Monitoring Ibuprofen Release from Multiparticulates: In Situ Fiber-Optic Technique Versus the HPLC Method:A Technical Note

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INTRODUCTION

Traditionally, dissolution testing has been conducted by removing samples from vessels, either manually or automatically followed by UV or high-performance liquid chromatography (HPLC)-UV analysis.[1] For a UV analytical method, a single-dissolution run could sometimes require an entire day to complete. The time for analysis is further increased when formulations require HPLC analysis.[2] These make dissolution analysis a time-consuming and labor-intensive procedure.

The traditional methods of dissolution testing are now being changed by the introduction of in situ fiber-optic monitoring systems, which have significant advantages over traditional methods. Fiber optics brings the UV spectrometer to the sample solutions instead of the other way around. A real-time drug release is determined in situ or in the vessels without sample removal, greatly simplifying the testing procedure.[1]

Other than being an advantage to the in situ approach, the frequency of sampling (5 seconds to 2.5 minutes) is a great feature of fiber-optic monitoring systems. Data acquisition is fast and sampling can be done in a matter of seconds, leading to greater "data density" over time. Generation of test results is virtually instantaneous. Acquisition of data at more frequent time points might also enhance the ability to obtain a more discriminating test profile. The reliability of the dissolution profile in spite of an error at any single data acquisition point is also increased.

Josefson et al[3] published early research in this field in 1988. They explored the feasibility of using fiber optics for in situ dissolution monitoring and to overcome sample turbidity interference without filtration. In 1993, Brown and Lin[4] used a single optical fiber and a photo diode array (PDA) UV/Vis spectrometer to track dissolution in a single vessel. This work was extended thereafter to use 6 optical fibers and a PDA spectrometer for multiple dissolution vessels.[5] Since the late 1990s there has been an increased interest in the field of in situ dissolution monitoring.[6-10]

The purpose of this study was to compare the fiber-optic probe system (FOPS) with the HPLC method. Amount of drug released from immediate- and prolonged-release microparticulate solid dosage formulations containing ibuprofen was monitored.

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MATERIALS AND METHODS

Materials

Immediate-release (IR) and controlled-release (CR) ibuprofen multiparticulate spheroids were prepared in-house for this study. All dissolution tests were conducted in simulated intestinal fluid (phosphate buffer pH 7.4).

Methods

Linearity test

A spectrophotometric linearity test was performed to test each individual probe for both linearity and reproducibility. Aliquots (2 mL) of a 6-mg/mL standard solution were added to 200 mL of simulated intestinal fluid (phosphate buffer pH 7.4) in succession to increase the ibuprofen concentration of the fluid by 60 μg/mL each time (range: 0 to 300 μg/mL). Spectra were acquired by the Delphian "RAINBOW" monitoring system (*p*ION Inc, Woburn, MA) after each addition.

Dissolution analysis

Dissolution was performed using USP Apparatus II and 900 mL of simulated intestinal fluid (pH 7.4) at 37 ± 0.3ºC. The sampling interval for the FOPS was preset at 2.5 minutes per scan; for HPLC analysis, the sampling intervals were longer for both IR and CR formulations.

Preweighed samples (324.0 mg) of the multiparticulate ibuprofen spheroids were introduced into each vessel and the dissolution tests were run for 2 hours for immediate release (IR) formulations and 12 hours for polymer-based controlled-release (CR) formulations. CR formulations containing 3 different levels of polymer (level 1, level 2, and level 3) were tested.

Second-Derivative Plot

The second-derivative pretreatment is used in spectral analysis to enhance the resolution of peaks and to eliminate baseline shifting. This treatment results in a negative peak (a trough) at the same location where the original spectrum showed an absorption peak. The second derivative algorithm was employed to correct for the sloping baseline that could be caused by turbidity from possible leaching of the microparticulates.

Results and Discussion

Linearity Test

The Delphian system calculated the coefficient of determination (R^2) and percent relative standard deviation (%RSD) for each probe as consecutive aliquots of the standard solution were added. The R^2 and %RSD for each of the 6 probes was calculated over 6 different concentration levels. The R^2 for the 6 probes ranged from 0.9997 to 0.9999 demonstrating the linearity of the method. Also, the %RSD for each probe was very low (ranging from 0.014% to 0.034%), indicating that the FOPS method was stable and reproducible over the range of concentrations tested.

