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The multicomponent automated dissolution system: an alternative in the development and pharmaceutical analysis of generic polydrugs

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Abstract

The necessity of assuring the quality of polydrugs, especially those with low aqueous solubility and in vivo absorption, has led to the development and evaluation of new techniques that can reduce the time and cost of analysis. This study examines the efficiency and accuracy of an automated dissolution system, fitted with an integrated multicomponent detector, for analysis of generic polydrugs using multiple linear regression (MLR). Trimethoprim and sulphamethoxazole were chosen as model drugs for this study and comparison was made with a conventional analysis based on HPLC. Both analytical systems under study gave reproducible and accurate results. Analysis of variance showed that there was no significant statistical difference between the methods of analysis, nor any statistical difference between the measured amounts of drug in the three different formulations. We have demonstrated that low cost instrumentation coupled with MLR data processing provides entirely satisfactory drug analysis to standard *at least* as good as that achieved using HPLC and provides an opportunity to reduce the time and analysis cost of other generic formulations.

Keywords: Automated dissolution system; Multicomponent UV/vis analysis; Polydrugs

1. Introduction

In recent decades, the development of new formulations has become a key function in pharmaceutical companies, principally because of the need to improve drug efficacy and minimise unwanted side-effects. An important feature of drug production is the necessity to ensure appropriate quality control and this requires accurate, often sophisticated but where possible fast, cost-effective analysis. The complexities of drug analysis are clearly increased when the number of drugs or excipients in the formulation increase. Thus the importance of ease of analysis is especially impor-

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tant for dosage forms containing more than one drug.

Where drugs have poor absorption characteristics in vivo, or more especially have poor dissolution characteristics from their chosen dosage form, regulations require drug formulations to be subject to dissolution analysis. Conventionally, high-pressure liquid chromatography (HPLC) has been chosen for monitoring drug release from such formulations because of the generally excellent resolution and sensitivity of the technique. However, analysis of multiple drug components in a mixture has also been demonstrated using first and second derivative spectrophotometry [1,2]. More recently, this type of approach has been incorporated in the development of UV–visible multicomponent automated dissolution systems (ADS). This instrumentation relies for its analysis on the principles of absorption additivity. In the study presented here, the analyte concentration in multicomponent mixtures is determined mathematically by straightforward multicomponent linear regression. The main condition to be met is that the number of monitoring wavelengths must be similar to the number of components present in the solution [3,4]. An alternative approach is to employ the more complicated but also more powerful principal component regression (PCR), in which case spectra from selected wavelength range are resolved using an appropriate algorithm [5].

The level of sophistication of these devices is now such that ADS have been assembled with multiple in situ fibre optic probes interfaced to diode array spectrophotometers with PC control and analysis [6–8]. Given the cost constraints incumbent on analytical facilities it is reasonable to question whether such a high level of sophistication is always necessary. We aim to demonstrate that excellent results can be achieved with simple, modest and robust instrumentation. In the system described here, the dissolution medium is circulated through an in-line filter and delivered to a tailored spectrophotometer having the capacity to monitor seven separate cells. A multichannel pump circulates the dissolution medium around seven dissolution flasks and through the seven flow cells in the sample chamber unit, each having direct UV monitoring of the two drugs simultaneously. These simple systems have enormous potential to reduce the cost and time of analysis, and significantly improve the overall reliability and reproducibility of testing procedures without reducing accuracy.

2. Material and methods

2.1. Materials

Sulphamethoxazole, trimethoprim and azetazolamide were USP standards and supplied by Rockville, USA. Prednisone tablets were also supplied by Rockville. The three generic polydrug formulations contained (nominally) the same concentrations of drug and were provided by three different companies. HPLC solvents for analysis were supplied by Milinchroph and 0.22 μm Millipore HA and HF filters were used for filtration of the sample and mobile phase.

2.2. HPLC analysis

A modular Perkin Elmer Model 200 Chromatograph comprised a pump, autoinjector, 30 cm C_{18} reverse phase analytical column, variable wavelength absorbance detector and computer-based Turbochrom analytical software. The components of the mobile phase were filtered, mixed

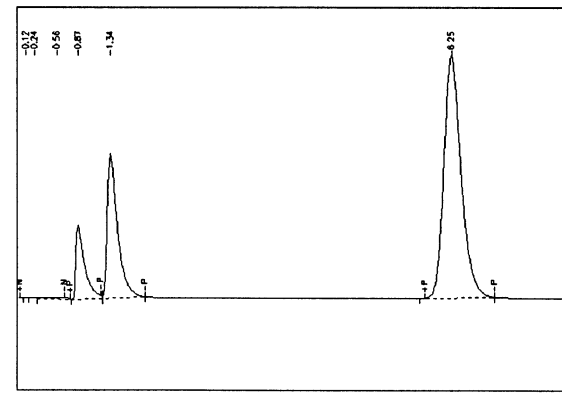

Fig. 1. Typical HPLC trace for a solution containing azetazolamide (15.0 μg/ml), trimethoprim (8.0 μg/ml) and sulfamethoxazole (40.0 μg/ml). Retention times were 0.45, 0.57 and 6.45 min respectively.

