures and two deaths were linked to carbamazepine tablets that failed to dissolve properly (9). At least one lawsuit has been filed in connection with these incidents (10). These reports, as well as numerous other complaints to the FDA, resulted in the recall of more than 50 million tablets (10). Reports of variations in carbamazepine effectiveness and the possible link to moisture served as the impetus for this study, which examines the changes in near-infrared spectra of carbamazepine tablets upon exposure to water vapor.

Spectrophotometric examination of intact tablets requires a unique system of sampling optics (6) which are able to separate specular reflectance (direct reflectance containing much information about the light source used) from diffuse reflectance (which contains information about the sample in the light scattered by the sample). This paper presents the use of these optics with near-infrared spectrophotometry, principal-component regression, and the bootstrap error-adjusted single-sample technique to predict the extent of tablet dissolution. Near-IR spectra were obtained from reference tablets prior to dissolution, and these spectra were used by a parallel computer algorithm to predict the extent of tablet dissolution following 1 hr in a standard dissolution apparatus.

MATERIALS AND METHODS

Materials. The dissolution medium consisted of 1% sodium lauryl sulfate (95% pure, Sigma) and 1% methanol (HPLC grade, Fisher) in distilled water. Brand and generic, commercially available sources of carbamazepine tablets were used (Tegretol, Ciba-Geigy, Lot No. 1T130122, and Purepac, Kalipharma, Lot No. 053A9, respectively). Carbamazepine reagent powder was obtained from Sigma (Lot No. 28F-0109).

Instrumentation. The near-infrared spectrophotometer employed in this study was an InfraAlyzer 500 (Bran+Luebbe, Elmsford, NY). Reflectance values were obtained from intact tablets every 2 nm from 1100 to 2500 nm. The spectrophotometer was operated with an IBM PS/2 Model 50 computer (International Business Machines, Armonk, NY) and used a 10-nm bandpass. Data analysis was

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performed with a MicroVAX II computer (Digital Equipment, Maynard, MA) and an IBM 3090-600J vector supercomputer (International Business Machines). The IBM PS/2 computer ran IDAS data-collection software (Bran+Luebbe) while the MicroVAX and IBM 3090-600J used software written in Speakeasy IV Epsilon and Zeta (Speakeasy Computing Corporation, Chicago, IL).

The atmospheric conditions surrounding the tablets were controlled using a hydrator, which consisted of a desiccator in which the desiccant was replaced with distilled water. The tablets were exposed to moisture by placing them in uncapped scintillation vials and placing the vials in the hydrator.

A VanderKamp 600 six-spindle dissolution tester (VanKel Industries, Edison, NJ) was used to conduct the dissolution test. Apparatus II was used according to the USP dissolution guidelines for carbamazepine (11), with the exception that the dissolution medium consisted of 900 ml of distilled water containing 1% sodium lauryl sulfate and no more than 1% methanol. The solutions were maintained at 37°C. The paddles rotated at 75 rpm.

An ultraviolet (UV)–visible recording spectrophotometer (Shimadzu UV2100, Columbia, MD) was used in this study for direct measurement of dissolved carbamazepine.

Mathematical Analysis. Principal-component regression (PCR) and the bootstrap error-adjusted single-sample technique were employed to analyze the spectra of intact tablets (6). Principal-axis transformation (PAT) usually begins with a normalization of the spectra in T:

$$z_{ij} = [t_{ij} - \mu(t_j)]/\sigma_{SD}(t_j) \quad (1)$$

The normalized spectral matrix Z is then transposed and retained until the transformation matrix is formed. Normalization gives information at each wavelength equal weight in the posttransformation spectral hyperspace.

The transformation matrix $\mathbf{L}^{-1}$ is formed from the eigenvalues $\boldsymbol{\lambda}$ and eigenvectors $\mathbf{X}_\lambda$ of a correlation matrix R:

$$r_{jk} = \sum_{i=1}^{n} \frac{[t_{ij} - \mu(t_j)][t_{ik} - \mu(t_k)]}{(n-1)\sigma_{SD}(t_j)\sigma_{SD}(t_k)} \quad (2)$$

The square roots of the eigenvalues $\boldsymbol{\lambda}$ of R are used to diagonalize a square matrix. The matrix product of the square root of these eigenvalues and $\mathbf{X}_\lambda$ gives L, which becomes the transformation matrix on inversion. The transformation matrix effectively serves as a map connecting the original spectral hyperspace to the new hyperspace, which is generally of smaller dimension.

New spectral coordinates, expressed in principal-axis space for the sample spectra in T, are given by

$$\mathbf{T}_p = \mathbf{L}^{-1}\mathbf{Z} \quad (3)$$

The new spectra are employed profitably in both qualitative and quantitative analysis of samples, using regression and discriminant analysis. The PAT process eliminates the collinearity problem in the near-IR spectra of samples and significantly reduces (often to less than one-half dozen) the effective number of wavelengths (dimensions in hyperspace) that need to be considered in qualitative and quantitative analysis of the components of samples.

