

In Situ Fiber-Optic Dissolution Assisted by a Mathematical Separation Model of Dynamic Three-Wavelength K-Ratio Spectrophotometry

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ABSTRACT

The aim of this study was to monitor the drug release of ibuprofen sustained-release capsules in real time in situ. A mathematical separation model of dynamic three-wavelength *K*-ratio spectrophotometry was established to eliminate the interference of gelatin capsule shells when drug release was monitored by a fiber-optic drug dissolution in situ test system. A control experiment with high performance liquid chromatography was performed simultaneously. Within 7 h, real-time drug release profiles were obtained. The average drug release rates were 19.79%, 37.34%, 63.13%, and 88.41% by the fiber-optic drug dissolution in situ test system at the respective time points of 1 h, 2 h, 4 h, and 7 h. There were no significant differences between the in situ and control methods. Drug release of ibuprofen sustained-release capsules can be monitored by the fiber-optic drug dissolution in situ test system assisted by the mathematical separation model of dynamic three-wavelength *K*-ratio spectrophotometry. Information about the entire dissolution process can be produced by the real-time release profile.

INTRODUCTION

The determination of the release rate of active ingredients from drug formulations is an important procedure in pharmaceutical research. Without automation, it is a labor-intensive process. The fiber-optic sensor based on ultraviolet–visible (UV–vis) absorption analysis for dissolution testing is a technique that has been under investigation for many years (1–3). Drug dissolution process analysis with fiber-optics uses a fiber-optic probe inserted directly into each vessel, and the absorbance of the solution is measured in situ instead of extracting samples and determining the concentration of active ingredient with UV spectrophotometry or high performance liquid chromatography (HPLC). This approach is rapid and efficient, with less handling of the samples and consequently fewer sources of error.

A pharmaceutical tablet, however, always contains a number of other compounds (i.e., excipients), and sometimes these compounds can influence the determination of the active ingredient. When samples from the dissolution test are analyzed without any separation, excipients that have absorbance at the same wavelength as the drug may have a large influence on the dissolution data. Scattering can be generated from undissolved particles and excipients, which can contribute significant interference. This type of scattering may be either wavelength-independent

or wavelength-dependent. Both of the two interferences can be eliminated by some algorithm (4). The use of fiber optics, an automatic controlling system, and software, together with powerful chemometric data evaluation, can open up new possibilities for a deeper understanding of in vitro dissolution testing (5).

In 1988 a partial-least-squares (PLS) statistical method was used to correct for the disturbance caused by solution turbidity in dissolution testing (1). In 2000 a fiber-optic sensor system was utilized by Chen et al. (6) for on-line dissolution monitoring of multicomponent solid preparations containing vitamins B₁, B₂, and B₆. In addition, in 2008 it was reported that thirty-five excipient samples and five placebos were selected to evaluate the Delphian fiber-optic dissolution system in the wavelength range of 200–400 nm (3).

Fenbid (Ibuprofen Sustained-Release Capsules), a product of GlaxoSmithKline (Sino-American Tianjin SmithKline and French Lab., Ltd), is an ibuprofen pain reliever featuring a 12-h sustained-release formula. The absorbance of the gelatin capsule shells at 264 nm can interfere with the measurements of ibuprofen, which has a maximum absorbance at about 264 nm. The vessels were sampled at 1, 2, 4, and 7 h, then determined by HPLC according to the *Chinese Pharmacopeia 2005 (Ch.P)* (7). In this paper, a mathematical separation model of dynamic three-wavelength *F*-ratio spectrophotometry, which can eliminate the interference of gelatin capsule shells, was investigated. The drug release of ibuprofen

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sustained-release capsules can be monitored in real time in situ with a fiber-optic drug dissolution test system. The in situ dissolution data were compared with data determined by a control off-line HPLC assay. There were no significant differences between the in situ and control methods.

MATERIALS AND METHODS

Instruments

A fiber-optic drug dissolution test system (FODT) was developed by Chen et al. (6) of Xinjiang Medical University and Xinjiang FOCS Biotech Development Co., Ltd. The system was strictly validated for both the UV-vis spectrophotometry and dissolution test methods of the *Ch.P.* It consists of a deuterium (D_2) lamp, six fiber-optic dipping probes, and a detector with a charge-coupled device (CCD) that can collect data at each wavelength point. Light from the deuterium lamp passes through incident optical fibers, which transfer the light from the source to the probes immersed in the vessels during testing. Light again reflects back from the mirror at the bottom of the probe tip to the CCD through the detection fiber. The probe path can be altered to 0.5, 1.0, 2.0, and 5.0 mm to adjust the sensitivity. The UV-vis spectra (220–600 nm) from six fiber channels with low noise can simultaneously be collected with the system. Data acquisition and processing was accomplished by the software, which was compiled by Xinjiang FOCS Biotech Development Co., Ltd.

A spectrophotometer (Cintra 40, GBC, Australia) was utilized for the spectral scans, and an HPLC (LC-20AT, Shimadzu, Japan) for the off-line control determination.