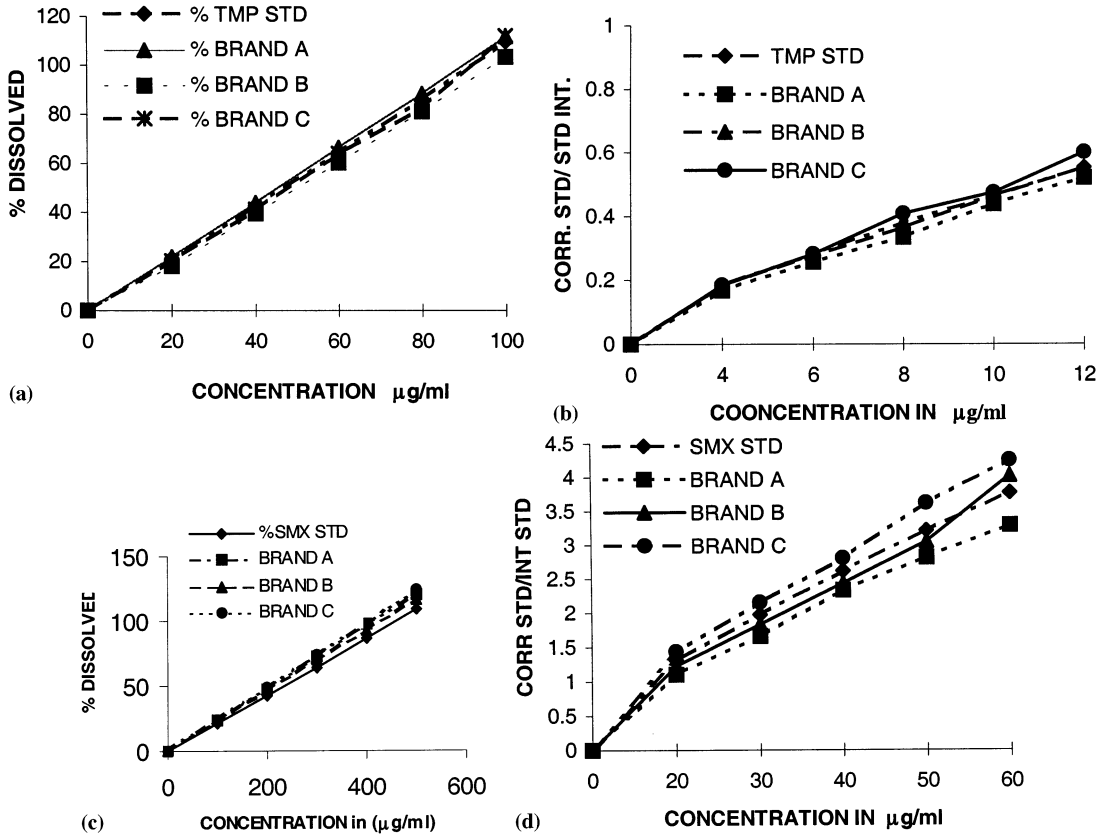

Fig. 2. Calibration plots for trimethoprim and sulfamethoxazole in different commercial brands. Each point represents the mean average of three measurements: (a) trimethoprim by multicomponent analysis (b) trimethoprim by HPLC analysis (c) sulfamethoxazole by multicomponent analysis (d) sulfamethoxazole by HPLC analysis.

and deaereated under vacuum prior to use. The column was eluted isocratically with 84.5:14.5:1 water : acetonitrile : glacial acetic acid (pH 2.5 ± 0.05) at 2 ml/min with detection at 250 nm. The detection wavelength represents a compromise between the extinction coefficients of the two analytes in the HPLC mobile phase, and their relative concentrations in the formulation. Calibration curves for HPLC analysis were prepared from standard solutions of the drugs in the mobile phase covering a range of 0–60 µg/ml for sulphamethoxazole and 0–12 µg/ml for trimethoprim by analysis in triplicate of 100 µl standards containing 15.0 µg/ml of the internal standard azetazolamide. Routine checks on the response factors were made by daily analysis of a standard solution containing 40.0 µg/ml sulphamethoxazole, 8.0 µg/ml of trimethoprim and 15.0 µg/ml azetazolamide.

