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Assay of drugs in the presence of spectral interferants in tablets

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Summary

The calibration and standard addition methods were compared in the spectrophotometric assay of drugs in the presence of tablet excipients and in tablet dosage form by the zero, first and second derivative techniques. There was no significant difference between both methods in the zero and first derivatives but in the second derivative, the standard addition method was better than the calibration method. The general trend in accuracy was that the results of the first and second derivatives were better than those of the zero derivative. The precision of the second derivative technique was better than those of the first and zero derivatives.

Introduction

Electronic absorption spectrophotometry is one of the techniques most extensively used in official methods as the determinative step in the assay of drugs in dosage forms. This is in part a result of the rapidity, sensitivity and simplicity of the technique (Doyle et al., 1974). However, pharmaceutical preparations contain medicaments and excipients, and solutions of excipients absorb or scatter ultraviolet and visible (UV-Vis) light. These excipients thus interfere spectrally with simple spectrophotometric assays of drugs in dosage forms.

The 'irrelevant absorption' due to such excipients are generally broad and increase in intensity towards shorter wavelengths (Connors, 1982). It may be so strong as to make it impossible to determine the concentration of the drug in the dosage form as a result of serious systematic errors in the calibration curve and even impossible to identify the presence of the drug as a result of the complete masking of the absorption of the drug by that of the excipients. This is why it is generally necessary to carry out the extraction of the drug (which in some cases is cumbersome) before it can be determined by UV-Vis spectrophometry. This requirement will detract from the advantages inherent in UV-Vis spectrophotometric assay of drugs in dosage forms (O'Haver and Green, 1976; O'Haver, 1979a).

Several techniques have been devised to correct for irrelevant absorptions. These include the method of changing parameters (Shatkay, 1968), the use of orthogonal polynomials (Ashton and Tootill, 1956) and orthogonal functions (Glenn, 1963; Wahbi, 1971), the use of Fourier functions (Wahbi et al., 1978) and difference spectrophotometry (Doyle and Fazzari, 1974; Davidson,

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1976; Gurka et al., 1980). However, many of these methods require special attention to operational parameters (Wahbi and Abdine, 1971; Williams, 1976) which limit their applicability to many practical problems in pharmaceutical analysis. The generalized standard addition method has also been used to correct for matrix effects in multicomponent analysis (Saxberg and Kowalski, 1979). It has been successfully applied in spectrophotometry (Jochum et al., 1981).

The advent of simple electronic analogue devices for rapidly transforming the plot of absorbance (A) versus wavelength (λ) into the first derivative ($dA/d\lambda$) vs wavelength, the second derivative ($d^2A/d\lambda^2$) versus wavelength and higher derivatives has offered an elegant and simple approach to resolving spectral overlap and interference. This technique termed derivative spectrophotometry generally increases the features in the graphical display and enhances the discrimination of smaller spectral features (O'Haver and Green, 1976; O'Haver, 1979a). It is already established in the fields of environmental analysis (Hawthorne and Thorngate, 1979) and clinical chemistry (O'Haver, 1979b; Fell, 1979; Ichikawa and Terada, 1977, 1979). It has also found biomedical applications in the analyses of phenol and aromatic alcohols (Fell, 1978), steroid structure determination (Olsen and Alway, 1960), bilirubin (Cook et al., 1977) and urinary porphyrins (Jones and Sweeney, 1979).

UV-Vis derivative spectrophotometry is an analytical technique that offers enhancement of qualitative features and therefore increases finger printing utility for the specific identification of organic compounds (Cahill, 1979). The experimental procedure is simple and time-saving when compared with the conventional UV-Vis spectrophotometry where prior extraction of the sample from the matrix is required as a first step in its characterisation and quantitation.

