A Drug Dissolution Monitor Employing Multiple Fiber Optic Probes and a UV/Visible Diode Array Spectrophotometer

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A traditional dissolution pumping system was recently replaced with a fiber optic interface between the spectrometer and the samples. However, the system was limited to a single sample vessel. In this study, a dissolution testing system with six vessels connected to a diode array spectrometer via six optical fibers was investigated. A bifurcated fiber optic bundle was used to transfer the light from the source to the dissolution vessels and was networked so that spectra of each sample can be measured periodically. A full spectrum calibration method based on Principal Component Regression (PCR) was used to determine the concentrations of active ingredients and to account for interferences due to excipients in tablet formulations. Results on this new fiber optic interface system are compared with those obtained previously with the traditional pumping system. Standard errors of prediction are between 1.5 and 3.2% using cross-validation and between 1.1 and 1.7% for the direct validation of two active ingredients in two different drug formulations.

KEY WORDS: drug dissolution; fiber optic probes; UV/Visible diode array spectrometer; principal component regression (PCR); Fourier transform.

INTRODUCTION

The determination of the release rate of active ingredients from drug formulations is an important procedure in pharmaceutical laboratories. This information is valuable to formulators in selecting an optimum solid dosage formulation and to satisfy FDA requirements (1). Currently, chromatographic (2,3) and UV spectroscopic (4,5) methods are employed to perform drug dissolution tests.

The chromatographic methods include high-performance liquid chromatography (HPLC) and flow injection analysis (6). HPLC is one of the most widely performed analysis and the major in-vitro method for dissolution testing of complex, multicomponent formulations because of its high sensitivity and separation capability. However, compared to the UV spectroscopic methods, chromatographic procedures are more expensive and time-consuming.

Traditionally, UV spectroscopic methods have been used for analysis of single components with well-separated absorptions. In dissolution tests, unwanted absorptions are caused both by formulation excipients and the gelatin shell. Recent investigations on UV spectroscopic methods combined with multivariate analysis provide a solution to the problem of excipient inferences and overlapping UV absorptions (7–12). Spectroscopic determinations of active ingredients in dosage formulations is the most economical and rapid of the current methods (5,7).

Previously, a fiber optic interface was used for the spectroscopic analysis in a single dissolution apparatus (6,13). This paper presents a new automated drug dissolution system employing six fiber optic probes and a UV/visible diode array spectrometer. Analysis was performed in the UV region of 220 to 380 nm using a full spectrum calibration method based on Principal Component Regression (PCR). Turbidity and excipient interferences were reduced by Fourier preprocessing the spectral data.

MATERIALS AND METHODS

Spectrophotometer

UV-visible spectra were measured on a Beckman DU-7500 diode array UV-visible spectrophotometer (Beckman, Fullerton, CA). The spectra can be measured in a selected range from 190 nm to 800 nm at 1.25 nm intervals. The diode array consists of 512 elements and the spectrophotometer reads each of the diodes every 0.1 seconds. In the present analysis, each spectrum was signal averaged for 10 seconds. The total time for scanning, data acquisition and changing the positions of source fibers was 90 seconds for the six vessels.

The spectrophotometer was interfaced to an IBM PS/2 Model 50z computer through a RS-232 communication interface. All the spectral measurements were transferred to the computer for storage and processing.

Dissolution Apparatus

A Hanson Research (Chatsworth, CA) Mode 72 test station was used for dissolution experiments. Dissolution tests were performed on individual tablets according to the United States Pharmacopeia (USP XXII). The dissolution parameters were set up using apparatus 2 (paddle method), 500 ml of distilled water at 37.0 ± 0.5°C was stirred at 50 rpm. The dissolution profiles were determined by continuously monitoring the absorbance of the media through fiber-optic sensors without filtration.

Fiber-optic Probes

The fiber-optic probes (14) were made with Superguide Fiber (Fiberguide Industries, Stirling, NJ). The diameters of the silica core, cladding, and nylon jacket were 600, 630, and 680 μm, respectively. Each probe was constructed with two 1 meter fibers held in a coaxial, face-to-face position across a plexiglass plate with 1 cm diameter hole in the center (13). There was a 2 mm gap between the two fibers.

