Journal of Pharmaceutical & Biomedical Analysis
Vol. 8, Nos 8–12, pp. 987–989, 1990
Printed in Great Britain

0731–7085/90 $3.00 + 0.00
Pergamon Press plc

Short Communication

Dissolution testing using continuous multicomponent UV analysis to correct for excipient interference*

N.H. ANDERSON, D. JOHNSTON‡ and P.R. VOJVODIC†

Sterling Research Group, Alnwick, Northumberland NE66 2JH, UK

Keywords: *Dissolution testing; multicomponent analysis; excipient interference.*

Introduction

Measurement of dissolution rate is an essential part of the development process for tablets and capsules. Excipient interference, particularly titanium dioxide (present in opaque capsule shells and some tablet film coats) is often significant, precluding the use of simple UV analysis. At low wavelengths interference from gelatin may also be present. HPLC analysis may be used to achieve the desired analytical accuracy but it is laborious and time consuming. Multicomponent UV analysis is an alternative to HPLC and is easily automated [1–4]. The application of multicomponent UV analysis using the Hewlett–Packard HP8451A automated dissolution system to the dissolution of capsules containing a developmental drug is described here.

Multicomponent analysis enables the composition of a mixture to be determined by comparing the sample spectrum with the spectra of the individual components of the mixture. This is done by optimizing the spectral fit between the sample spectrum and a weighted combination of the spectra of the individual components. Requirements for multicomponent analysis are that the individual components obey Beer's Law and that the spectra of the pure individual components are available. Additionally, there should be no interaction between the components, i.e. they should obey Beer's Law in the mixture. The UV spectrum of the dissolved capsules being considered here comprises two components, one due to the drug and a second due to titanium dioxide present in the capsule shell. (Absorbance by gelatin is not significant in the wavelength range used for multicomponent analysis.) The UV spectrum attributed to titanium dioxide is due to light scattering rather than absorption of light, but still satisfies the requirements for multicomponent analysis. Spectra of the drug and capsule shell are shown in Fig. 1. A typical sample spectrum is shown in Fig. 2.

Methods

The optimum wavelength range for analysis was found by minimizing the relative fit error and the independence of standards factor, both of which are calculated automatically by the spectrophotometer. Relative fit error is a measure of how well the spectra of the individual components can be combined to match the spectrum of the mixture. The independence of standards factor indicates the degree of similarity of the spectra of the individual components. Both values should be low if multicomponent analysis is to give accurate results. Table 1 shows how these factors vary with wavelength range. The optimum range was found to be 240–400 nm. This range represents the spectral region where the drug and capsule shell spectra exhibit the maximum difference.

Six vessels are used for dissolution. A

*Presented at the "Second International Symposium on Pharmaceutical and Biomedical Analysis", April 1990, York, UK.

†Author to whom correspondence should be addressed.
‡Current address: Sterling Research Group, Rensselaer, NY 12144, USA.

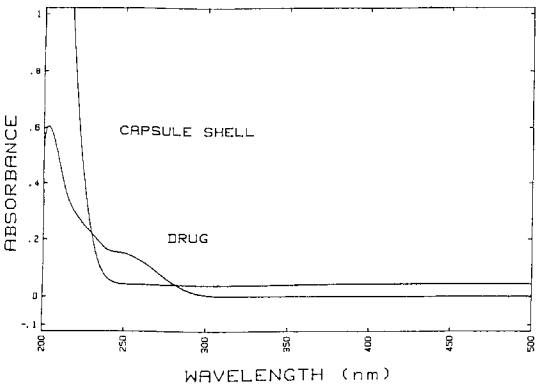

Figure 1
Individual UV spectra of the capsule shell and the drug. Capsule shell spectrum prepared by dissolving a capsule shell in 900 ml of dissolution medium (0.1 M HCl). Drug spectrum corresponds to 1 unit dose (5 mg) in 900 ml of dissolution medium.

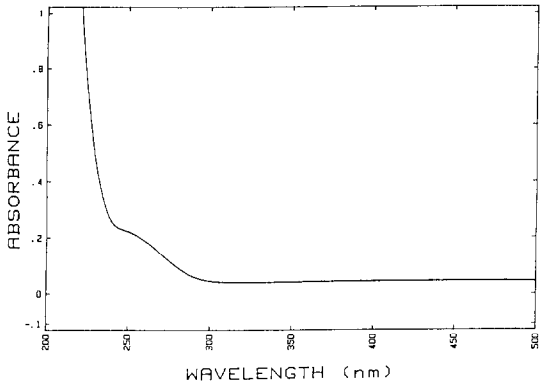

Figure 2
UV spectrum of capsule shell and drug. Spectrum prepared by dissolving a capsule containing drug in 900 ml of dissolution medium (0.1 M HCl).