The bootstrap error-adjusted single-sample technique (BEST) is a parallel discriminant classification technique for analyzing multivariate spectral data distributions. The method estimates the population from which a sample is drawn by using a bootstrap procedure. Qualitative and quantitative decisions are made about test samples based on the distribution of bootstrap points in the space between the center of the bootstrap-distribution cluster and the specific test sample. Samples are identified and their components are quantified according to the distance of the sample (in multidimensional standard deviations) from the center of the bootstrap distribution.

Cross validation was used to verify that the hyperplane produced by the modeling process was actually the best hyperplane to use to describe the function relating dissolution rate to near-IR spectra of the tablets. The first step of cross validation took training-set samples and fit the best hyperplane to near-IR spectra of these samples using the reference values obtained by dissolution and UV–visible spectrophotometry. A standard error of estimate (SEE) was calculated from these training samples. The validation step was accomplished by analyzing an equal number of samples that were not included in the training set. The dissolution percentages of these validation samples at 1 hr were predicted with the hyperplane calibration equation developed on the training set, and a new standard error, called the standard error of prediction (SEP), was calculated from the validation residuals. The goal of the modeling process was to minimize both the SEE and the SEP. When the SEE and SEP were minimal and approximately the same, the calibration process was said to have produced a valid predictive model.

Procedure. The near-infrared spectrum and the extent of dissolution were determined daily for six tablets (three brand and three generic). Initially, baseline spectral data were obtained from dry tablets stored in a normal desiccator. The tablets were then stored in the hydrator described earlier. Each of the six tablets analyzed each day was removed from the hydrator, scanned, and returned immediately to the hydrator. The total elapsed time out of the hydrator was approximately 90 sec. The tablets were transferred from the hydrator to the dissolution apparatus, and the dissolution test was conducted as described earlier. Three-milliliter samples were taken from each vessel at intervals of 5, 10, 20, 30, 40, 50, and 60 min. The dissolution medium removed was replaced by fresh medium. The concentration of each solu-

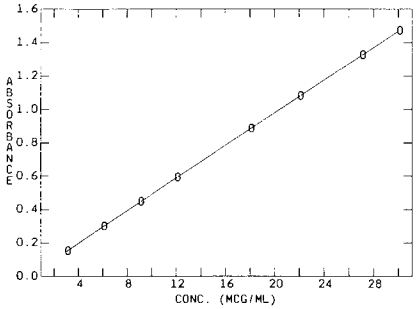

Fig. 1. UV spectrophotometric standard curve of carbamazepine at λ_{max}.

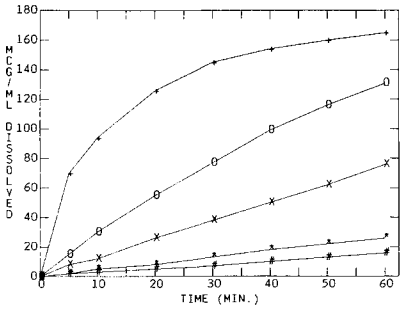

Fig. 2. Dissolution profile of brand tablets exposed to moisture for up to 5 days. (+) Day 1; (○) day 2; (×) day 3; (*) day 4; (≠) day 5.

tion was determined spectrophotometrically. Each solution sample was analyzed twice. The average of the two values was used for regression analysis. Solutions were diluted 10-fold when necessary (i.e., when solution absorbance was greater than 1.5 absorption units). The data were collected on the computer in a way that recorded each tablet's near-infrared spectrum and corresponding rate of dissolution.

RESULTS

UV spectrophotometry was used to determine carbamazepine in the dissolution medium. The standard curve for carbamazepine using a single wavelength (λ_{max}) is shown in Fig. 1 (r^2 = 0.999). Carbamazepine has an absorbance maximum at 287 nm. In Figs. 2 and 3, the dissolution profiles for the brand and generic tablets are shown. The rate of dissolution of brand tablets (when not exposed to moisture) meets USP requirements. Within the first 5 min of dissolution, over half of the total drug is dissolved. After 1 hr, 86% of the total drug is dissolved. The rate of dissolution decreased with the time spent in the hydrator. The rate of dissolution of the brand drug steadily decreased until Day 5. No significant change in the dissolution rate was observed beyond this point. By Day 5, the effect of moisture on the dissolution rate of the brand tablets was visibly evident, and the tablet did not disintegrate even after 1 hr in the dissolution apparatus.