Despite the inherent advantages of derivative spectrophotometry, only few applications to drug analysis have been published. These include the determination of chlorpromazine sulphoxide in degraded chlorpromazine formulations (Fell and Davidson, 1980), thiamine and pyridoxine in commercial solid dosage forms (Such et al., 1980), salicylic acid in aspirin powder (Kitamura and Majina, 1983). Others include the qualitative and quantitative analysis of some illicit drugs (Lawrence and Macneil, 1982; Lawrence and Kovar, 1985).

These studies support the idea that derivative spectrophotometry can have considerable potential in routine qualitative and quantitative analysis. However, no systematic study has been done on the general utility of derivative spectrophotometry in the analysis of drugs in the presence of excipients in dosage forms. In the first part of this study, our aim is to systematically apply first and second derivative spectrophotometry to assay single drugs in the presence of tablet excipients and in tablet dosage forms - that is without prior extraction of the drug. We also want to compare the results obtained by the zero order with those obtained with the first and second derivative techniques. Since most of the analyses using the derivative techniques have been based on the conventional calibration method, we also want to compare the results obtained by the calibration method with those obtained by standard addition method. The overall intention is to develop a precise, sensitive, accurate and simple method of analysis of drugs in tablet dosage form without resort to tedious and expensive extraction step.

Materials and Methods

Substances

The following excipients and drug compounds were used as obtained. Talc fine powder, lactose, starch, stearic acid, acacia, ephedrine hydrochloride, sodium phenobarbitone and caffeine were obtained from BDH Chemicals Ltd., Poole, U.K., Gelatin was obtained from Halewood Chemicals Ltd., U.K.; chloroquine phosphate powder was from Afro-Arab Techni Chemicals, Lagos, Nigeria, while paracetamol powder was obtained from Stinpex Chemicals (Nig.) Co., Benin City, Nigeria. Commercial tablets of the different drugs were purchased from pharmacies.

Equipment

Spectral measurements were made with Perkin-Elmer UV-Vis spectrophotometer Model 550S with

TABLE 1

Percentage recoveries in the assay of drugs in the presence of tablet excipients and dosage form

Drug	Excipient	Standard addition method						Calibration method					
		Zero order	*n*	First order	*n*	Second order	*n*	Zero order	*n*	First order	*n*	Second order	*n*
Ephedrine hydrochloride [a]	Gelatin	275.77 ± 9.17 [g]	12	101.42 ± 0.88	12	103.63 ± 0.59	12	311.55 ± 21.33	12	106.53 ± 3.44	12	103.25 ± 1.43	12
Ephedrine hydrochloride [b]	Lactose	134.68 ± 6.44	12	96.21 ± 2.13	12	98.44 ± 0.57	12	150.63 ± 6.94	12	97.17 ± 2.19	12	98.74 ± 0.58	12
	Talc	115.58 ± 2.35	12	99.98 ± 1.85	12	98.93 ± 0.79	12	118.29 ± 2.38	12	99.75 ± 2.03	12	98.74 ± 0.79	12
Sodium Phenobarbitone [c]	Starch	119.79 ± 1.68	6	100.21 ± 1.41	6	101.84 ± 0.24	6	120.93 ± 1.99	6	93.67 ± 0.98	6	100.88 ± 0.78	6
	Stearic acid	171.92 ± 14.23	6	96.43 ± 1.26	6	98.63 ± 0.77	6	191.20 ± 11.88	6	98.82 ± 3.00	6	104.39 ± 0.29	6
	Acacia	131.17 ± 12.23	6	97.98 ± 1.70	6	101.42 ± 0.49	6	127.87 ± 9.45	6	98.25 ± 1.91	6	101.32 ± 1.25	6
Chloroquine phosphate [d]	Acacia	108.10 ± 1.07	6	97.92 ± 0.71	12	101.77 ± 0.78	12	105.98 ± 1.41	6	88.69 ± 1.47	12	92.55 ± 0.94	12
	Talc	110.78 ± 1.68	6	82.57 ± 6.88	12	97.47 ± 1.66	12	104.71 ± 0.81	6	74.58 ± 9.00	12	93.52 ± 2.59	12
	Lactose	107.75 ± 1.69	6	98.07 ± 1.10	12	100.20 ± 0.63	12	101.66 ± 1.28	6	93.02 ± 1.96	12	97.88 ± 0.73	12
	Brand												
Ephedrine hydrochloride [e]	A	118.06 ± 1.16	12	93.61 ± 1.55	12	96.98 ± 0.46	12	122.54 ± 0.98	12	87.33 ± 0.60	12	89.87 ± 0.61	12
	B	143.78 ± 4.17	12	95.96 ± 0.75	12	96.23 ± 0.47	12	162.81 ± 2.05	12	85.24 ± 0.39	12	87.27 ± 0.44	12
	C	124.54 ± 2.09	12	97.97 ± 0.62	12	99.50 ± 0.72	12	135.41 ± 1.49	12	92.27 ± 0.92	12	94.70 ± 0.38	12
	D	99.66 ± 3.58	8	10.03 ± 0.62	8	9.34 ± 0.45	8	95.44 ± 2.00	8	28.79 ± 1.32	8	18.62 ± 0.63	8
Phenobarbitone [c]	E	108.60 ± 0.85	6	96.67 ± 0.37	6	97.90 ± 0.46	6	107.79 ± 0.65	6	96.39 ± 0.63	6	97.07 ± 0.43	6
	F	107.11 ± 0.31	6	96.28 ± 0.40	6	97.65 ± 0.34	6	107.12 ± 0.57	6	96.15 ± 0.31	6	96.74 ± 0.44	6
Chloroquine phosphate [d]	G	105.36 ± 0.97	6	100.18 ± 0.88	12	101.36 ± 0.58	12	102.70 ± 0.96	6	96.86 ± 1.77	12	100.94 ± 0.88	12
	H	109.26 ± 0.85	6	99.74 ± 0.83	12	101.99 ± 0.38	12	103.99 ± 0.60	6	100.27 ± 2.87	12	102.16 ± 0.62	12