A diagram of the optical interface to the six dissolution vessels is shown in Figure 1. The optical system was networked so that spectra of each sample can be measured periodically. The networking was performed by mounting each of the six fibers into the six light cones. The light cone, having an entrance diameter of 0.6 cm and a length of 2.5 cm, was made of a plastic pipet tip of which the inner surface was lined with aluminum foil (14). The input ends of the source fibers were inserted into the tips of the light cones. Light

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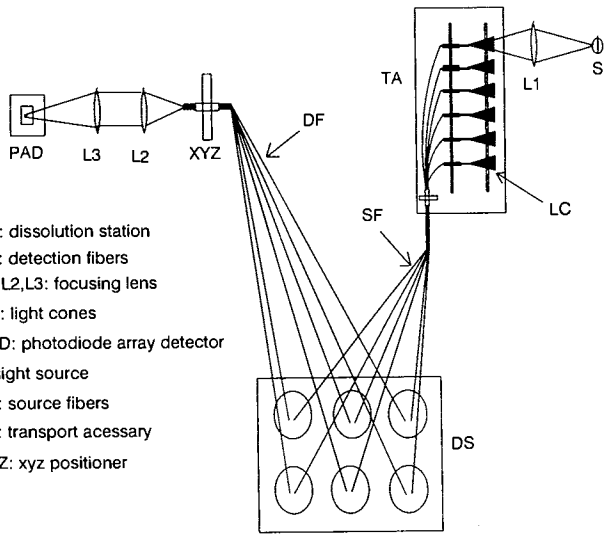

Figure 1. Schematic diagram of optical interface for multiple fiber-optic probes.

from the source was focused by a lens (9 cm focal length) into the light cone which launched the light into the source fiber. The light cones were held on an aluminum plate that was fixed to a Beckman Auto-6-Transport accessory. The position of this transport was controlled by the spectrometer which was controlled by the computer through the RS-232 interface. The light beam from the source fiber passed through the solution and into the detector fiber. The detector fibers from all six probes were bundled together. Light exiting the detector fibers were collimated and focused onto the entrance slits of the diode array detector using a 5 cm focal length lens.

Calibration and Validation

Calibration and validation were performed using spectra of standard solutions measured with the same optical interface. Each dissolution vessel and fiber optic interface was calibrated separately. The calibrations were performed by Principal Component Regression (PCR) (15). The selection of the number of factors in the PCR model is based on the lowest SEP obtained by cross-validation. For the cross-validation, one sample spectrum from a data set is left out and the remaining samples are used to perform the calibration. This calibration is used to calculate the concentration of the single sample left out. The sample is included back in the calibration set, another sample is left out, and the calculation is repeated. This is performed for all samples in the calibration set in order to find out the suitable number of factors in the processing. This calibration model is then tested by the separate validation set.

Reagents

Two commercial cold/allergy products were selected for evaluation of the dissolution analysis and used in the preparation of the standard samples. Commercial product Sudafed Plus (SPL) is formulated as a typical immediate-release tablet containing 60 mg of pseudoephedrine hydrochloride and 4 mg of chlorpheniramine maleate as the active ingredient. Commercial product Contac (CTC) is a sustained-release caplet containing 75 mg of phenylpropanolamine hydrochloride and 12 mg of chlorpheniramine maleate. The following USP grade chemical reagents were used in the preparation of standard samples: phenylpropanolamine hydrochloride (Sigma Chemical Company), pseudoephedrine hydrochloride, and chlorpheniramine maleate (Spectrum Chemical Company).

RESULTS AND DISCUSSION

Spectra of Samples

The active ingredients, pseudoephedrine hydrochloride, chlorpheniramine maleate and phenylpropanolamine hydrochloride all exhibit strong absorbance in the UV region. Figure 2 shows spectra of SPL and CTC measured from turbid drug solutions. The spectra were measured with a fiber-optic probe at concentrations found in the commercial products. The wavelength range of all spectra measured in this experiment was from 220 nm to 350 nm. In the shorter wavelength region (220 nm to 230 nm) the significant baseline shift was caused by light scattering due to turbidity from the excipients. The spectra measured from one of the vessels in the dissolution test for SPL tablets are shown in Figure 3. In the longer wavelength region the spectra also exhibit a baseline shifted by turbidity.