Analysis of the generic polydrugs involved dissolving tablets containing 400 mg sulphamethoxazole and 80 mg of trimethoprim in 900 ml of 0.10 M HCl using the ADS. The conditions were specified by the USP XXII Pharmacopoeia for this product (USP apparatus 2, paddle, 50 rpm for 60 min, 37°C). After 1 h, 1.0 ml was removed into 9.0 ml of a 1.5 µg/ml solution of internal standard made up in the mobile phase described earlier. The diluted samples were filtered and analysed by HPLC.

2.3. Multicomponent automatic dissolution system

The instrument was fitted with a model AT7 Sotax Dissolutor, 8-channel peristaltic pump, seven vessels, PC directed control through the Perkin Elmer software and a Lambda 20 UV/vis spectrophotometer fitted with a linear 8-cell transporter. The flow-cell pathlength was 1.0 mm. Dissolution conditions were identical to those described above. The analytical instrumentation was checked for wavelength accuracy and repeatability. The dissolution apparatus was set-up, calibrated and operated in compliance with the USP compendia using the recommended 50-mg prednisone tablets.

Calibration curves for the individual drug standards were obtained by measuring the absorption at 265 and 271 nm. Standards were prepared in 0.10 M HCl in the concentration range 0–100 μg/ml for trimethoprim and 0–500 μg/ml for sulphamethoxazole. Extinction coefficients were calculated for the two drugs at both wavelengths and employed in the multicomponent analysis software. Subsequently, the appropriate dissolution conditions for the polydrug samples were established. The analytical method was then validated for linearity, accuracy and precision [9].

The linearity of the calibration curves were confirmed over a concentration range equivalent to 10–125% dissolution of the drug. For accuracy, samples were prepared by spiking with drugs and excipients in the specified volume of dissolution fluid. Accuracy was determined by testing six samples of each formulation according to the dissolution method. Specificity was confirmed by comparing the results of the HPLC and multicomponent analysis.

Table 1
A comparative summary of drug assays obtained by HPLC and by UV/vis multicomponent analysis using different commercial brands[a]

HPLC analysis		Multicomponent analysis	
Drug	Assay ± VC	Drug	Assay ± VC
SMX A	100.6 ± 0.3	SMX A	100.3 ± 0.4
SMX B	98.9 ± 1.4	SMX B	98.7 ± 0.2
SMX C	101.4 ± 2.1	SMX C	101.5 ± 0.6
TMP A	103.9 ± 0.1	TMP A	98.9 ± 1.0
TMP B	103.0 ± 1.7	TMP B	97.6 ± 1.7
TMP C	103.8 ± 0.2	TMP C	97.5 ± 0.9

[a] Each value represents the mean average of three measurements; VC, variation coefficient.

Table 2
Analysis of whole tablets from the three generic brands[a]

HPLC analysis		Multicomponent analysis	
Drug	Assay ± VC	Drug	Assay ± VC
SMX A	100.2 ± 0.1	SMX A	103.7 ± 0.2
	102.5 ± 0.1		104.3 ± 0.1
SMX B	99.6 ± 1.1	SMX B	98.9 ± 1.4
	95.8 ± 0.3		95.1 ± 2.3
SMX C	104.1 ± 3.6	SMX C	105.2 ± 1.0
	101.2 ± 1.3		103.0 ± 0.2
TMP A	104.1 ± 3.7	TMP A	104.1 ± 3.73
	103.5 ± 0.4		104.1 ± 1.26
TMP B	104.1 ± 1.8	TMP B	104.7 ± 4.61
	103.8 ± 2.5		99.2 ± 1.3
TMP C	102.7 ± 0.3	TMP C	104.3 ± 1.4
	103.7 ± 0.8		95.8 ± 2.0

[a] Each value represents the mean average of six determinations, with analyses performed on two different days.

2.4. Design of the study

After construction of appropriate calibration plots, the analytical methods were further validated by assaying a homogenate of twenty tablets from each generic brand. Six tablets from each brand were then separately analysed on two different days using the ADS as described earlier. Using the UV multicomponent analysis, the amount of each drug dissolved was initially measured at 2-min intervals for the first 10 min, after which time the drug concentration was measured at 10-min intervals. After 60 min, the solution was analysed by HPLC for comparative purposes and the experiment halted.