Reagents and Drugs

The purified water was made in the laboratory and degassed before use. Sodium hydroxide, potassium dihydrogen phosphate, and hydrochloric acid were all analytical reagents obtained from Fuchen Chemical Reagents (Tianjin, China). Ibuprofen reference substance (Batch No.100179-200303) was from the National Institute for the Control of Pharmaceutical and Biological Products of China.

Ibuprofen sustained-release capsules (Fenbid, Sino-American Tianjin SmithKline and French Lab., Ltd, 300 mg, Batch No.08040807) were from the commercial market.

UV Spectral Characteristics of Ibuprofen

Solutions of ibuprofen reference substance, gelatin capsule shells, and ibuprofen sustained-release capsules were prepared with phosphate buffer (pH 6.0) to be scanned by UV spectrophotometry.

The determination data of ibuprofen reference substance, gelatin capsule shells, and ibuprofen sustained-release capsules were obtained from UV spectra, which is the foundation for establishing the mathematical separation model of dynamic three-wavelength *K*-ratio spectrophotometry.

Linearity

A channel was chosen to study linearity with a series of different concentrations of ibuprofen substance at 19.23%, 38.46%, 57.69%, 76.92%, 96.16%, and 115.39% according to the established method.

Precision and Recovery

Solutions at high, middle, and low concentrations were determined five times in one day continuously and once daily for five days to calculate the precision.

Samples at high, middle, and low concentrations with backgrounds that were withdrawn from the release solution were determined to calculate the recovery.

Drug Release Test Methods

Drug release testing was performed in 900 mL of phosphate buffer (pH 6.0) at 37 ± 0.5 °C for 7 h with Ch.P Apparatus I, the same as USP Apparatus 1. The stirring speed was 30 rpm. The sampling interval for the FODT was preset at 5 min. The real-time drug release data and profiles were acquired within 7 h.

For HPLC analysis, the sampling time points were set at 1, 2, 4, and 7 h. Samples were extracted from the dissolution vessels and filtered through 0.45- μ m filters, and then injected into the HPLC.

RESULTS

UV Spectral Characteristics

Figure 1 shows UV spectra of ibuprofen reference substance, gelatin capsule shells, and ibuprofen sustained-release capsules with a concentration of 100% of the labeled amount for the formulated product, equivalent to dissolving one capsule in 900 mL of phosphate buffer (pH 6.0). Probes with a path of 5 mm were utilized according to the absorbance at the maximum absorption wavelength. Ibuprofen has an absorbance maximum at 264 nm. UV spectra revealed that the gelatin capsule shell has absorbance maxima at 264 and 425 nm, and strong-end absorbance below 250 nm, while the other excipients do not interfere with the measurements after baseline correction.

According to the HPLC analysis method in *Ch.P.*, samples were determined at 263 ± 1 nm after chromatographic separation; however, the absorbance of the gelatin capsule shell interferes with the ibuprofen measurement when the determination was performed with FODT. In order to monitor the release in situ without any physical or chemical separation, a mathematic method should be utilized.

Our FODT system utilizes a CCD detector that can simultaneously determine absorbance at multiple wavelengths. The absorbance of gelatin capsule shells at both 264 nm and 425 nm was determined, and a *K*-value was defined whereby $A_{264} = K \cdot A_{425}$. The *K*-value for the gelatin capsule shell was determined with the same dissolution condition as for ibuprofen sustained-release capsules before a release test.

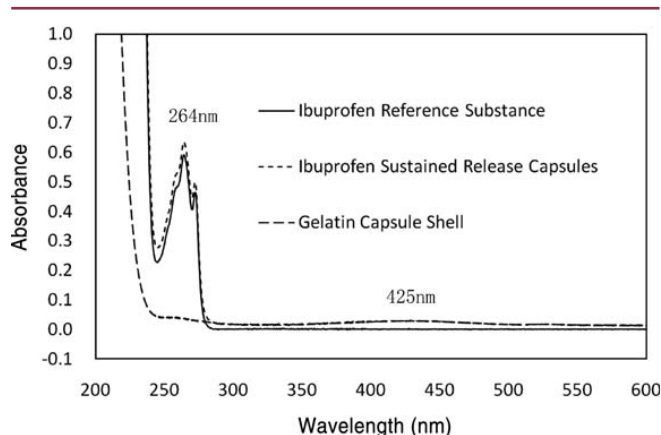


Figure 1. UV absorbance spectra of ibuprofen reference substance, gelatin capsule shell, and ibuprofen sustained-release capsules.