[a] $7.20–14.40 \times 10^{-4}$ M; [b] $1.80–12.60 \times 10^{-4}$ M; [c] $3.60–8.10 \times 10^{-5}$ M; [d] $2.70–7.20 \times 10^{-5}$ M; [e] $6.30–15.30 \times 10^{-4}$ M; [f] $8.10–13.50 \times 10^{-4}$ M; [g] S.E.M.

TABLE 2a

Analysis of variance

	Excipients						Tablets					
	SAM			CM			SAM			CM		
	0	1st	2nd	0	1st	2nd	0	1st	2nd	0	1st	2nd
Means	150.13	96.47	100.18	159.44	94.02	98.40	120.39	97.34	98.89	126.32	93.64	95.32
S.E.M.	62.35	11.16	3.44	79.55	15.77	5.64	15.29	3.82	2.75	22.09	6.74	5.76
$\Sigma\Delta^2$	276001	11086	1055	449327	22140	2828	13797	1036	537	28788	3225	2352
ΣX_i	10809	8682	9016	11480	8461	8856	7224	7009	7126	7579	6742	6863
$(\Sigma X_i)^{2/n_i}$	1622821	837497	903243	1830384	795488	871430	869676	682205	705341	957349	631014	654185
n_i	72	90	90	72	90	90	60	72	72	60	72	72

TABLE 2b

Comparison of zero, first and second derivatives

SV	Excipients								Tablets							
	SAM				CM				SAM				CM			
	D.F.	S.S.	M.S.	*F*-ratio	D.F.	S.S.	M.S.	*F*-ratio	D.F.	S.S.	M.S.	*F*	D.F.	S.S.	M.S.	*F*.
BS	2	138763	69382	59.97	2	206559	103280	54.22	2	21035	10518	137	2	43937	21969	129
WS	249	288142	1157		249	474345	1905		201	15359	76		201	34349	171	
	$n_1 = 72$, $n_2 = 90$, LSD = 10.5				$n_1 = 72$, $n_2 = 90$, LSD = 13.53				$n_1 = 60$, $n_2 = 72$, LSD = 3.00				$n_1 = 60$, $n_2 = 72$, LSD = 4.48			
	$n_1 = n_2 = 90$, LSD = 9.94				$n_1 = n_2 = 90$, LSD = 12.75				$n_1 = n_2 = 72$, LSD = 2.86				$n_1 - n_2 = 72$, LSD = 4.27			