Table 1
Wavelength range and spectral fit parameters

Wavelength range (nm)	Relative fit error	Independence of standards
190–400	2898	2.51
210–400	3337	2.48
230–400	1539	2.47
240–400	26	1.88
250–400	6	1.53
240–300	68	8.04

seventh containing dissolution medium is used as a reference for UV. A peristaltic pump circulates solvent through the UV cell-switching device and back to the dissolution vessels. The cell-switching device contains seven flow through cells; one for each of the vessels. Standard solutions consisting of drug dissolved in dissolution medium and an empty capsule shell dissolved in the same solvent are used to calibrate the instrument. The spectra of these solutions are recorded prior to the start of the dissolution run. In practice these standard spectra are stored electronically on disc, thus avoiding the need to prepare fresh solutions for each dissolution test. During the course of the dissolution test the UV spectra of the seven vessels are recorded at 5-min intervals. Multicomponent analysis and calculation of the percentage of drug dissolved is performed automatically by the integral computer.

Results

Validation of the method

To demonstrate the suitability of the method compliance with Beer's Law was first of all checked for the drug substance and for the capsule shell. Linearity of absorbance against drug concentration, at up to twice the maximum concentration encountered in a dissolution test, was demonstrated over the wavelength range 240–280 nm. (Absorbance at wavelengths above 280 nm is negligible.) Solutions of capsule shell, at concentrations corresponding to up to 10 times the concentration encountered in a dissolution test, showed linearity of absorbance over the whole wavelength range used for multicomponent analysis (240–400 nm).

To further demonstrate the suitability of the method for the formulation, solutions containing known amounts of drug, capsule excipients and a capsule shell were prepared. The UV spectra of the solutions were recorded, multicomponent analysis performed and the amount of drug found was calculated. These recovery data, shown in Table 2, show the method to be both accurate (99.28%) and precise (0.32).

Table 2
Recovery of drug from spiked solutions

Drug added		Drug found		Recovery
$\mu g\ ml^{-1}$	% of theory	$\mu g\ ml^{-1}$	% of theory	(%)
0	0	−0.027	−0.49	N/A
0	0	−0.038	−0.68	N/A
3.288	59.18	3.213	57.83	97.7
3.288	59.18	3.250	58.50	98.8
4.384	78.91	4.325	77.84	98.7
4.384	78.91	4.364	78.55	99.5
5.480	98.63	5.456	98.20	99.6
5.480	98.63	5.448	98.06	99.4
6.576	118.36	6.528	117.49	99.3
6.576	118.36	6.540	117.71	99.5

The baseline correction approach, whereby drug + excipient absorbance measured at one wavelength (e.g. 250 nm) can be corrected by subtracting excipient absorbance measured at a second wavelength (e.g. 350 nm), is a second frequently used solution to excipient interference. This approach gives satisfactory results in many cases but is not available for automated use on the HP8451A. Automated single wavelength UV analysis was found to be unsuitable, as would be expected, producing errors of 20–25%.

Conclusions

The suitability of UV multicomponent analysis has been demonstrated for the dissolution of a product where interference from suspended titanium dioxide is a problem. This procedure is potentially widely applicable as many products contain titanium dioxide. These products include opaque capsules and some film-coated tablets. Automated multicomponent analysis is a viable alternative to HPLC analysis in those cases where excipient interference presents a problem.

References

[1] A.F. Fell, B.J. Clark and H.P. Scott, *J. Pharm. Biomed. Anal.* **1**, 557–572 (1983).
[2] C.J. Warwick and D.A. Baygon, *Chromatographia* **15**, 443–446 (1982).
[3] H. Ueda, R. Pereira-Rosario, C.M. Riley and J.H. Perrin, *J. Pharm. Biomed. Anal.* **7**, 309–320 (1989).
[4] H.K. Chan and G.P. Carr, *J. Pharm. Biomed. Anal.* **8**, 271–277 (1990).

[*Received for review 6 April 1990; revised manuscript received 16 July 1990*]