Optical Interface of Fiber-Optical Probes

Previously, a single fiber-optic probe interface between the spectrometer and a single sample vessel dissolution testing system indicated that the optical interface decreased the light through-put through the six fibers by 2 to 5% of the original intensity. The reasons for the decrease are loss of light at the probe caused by divergence from the source fibers and loss of light during propagation inside the fibers due to scattering and absorption.

In this multiple fiber-optic probe system, a testing system with six vessels was connected to the spectrometer through six fiber-optic probes. Each individual fiber-optic

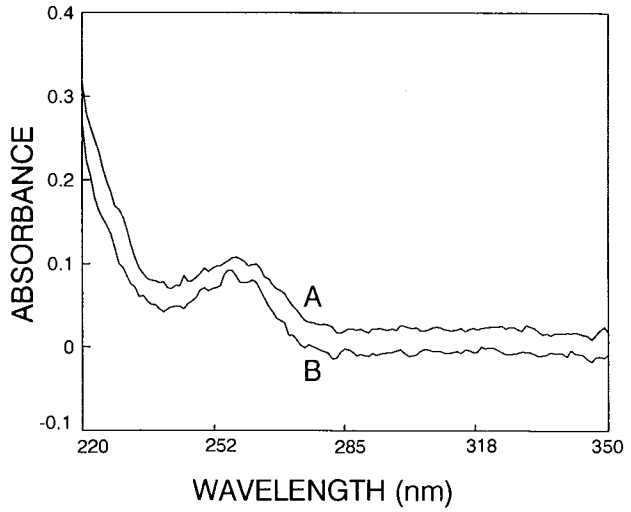

Figure 2. Spectra of product CTC (A) and Product SPL (B) turbid drug solutions measured with the fiber-optic probe.

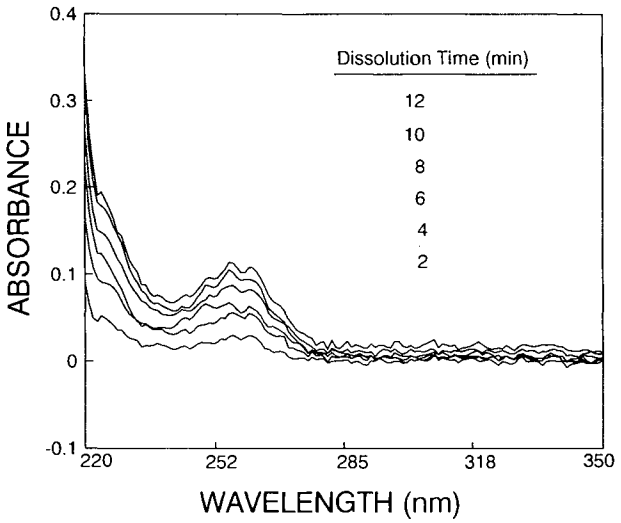

Figure 3. Difference spectra of dissolution test for Product SPL tablet.

probe was an independent system. A reference spectrum was measured in air and a blank spectrum was measured from each fiber optic probe in distilled water. The blank sample was subtracted from each of the spectra measured with the fiber optic probes. The difference spectra were used for calibration and prediction.

Calibration Model

In order to define the calibration model, standard samples were prepared from mixtures of pure components and stock solutions of commercial products. The stock solutions of the commercial products were used to provide concentrations of excipients to account for the turbidity in actual samples. Different calibration models were used for SPL and CTC. Furthermore, each dissolution vessel was calibrated separately.

In developing a calibration model, we used two different sets of spectra. The training set of 21 standards containing concentrations of both components at approximately equal increments from 0 to 130% of the label claims was used to construct the model. A validation set consisting of 10 standard samples with known concentrations of each species equally spaced over the range of 0 to 130% was used to evaluate the model. The training and validation sets for SPL contained pseudoephedrine-HCl from 0 to 171 mg/L and chlorpheniramine maleate from 0 to 11.4 mg/L, whereas the standard sets for CTC contained phenylpropanolamine-HCl from 0 to 220 mg/L and chlorpheniramine maleate from 0 to 34.2 mg/L.