Second-Derivative Pretreatment

Figure 1 shows a normal absorbance plot and Figure 2 shows a second-derivative plot for the linearity experiment. The second derivative corrects the slight baseline shift that is observed in the absorbance plot. In many cases, the disintegration followed by dissolution of the dosage form causes turbidity in the vessel, which may interfere with the in situ analysis. The particles may pass through or stick to the probe causing changes in absorbance intensity. Such situations can be remedied by use of a second-derivative spectral pretreatment, which eliminates the problem of shifting baselines.

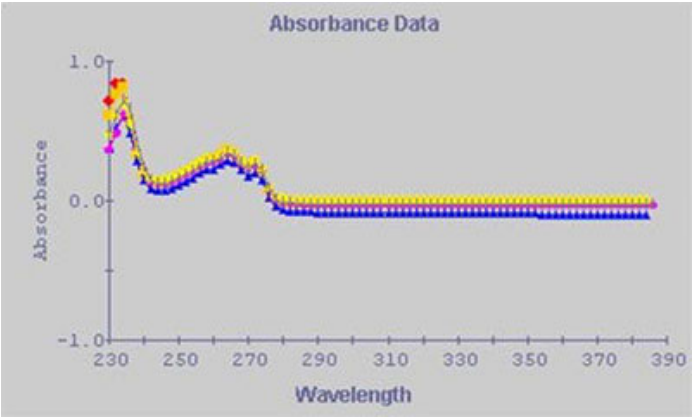

Figure 1. UV absorbance plot of ibuprofen for the linearity experiment.

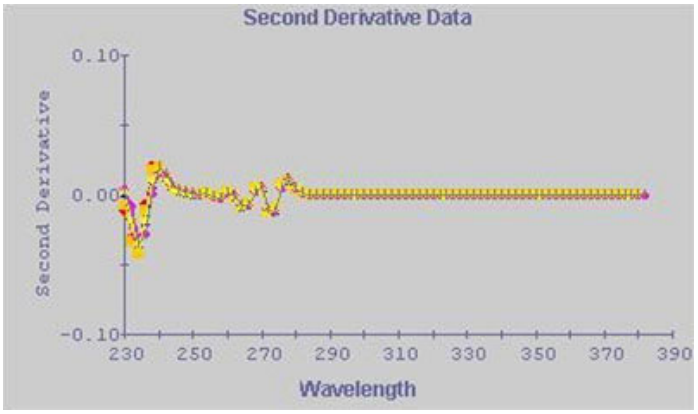

Figure 2. Second-derivative absorbance plot of ibuprofen for the linearity experiment.

Dissolution Analysis

Immediate-Release Formulation

Table 1 and Figure 3 show data and dissolution profiles of the IR formulation using the HPLC and FOPS methods. The amount of ibuprofen released as tested by HPLC was lower than that calculated by the fiber-optic probe system at each data point. The profile obtained by HPLC analysis showed high %RSD between vessels at earlier time points, which decreased with time. The %RSD between the vessels was consistent for the FOPS system. The %RSD data for both the techniques showed that the FOPS technique was more dependable. A single dissolution run using the FOPS method was completed in ~2 hours compared with the HPLC method, which lasted ~18 hours (including data analysis).

Controlled-Release Formulations

The dissolution test and in situ monitoring with FOPS for controlled-release microparticulates was conducted over 12 hours, whereas the HPLC analysis lasted for up to 48 hours. The dissolution profiles for the controlled-release microparticulates are shown in Figure 4 and Figure 5. The HPLC results showed that level 2 formulation released

Table 1. Comparative Dissolution data for FOPS and HPLC Analyses (IR Formulation)

	FOPS		HPLC	
Time, min	% Released	%RSD	% Released	%RSD
10	73.65	5.53	75.73	18.38
20	87.79	4.90	83.27	6.03
40	97.17	3.94	85.86	1.20
60	100.3	3.71	86.27	1.07
120	102.0	2.92	86.41	0.62

FOPS indicates fiber-optic probe system; HPLC, high-performance liquid chromatography, IR, immediate release; %RSD, percent relative standard deviation.