In the following equations, I refers to ibuprofen from ibuprofen sustained-release capsules and II refers to the gelatin capsule shell. The absorbance of ibuprofen I (A) was calculated using the equations

$$\begin{aligned} A &= A_1 - KA_2 = (A_{264} - A_{550}) - K(A_{425} - A_{550}) \\ &= A_{264}^I + A_{264}^{II} - A_{550} - K(A_{425}^{II} - A_{550}) \quad (\because A_{264}^{II} = KA_{425}^{II}) \\ &= A_{264}^I + (K - 1)A_{550} \end{aligned}$$

where A_1 and A_2 are the absorbances determined at 264 nm and 425 nm, and A_{550} is the background absorbance signal. A_{550} was subtracted to correct small baseline offsets due to the turbid system. The correction wavelength could be set at 550 nm or any other at which there is no absorbance. Therefore, the absorbance calculated in the vessels depends only on the absorbance of ibuprofen active ingredient at 264 nm and the baseline offset. A mathematical separation model of dynamic K -ratio three-wavelength spectrophotometry was constructed to eliminate the interference of gelatin

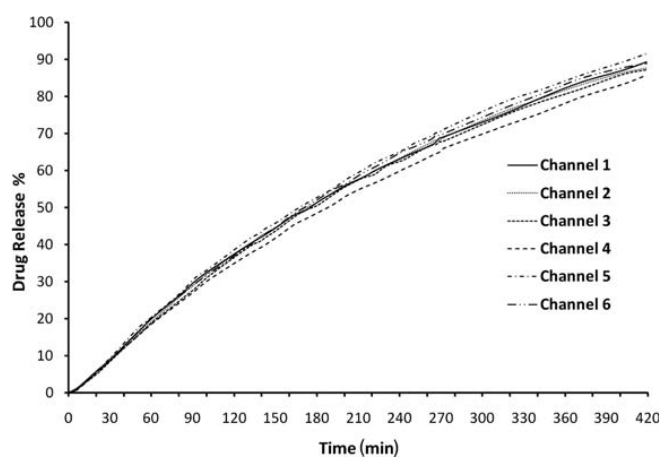


Figure 2. Release profiles of ibuprofen sustained-release capsules over 7 h.

Table 1. Comparison of FODT and HPLC Methods for Ibuprofen Sustained-Release Tablets Release ($n = 6$)

Time (h)	FODT		HPLC	
	Release (%)	RSD (%)	Release (%)	RSD (%)
1	19.79	3.66	18.68	2.46
2	37.34	3.28	36.12	3.34
4	63.13	2.48	61.75	2.36
7	88.41	2.24	87.42	2.51

capsule shells in monitoring drug release of ibuprofen sustained-release capsules in real time in situ by FODT.

Linearity

After calculation, a regression equation was performed, $C(\%) = 0.2 + 162.8 A$. The correlation coefficient (r) was 0.99996 for concentrations from 19.23% to 115.39%.

Precision and Recovery

The RSDs of intra- and interday determinations were less than 1.14%. The recovery values ranged from 98.97% to 102.07%, and the average RSD was 0.92%. The results demonstrate that the determination was unaffected by the gelatin capsule shell.

Drug Release Results

Figure 2 shows the real-time release profiles of ibuprofen sustained-release capsules over 7 h. Average release data of six channels of ibuprofen sustained-release tablets obtained by FODT and the control method (HPLC) are shown in Table 1. There was no significant difference between the FODT and the HPLC methods ($P > 0.05$).

DISCUSSION AND CONCLUSION

A fiber-optic drug dissolution in situ test system was proved useful for pharmaceutical solid formulations. Drug dissolution–release profiles were obtained in situ by FODT and displayed in real time on the computer screen. With the mathematical separation model of dynamic three-wavelength K -ratio spectrophotometry, dissolution testing of ibuprofen sustained-release capsules produced results that were in good agreement with HPLC.

After the release testing of gelatin capsule shells, the constant K was obtained. Therefore, K calculations were set in the program, and a mathematical separation model of dynamic three-wavelength K -ratio spectrophotometry, which can dynamically monitor the drug release of ibuprofen in situ by FODT, was constructed.

This mathematical separation model can also be utilized to eliminate interference from other ingredients or be expanded to apply to a multicomponent product. Drug dissolution of multicomponents with several partially overlapping but different spectra can also be monitored using other algorithms for multivariate calibration, thus

the need for separation with HPLC will be replaced in some dissolution tests.

It was reported that a second-derivative pretreatment was utilized to eliminate the problem of shifting baselines when ibuprofen release from multiparticulates was monitored by the in situ fiber-optic technique (8). However, because of limitations in instrument capability and accuracy, the wavelength and absorbance values have some fluctuations that can enlarge the errors in derivative spectrometry, especially at higher orders. The *K*-ratio method that we report here for eliminating the excipient disturbance does not perform a derivative transformation and is not affected by derivative-related errors.

Although UV determination is a common method for dissolution analysis, it involves sample removal and manipulation, which can be potential sources of error. For example, the active component might be adsorbed onto the sample filter causing an error in the amount of dissolved drug. The HPLC method, which is commonly employed for dissolution analysis, also has shortcomings (e.g., is labor-intensive and time-consuming). This FODT system has high potential application for sustained-release preparations because of its ability to perform with great stability over many hours or even several days. However, an FODT-based method cannot replace HPLC completely for drugs that have no UV-vis absorbance.

ACKNOWLEDGMENTS

Authors would like to acknowledge Xinjiang FOCS Biotech Co., Ltd., China, for its contribution to this work.

This work was supported by National Key Project of Scientific and Technical Supporting Programs Funded by Ministry of Science & Technology of China during the 11th

Five-year Plan (NO.2006BAK03A16) and National Natural Science Foundation of China (No.30960365).

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