Evaluation of Calibration Model

The preparation of standard samples from pure components and stock drug solutions makes it possible to consider factors such as turbidity, component interactions, and spectral shifts in the multicomponent systems.

The spectra range from 220 nm to 340 nm was used for SPL whereas the spectra range from 230 nm to 340 nm was selected for CTC due to the severe baseline shifts in shorter wavelength (220 nm to 230 nm). In order to reduce the background and noise, spectra were processed by taking the Fourier Transform prior to the calibration and analysis. Contributions from broad background absorptions appear in the first few terms of the Fourier Transform, whereas high frequency noise appears in higher terms of the transform. In the Fourier Transform, the first four terms were eliminated to reduce background variations and the following 16 terms were used for calibration; this range was selected by systematically processing all possible combinations. Comparisons between the standard errors of prediction for spectral and Fourier domains are shown in Table I for one dissolution vessel. The errors are reduced by ~20% after pre-processing with the Fourier Transform.

Results of the cross-validation using the leave-one-out method and validation of each of the six vessels after pre-processing with the Fourier Transform are given in Tables II and III for SPL and CTC, respectively. The SEP and average percent error for the calibration sets of both formulations

Table I. Percent Standard Error of Prediction for Cross-Validation

CALIBRATION SET FOR PRODUCT SPL				
DOMAIN	#FACTORS	PEH[a]	CPM[b]	TOTAL
SPECTRAL	6	2.70	1.74	2.22
FOURIER	6	2.01	1.56	1.78
CALIBRATION SET FOR PRODUCT CTC				
DOMAIN	#FACTORS	PPH[c]	CPM	TOTAL
SPECTRAL	6	3.75	2.63	3.19
FOURIER	6	3.20	1.94	2.57

[a] PEH—Pseudoephedrine Hydrochloride
[b] CPM—Chlorpheniramine Maleate
[c] PPH—Phenylpropanolamine Hydrochloride

Table II. Percent Standard Error of Prediction for Analysis of Product SPL

CROSS-VALIDATION FOR CALIBRATION SET				
VESSEL	#FACTORS	PEH[a]	CPM[b]	TOTAL
1	6	1.94	1.46	1.70
2	6	2.27	1.85	2.06
3	6	2.63	1.96	2.29
4	6	1.41	1.13	1.27
5	6	2.16	1.91	2.04
6	6	1.64	1.06	1.35
AVERAGE		2.01	1.56	1.79
VALIDATION SET				
VESSEL	#FACTORS	PEH	CPM	TOTAL
1	6	0.76	1.16	0.96
2	6	2.11	2.53	2.32
3	6	2.42	2.35	2.38
4	6	1.19	0.95	1.07
5	6	1.83	1.99	1.91
6	6	1.61	1.21	1.41
AVERAGE		1.65	1.69	1.67

[a] PEH - Pseudoephedrine Hydrochloride
[b] CPM- Chlorpheniramine Maleate

Table III. Percent Standard Error of Prediction for Analysis of Product CTC

CROSS-VALIDATION FOR CALIBRATION SET				
VESSEL	#FACTORS	PPH[a]	CPM[b]	TOTAL
1	6	2.90	1.27	2.09
2	6	3.46	3.03	3.25
3	6	2.36	0.76	1.56
4	6	3.50	2.51	3.00
5	6	3.55	2.09	2.82
6	6	3.40	1.96	2.68
AVERAGE		3.20	1.94	2.57
VALIDATION SET				
VESSEL	#FACTORS	PPH	CPM	TOTAL
1	6	1.54	1.09	1.32
2	6	2.05	1.44	1.75
3	6	0.80	0.56	0.68
4	6	1.00	0.70	0.85
5	6	2.71	1.90	2.31
6	6	1.57	1.10	1.33
AVERAGE		1.61	1.13	1.37

[a] PPH- Phenylpropanolamine Hydrochloride
[b] CPM- Chlorpheniramine Maleate

reach a minimum with six factors. The major source of errors are due to small S/N ratios and weak absorbances at the lower concentration.