model 561 recorder using quartz cells of 1 cm pathlength. The spectra were obtained with a bandwidth of 2 nm, a scanning speed of 60 nm/min and a recording chart speed of 30 mm/min. The spectrophotometer has a switch selectable derivative range that can record optionally the zero, first and second derivative spectra.

Procedure

Distilled water was used as the solvent for all drugs except for phenobarbitone where 0.1 M potassium hydroxide was used as solvent. Standard drug solutions were prepared from pure drug samples. For the assays of the pure drugs in the presence of excipients, a known volume of the standard drug solution was added to 0.5 g of the solid excipient suspended or dissolved in 100 ml volumetric flask. This was made up to mark and shaken. This became the sample solution.

For the standard addition method, 3 drug solutions were prepared from the sample solution by taking 18 ml each of this sample solution into 3 different 20 ml volumetric flasks. To these flasks was added 2 ml of distilled water or one of two quantities of the standard solutions of the pure drug. For example, in the assay of 6.00×10^{-5} M chloroquine phosphate in the presence of acacia, three 18 ml aliquots of the sample solution were put into 3 different volumetric flasks and 2 ml of distilled water, or 4.44×10^{-5} M or 8.89×10^{-5} M of standard chloroquine phosphate solution were added to the first, second and third flasks respectively. These preparations were shaken and

TABLE 2c

Comparison of SAM and CM

SV	Excipients				Tablets			
	D.F.	S.S.	M.S.	*F*	D.F.	S.S.	M.S.	*F*.
Zero derivatives								
BS	1	3208	3208	0.63	1	1053	1053	2.92
WS	142	725328	5108		118	42585	361	
First derivatives								
BS	1	305	305	1.63	1	94	94	3.13
WS	178	33226	187		142	4261	30.0	
Second derivatives								
BS	1	187	187	8.34	1	553	553	27.2
WS	178	3883	21.82		142	2890	20.4	

D.F., degree of freedom; S.S., sum of squares: M.S., mean squares; SAM, standard addition method; CM, calibration method; B.S., between set; WS, within set; S.D., standard deviation; SV, source of variation; LSD, least significant difference = $t\sqrt{S_p^2(1/n_1 + 1/n_2)}$, where S_p^2 is pooled variance.

allowed to settle and their zero, first and second derivative spectra recorded in the wavelength range where the drug absorbs radiant energy. To determine the degree of spectral interference of an excipient, 0.5 g of it was suspended or dissolved in 100 ml volumetric flask, shaken and 18 ml of the resulting solution diluted to 20 ml and its spectra recorded. The procedure for drugs in tablet dosage form is the same except that the powder of 20 tablets of drug weighed and powdered was used in the preparation of the sample solution.

For both the calibration and standard addition plots, the absorbance at the wavelength of maximum absorption and the peak-to-peak height (PPH) from a maximum to an adjoining minimum or vice versa were used for the zero and derivative techniques respectively.

Results and Discussion

It was observed that different tablet excipients interfered spectrally to different extents. Gelatin had the greatest interference, stearic acid was moderate while lactose, starch, acacia and talc had low interferences. As expected, the level of interference by the excipients generally increased towards shorter wavelength in the zero order spectrum (Connors, 1982).