The rate of dissolution of the generic tablets was also high initially. However, the effect of exposure to moisture on the dissolution rate of generic tablets was not as extreme as the effect of moisture on the brand tablets (see Fig. 4). The rate of decrease in dissolution also levels off at an earlier time, and increasing the duration of exposure to humidity

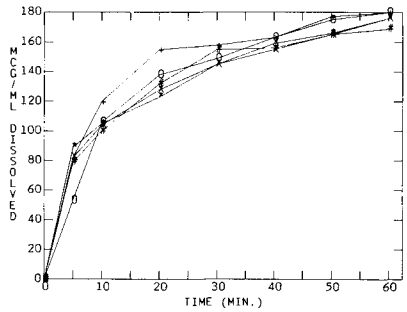

Fig. 3. Dissolution profile of generic tablets exposed to moisture for up to 5 days. (+) Day 1; (○) day 2; (×) day 3; (*) day 4; (≠) day 5.

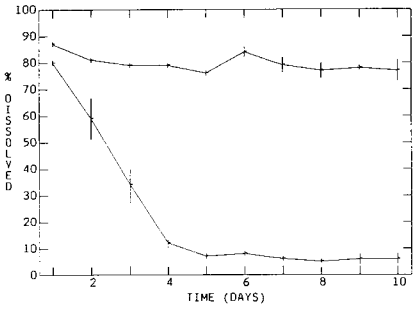

Fig. 4. Comparison of percentage dissolution of brand and generic carbamazepine tablets after a 1-hr dissolution test. The upper trace graphs the dissolution of the generic tablets, while the lower trace graphs the dissolution of the brand tablets. The error bars provide the range of three replicate dissolution tests.

beyond Day 4 does not further decrease the dissolution rate or extent of dissolution (see Figs. 3 and 4). Throughout the study, the generic tablets always broke apart within the 1-hr period in the dissolution apparatus.

Figure 5 is the near-IR reflectance spectrum of pure carbamazepine. Figures 6 and 7 show the near-IR spectra of brand and generic tablets that were exposed to moisture in the hydrator. There are two peaks near 1450 and 1930 nm that correlate to moisture. These water peaks increase with time spent in the hydrator. The rate of dissolution of individual tablets was correlated to the near-IR spectra of individual tablets using the BEST and PCR methods, and a predictive model was formulated. Figure 8 shows the correlation between percentage dissolution at 1 hr predicted with the model and actual percentage dissolution (r^2 = 0.985) for the brand tablets analyzed during the first 4 days of the experiment (SEE = 4.5%, SEP = 6.8%). Including days 5 to 12 adds only noise to the predictive model because the dissolution rate no longer changes. Demonstrating this fact further, no correlation was found over either a 4-day or a 12-day period between predicted percentage dissolution and actual percentage dissolution for the generic tablets, primarily because the dissolution rate does not really change over this period.

In Fig. 6 a new peak appears just above 2200 nm in the tablets after 10 days in the hydrator. This new peak may indicate the presence of a degradation product in the tablets. This product peak appears clearly in the near-infrared difference spectra (see Figs. 9 and 10). This new peak was unexpected because an earlier study reported a high degree of stability for carbamazepine in suspension (12), and the

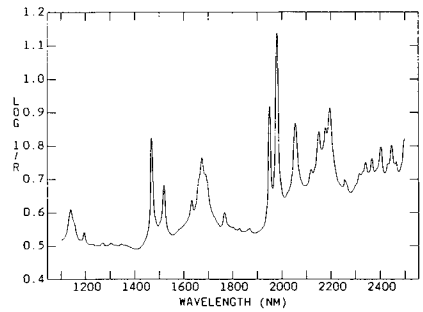

Fig. 5. Near-IR reflectance spectrum of pure carbamazepine.

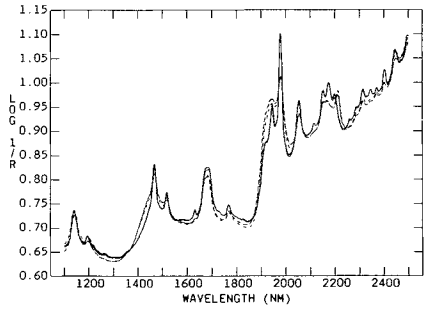

Fig. 6. Near-infrared spectra of single brand carbamazepine tablets. Dry-tablet spectra are shown with solid lines and tablets exposed to moisture for 10 days are shown with dashed lines.