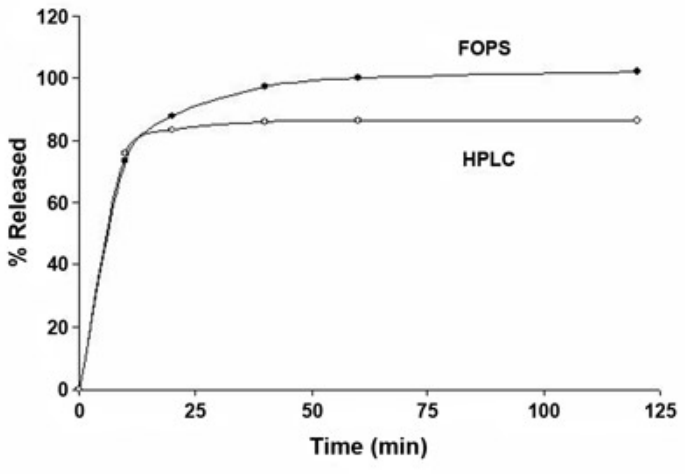

Figure 3. Comparative dissolution profiles using FOPS and HPLC analyses (IR Formulation).

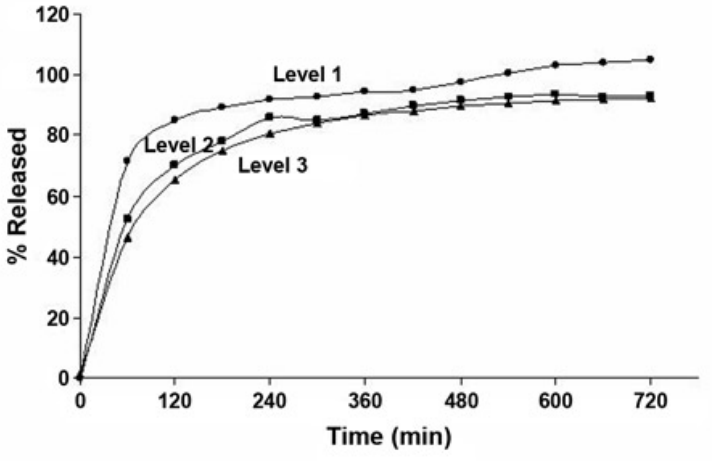

Figure 5. Dissolution profiles of CR formulations using 3 levels of coating (FOPS technique).

ibuprofen faster as compared with the level 1 formulation (Figure 4). There is a possibility that the coating of ibuprofen for the level 2 formulation may have been inefficient, leading to faster release. But results from FOPS monitoring showed the fastest release for level 1 followed by level 2 and level 3 formulations (Figure 5). This seems to indicate that the HPLC analysis for the level 1 and/or level 2 formulations may have involved a certain amount of error.

The comparative release profiles and %RSD values for a typical controlled-release formulation (level 3) are shown in Table 2 and Figure 6, respectively; and the results indicate that the %RSD obtained using the FOPS method were comparable to the HPLC technique, although more consistent. Moreover, the "hands-off" in situ monitoring and less operator involvement made FOPS remarkably superior.

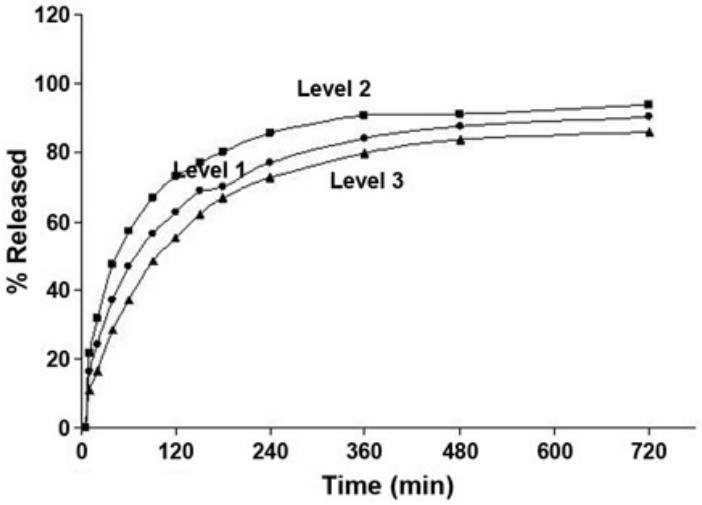

Figure 4. Dissolution profiles of CR formulations using 3 levels of coating (HPLC technique).