The results obtained for assays of pure drugs in the presence of excipients and in tablet dosage forms are shown in Table 1. As a result of the contribution by the excipient background absorption, the absorbance for each drug in the presence of excipients was higher than expected in the zero order. These higher values of the absorbance generally led to correspondingly higher concentrations of the drugs obtained from the graphs than actually taken. Thus in the zero order, both standard addition and calibration methods gave higher recoveries in the presence of excipients. These higher recoveries are in direct proportion to the level of spectral interferences by the excipients at the analytical wavelengths of the drugs. In contrast, the first and second derivative spectra reduced these interferences and hence improved the accuracy of the results. These improvements in the derivative technique were more significant at the lower concentrations of the drug sample where the zero order technique was not sensitive enough, as the broad background absorption of the excipients swamped the absorption of the drug thus introducing serious errors in the zero order results.

Analysis of variance (Table 2) was applied to find out whether there were significant differences between the percentage recoveries obtained in the zero, first and second derivative techniques. In the standard addition and calibration methods, the calculated F-ratios are greater than the tabulated $F_{2,249,0.05} = 3.00$, thus implying that the differences between them are significant. The least significant difference (LSD) procedure for multiple comparison

$$\left(5\% = t\sqrt{\left\{S_p^2\left(\frac{1}{n_1} - \frac{1}{n_2}\right)\right\}}\right)$$

was then applied to determine which means were different from each other. The first and second derivative means were found to be individually significantly different from the zero order mean both in the standard addition and the calibration methods. However, the first and second derivative means were not different in both methods. Thus, both first and second derivatives gave more accurate results than the zero derivative in both methods.

Upon comparing the percentage recoveries in the standard addition and calibration methods, the calculated $F = 0.63$ and 1.63 for the zero and first orders were less than the tabulated $F_{1,142,0.05} = 3.84$ and $F_{1,178,0.05} = 3.84$, respectively, while for the second order technique, the calculated $F = 8.34$ was greater than the tabulated value of $F_{1,178,0.05} = 3.84$. Thus in the zero and first order techniques, there was no statistically significant difference between the standard addition and calibration methods while in the second order technique a statistically significant difference was established. Thus in this second order technique, the standard addition method is more accurate than the calibration method (100.18 ± 0.36 (S.E.M.) versus 98.40 ± 0.60 (S.E.M.), $n = 90$ for each). The second derivative technique gave the most precise results in both the standard addition and the calibration

methods. This improved precision contributed in showing the difference between both methods which was not obvious in both the first and the zero derivatives where precision was lower.

Having established the usefulness of derivative spectrophotometry in the assay of drugs in the presence of excipients, we applied the technique to the assay of drugs in tablet dosage form without prior extraction of the drug. The trend observed here followed the same pattern as that in the presence of excipients. Zero order consistently gave higher recoveries than the label claim while the first and second derivatives gave more accurate results. The differences between the first and second derivatives respectively with the zero derivative were statistically significant but the difference between the first and the second was not statistically significant. Also in the second derivative, the standard addition method gave a result that is better than the calibration method. The standard addition method of the second derivative technique generally gave officially acceptable values of the label claim for each drug (British Pharmacopeia, 1980).

Particular note was taken of a brand of ephedrine hydrochloride (Brand D) where the zero order method gave officially acceptable values in both the standard addition and calibration methods while the derivative technique gave very low values of the content. Since the zero order method has consistently given higher values, the results obtained by it were suspect despite falling within the officially acceptable limits. To resolve the actual content, the USP method for ephedrine hydrochloride (United States Pharmacopeia, 1980) was applied for the assay of ephedrine hydrochloride. The result obtained (9.13%, $n = 4$) agreed very well with that of the standard addition method of the second derivative technique.

We have thus established that derivative spectrophotometry can be of great value in the assay of drugs in the presence of tablet excipients and in tablet dosage form. The standard addition method in the second derivative technique is superior to the other methods in terms of accuracy and precision in the assay of drugs in the presence of spectral interferents in tablet dosage form. The saving in cost and in time of extraction prior to assay in the conventional zero order technique is obvious. More work is in progress with other dosage forms to ascertain the general applicability of this technique.

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