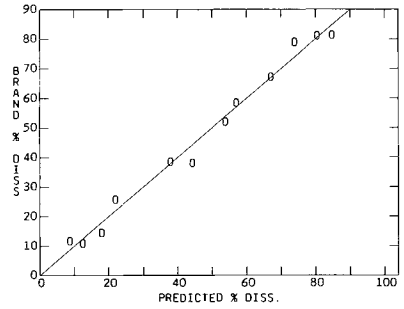

Fig. 8. Scatterplot showing the actual dissolution of single brand carbamazepine tablets after 1 hr and the dissolution determined previously by the near-IR predictive model. Data are from day 1 to day 4. The solid line represents a theoretical perfect correlation between the actual and the predicted dissolution values.

new peak may well arise from an excipient. The peak is found in a wavelength region that corresponds to the formation of an aldehyde and, occasionally, to the formation of an epoxide (13). A green mold was found growing on the brand tablets stored for 24 days in the hydrator. The mold was harvested mechanically from three tablets and its near-IR spectrum was obtained. The near-infrared spectrum of this mold shows a major peak below 2200 nm, seemingly eliminating the mold itself as a possible source of the new peak.

The generic tablets stored in the same hydrator with the brand tablets were not affected by the mold. The generic tablets appear to degrade more slowly than the brand tablets, and the peak ratios in the difference spectra of the generic tablets from day 9 and day 10 are most similar to those of the brand tablets in day 5 minus day 1.

By days 9 and 10 of the study the brand tablets slowed their uptake of water. The degradation product appeared to be forming more rapidly, however.

DISCUSSION

The rate of dissolution of intact, brand carbamazepine tablets exposed to humidity over a 4-day period was found to be predictable using near-infrared spectrophotometry with an error of only 6.8% of the total carbamazepine content per tablet.

The near-infrared method involves a parallelized system of pattern recognition, and models changes in the rate of dissolution of carbamazepine with the amount of water absorbed by the tablets. It was not until Day 5 of the study that appreciable additional changes appeared in the spectra that may be due to the degradation of the drug or excipients.

In contrast to the brand drug, the rate of dissolution of generic carbamazepine tablets did not correlate strongly with the amount of exposure to moisture. The tablets merely appeared to soften and become fragile with time in the hydrator.

The extent and rate of dissolution of brand and generic tablets at baseline are similar (see Fig. 3). However, exposure of the brand tablets to moisture was found to decrease the dissolution rate drastically, in agreement with the dissolution study cited earlier (7). The rate and extent of dissolution of generic tablets also decreased, but to a far lesser extent. It is apparent that improper storage of medications (such as in a bathroom medicine cabinet) may adversely affect these products.

This study has shown that it is possible to predict the rate of dissolution of an intact carbamazepine tablet by near-infrared spectrophotometry. Unlike other regression methods, the BEST parallel computational method permits information from all 701 spectral wavelengths to be incorporated into the predictive model if desired, leading to increased accuracy. Future studies will determine whether other drugs in timed-release tablet forms have similarly predictable dissolution rates. In such cases, the spectrophotometric testing method would permit intact tablets to be sorted after manufacture into dosages with different release rates and turn a potential liability (variable dissolution rate) into a therapeutic advantage (selected controlled release).

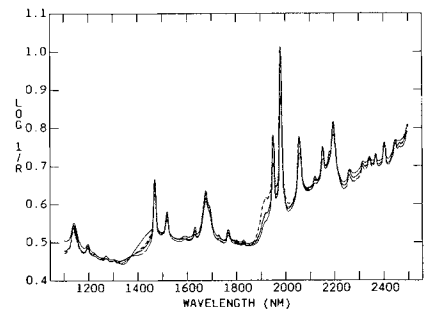

Fig. 7. Near-infrared spectra of single generic carbamazepine tablets. Dry-tablet spectra are shown with solid lines and tablets exposed to moisture for 10 days are shown with dashed lines.

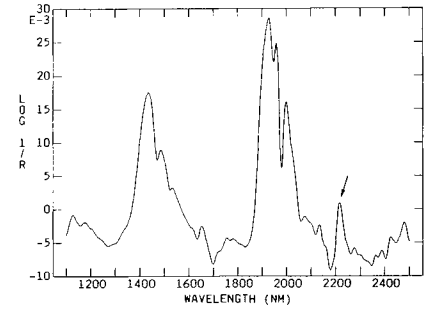

Fig. 9. Difference spectrum between brand tablets, day 5 minus day 1. The arrow indicates the new peak. The major peaks are due to water.

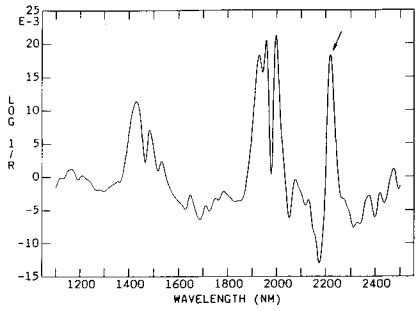

Fig. 10. Difference spectrum between brand tablets, day 10 minus day 6. The arrow indicates the growth in the new peak relative to continued moisture uptake.

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