3. Results and discussion

The first phase of the study, involved the validation of both techniques. The chromatogram in Fig. 1 clearly shows the peaks relating to the two

Table 3
Analysis of variance (by balanced design) for the data shown in Table 2

Source	Degrees of freedom	Sum of square	Media square	Fisher (F)	Probability (P)
Drugs	1	13.1	13.1	1.74	0.202
Brands	2	31.9	15.9	2.13	0.146
Methods	1	2.1	2.1	0.28	0.603
Error	19	142.3	7.5		
Total	23	189.3			

drugs of interest and the internal standard are well separated and essentially symmetrical. Fig. 2a–d show the calibration curves obtained for trimethoprim and sulphamethoxazole by HPLC and multicomponent analysis. Although both systems give essentially linear correlations, the multicomponent analysis seems to be more reproducible.

Results of the drug assays for 20 tablet homogenates of the different brands are summarised in Table 1. It is clear that all the brands were within the assay limits established for this product by the USP XXII (97–103%) when using the multicomponent analysis. The HPLC analyses gave a broadly similar result, however the trimethoprim assays were slightly higher than expected in all three brands. This may reflect the fact that the HPLC method could be further optimised. The variation coefficient was less than 3% for the HPLC system and less than 2% for the multicomponent analysis indicating that both methods are highly reproducible.

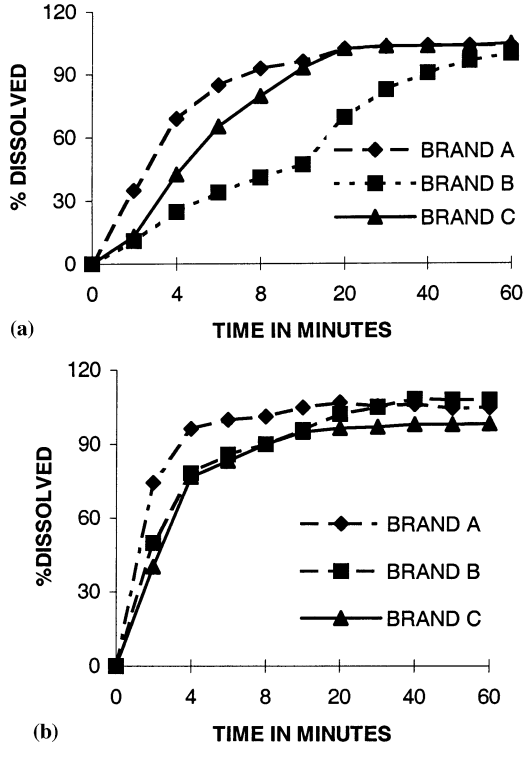

Fig. 3. Dissolution profiles for (a) sulphamethoxazole and (b) trimethoprim. Each value represents the mean average of 12 determinations.

Table 2 shows the results of the second phase of the study which involved assaying individually six tablets on two different days for each brand. Although the drug assays gave values that were more variable than those presented in Table 1, this was expected given that the analyses were conducted on single tablets rather than on the homogenates. The assay results provided using the two analytical techniques were in close agreement in most cases. Table 3 summarises the analysis of variance (by balanced design) and shows that there are no significant statistical differences among drugs, brands and systems. The variation between brands, appears to be the most significant while the least significant was the variation between systems.

The most notable contrasting feature which distinguishes the multicomponent analysis from the HPLC method is that of analysis time. HPLC is discontinuous and invasive whereas multicomponent analysis used in combination with the ADS gives direct in situ monitoring of the dissolution process. In the present study a low cost, relatively unsophisticated multicomponent ADS is able to deliver the dissolution profile of both drugs simultaneously in a short space of time.

This is illustrated by Fig. 3a and b where, for reasons of clarity, only a selection of the available data points have been plotted. The same analysis of samples by HPLC would take up to 6 h.

4. Conclusions

We have demonstrated the utility of the UV/visible multicomponent analysis for routine analysis of tabletted pharmaceuticals, especially polydrugs. This system when used to its full potential is capable of giving a complete profile of the drugs release. It may prove to be at its most versatile when dealing with formulations containing more than the two drugs used in the present study.

To ensure good results with the Multicomponent ADS, it is essential to calibrate the system, determine its suitability and validate the protocol. Particular attention should be focused on the filtration process, particularly for those brands where the excipients interfere with the measured absorbances. This can occur when the particle size is small enough to pass through the pores of the filter causing light scattering effects. Matters can be further complicated if the insoluble excipients contain chromophores, but these two problems can be largely eliminated through careful selection of the filter porosity. In conclusion, we believe that low cost Multicomponent ADS is highly effective analytical tool offering considerable advantages over competing chromatographic methods. We expect the technique to become increasingly important in the next few years, particularly in the analysis of generic polydrug formulations where there are likely to be considerable time and cost benefits.

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