Although HPLC has commonly been employed for dissolution analysis, it is labor intensive and time consuming and involves sample removal and manipulation, which can be a potential source of error. Small sample volumes lead to increase in the error associated with the technique, especially in the case of manual sampling procedures. Active drug may be adsorbed onto the sample filter causing the analysis to show a lower amount of dissolved drug. Volume corrections also add to the error. Thus, the accuracy and precision of the HPLC dissolution monitoring method are dependent on many factors beyond the accuracy and precision of the HPLC instrument. In this study, HPLC analysis consistently showed lower amounts of dissolved drug as compared with the FOPS system, which points toward possible errors during HPLC analysis and/or sampling. Traditionally, if a problem was suspected during an HPLC dissolution analysis, it would

Table 2. Comparative Dissolution Data using FOPS and HPLC Analysis (CR Formulation—Level 3)

	FOPS		HPLC	
Time, min	% Released	%RSD	% Released	%RSD
60	44.77	11.98	37.23	7.95
120	63.18	8.26	55.24	6.32
180	72.22	6.14	66.92	6.75
240	77.13	5.00	72.66	4.25
300	80.13	4.34	—	—
360	82.22	3.81	79.77	4.95
420	83.85	3.59	—	—
480	84.88	3.46	83.63	2.88
540	85.80	3.37	—	—
600	86.55	3.22	—	—
660	87.10	3.19	—	—
720	87.33	3.37	86.14	3.80

FOPS indicates fiber-optic probe system; HPLC, high-performance liquid chromatography, CR, controlled release; %RSD, percent relative standard deviation; —, not determined.

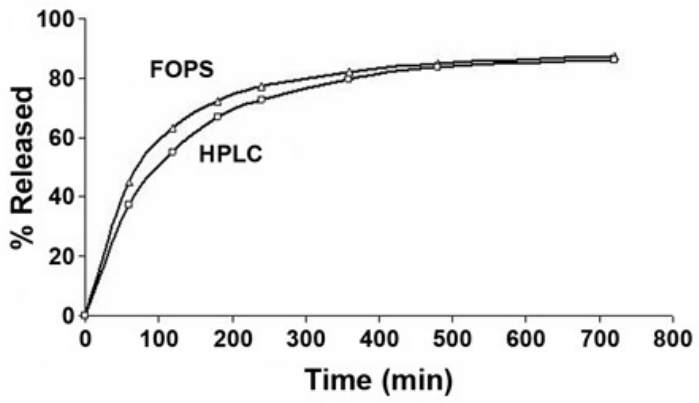

Figure 6. Comparative dissolution profiles using FOPS and HPLC analysis (CR formulation—level 3).

mean repeating the dissolution run, which would involve expenditure of effort, time, and money. The fiber-optic probe system was found to be free of many of the problems associated with the HPLC analysis. The frequent acquisition of data (high data density) reduced the possibility of a failed dissolution experiment that might otherwise have resulted, because a single erroneous data point could be eliminated and still allow for discriminating dissolution profiles compared with traditional methods like HPLC.

Summary and Conclusions

The results from the linearity test showed that the automated FOPS method was linear and reproducible in predicting ibuprofen concentrations, as was shown by a high R^2 and low %RSD over a range of concentrations. Second-derivative treatment of the UV spectrum makes it possible to remove the effects of the sloping baseline often encountered in spectra of highly turbid samples. The dissolution profiles obtained by FOPS were more accurate with lower and consistent %RSD as compared with the HPLC method, particularly in the case of immediate-release multiparticulates. The FOPS method was also faster and less labor intensive.

Because of its various advantages, fiber-optic dissolution is fast becoming an important tool for research and development. Its ease of use, high "data density," high data-collection speed, and hands-free monitoring make the FOPS method extremely useful as compared with the traditional methods of dissolution testing.

Acknowledgments

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