Drug Dissolution Tests

The dissolution of SPL (an immediate-release formulation) was measured every 2 minutes for the first 16 minutes and every 4 minutes thereafter. The dissolution profiles (percent dissolved versus time) for both active ingredients are shown in Figure 4. The relative standard deviation of percent dissolved for the six vessels ranged from 0.48% to 3.86% for pseudoephedrine hydrochloride and from 1.08% to 3.36% for chlorpheniramine maleate. Compared to the dissolution

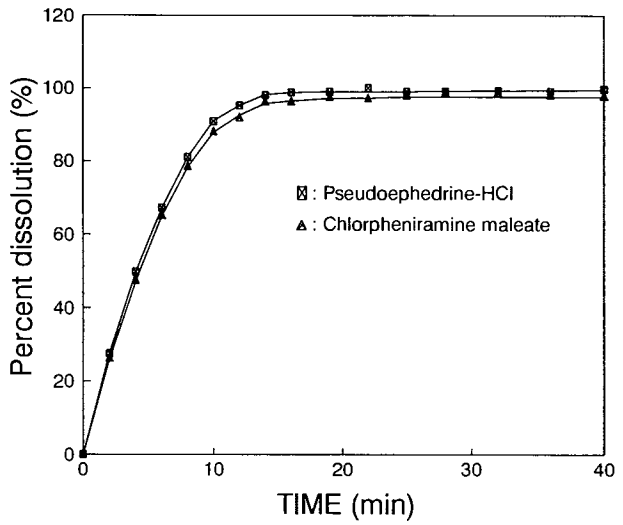

Figure 4. Dissolution profiles of Product SPL immediate-release tablets.

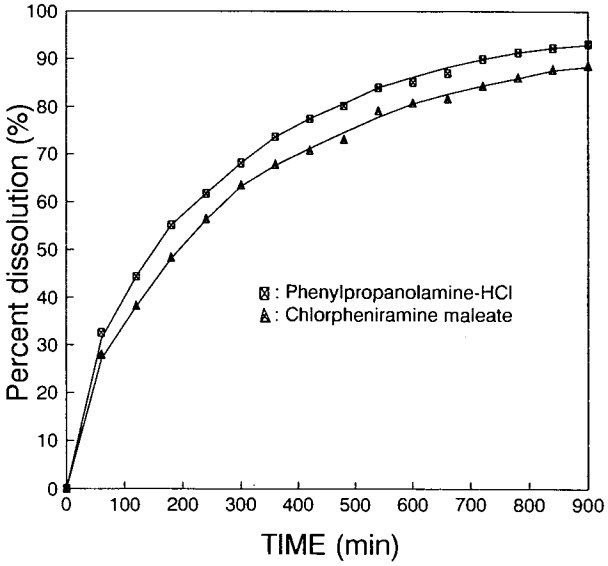

Figure 5. Dissolution profiles of Product CTC sustained-release caplets.

curves obtained with a flow cell system, the curves are very similar; however the dissolution curves obtained from flow cell system included a time-delay due to the pumping time. The fiber optic probes eliminate this delay.

The concentrations of CTC (a sustained-released caplet) were measured every hour for a total testing time of 15 hours. The dissolution curves are shown in Figure 5. The relative standard deviation of percent dissolved for the six vessels ranged from 0.17% to 1.85% for chlorpheniramine maleate and from 1.47% to 3.71% for phenylpropanolamine hydrochloride. The dissolution curves are very similar to those obtained from the flow cell system.

CONCLUSION

A new automated drug dissolution system employing multiple fiber-optic probes, a UV/Vis diode array spectrometer, and a dissolution apparatus with six vessels has been tested on the dissolution of two commercial cold/allergy products. Results from this new fiber optics interface system are similar to those obtained previously with the traditional pumping system. The procedure developed in this investigation can be adopted as a routine method for drug dissolution tests. This optical interface system has several significant advantages including: 1) spectra of the dissolution solutions are measured and processed automatically in real time, 2) turbid solutions can be analyzed without filtering the samples, and 3) the spectrometer measures absorbance at all wavelengths simultaneously allowing full spectral processing.

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