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Derivative spectrophotometric methods for determination of dronedarone in pharmaceutical formulation

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ABSTRACT

The objective of this study is to develop a highly, sensitive, derivative spectrophotometric methods has been developed for the determination of Dronedarone hydrochloride in pharmaceutical preparations. The method carried out by using methanol (solvent) ,the optimum results obtained in the measuring wavelength range 240-310nm.Beer's law was obeyed in the range of 3.0-20µg/ml. Calibration graphs constructed at their wavelengths of determination were linear in the concentration range of Dronedarone using 3-20 $\mu g.mL^{-1}$ (r^2 = 0.9940, r^2 = 0.9980, r^2 = 0.9968 and r^2 = 0.9975) for zero order, first order, second order and third order derivative spectrophotometric method. All the proposed methods have been extensively validated as per ICH guidelines. There was no significant difference between the performance of the proposed methods regarding the mean values and standard deviations. These methods were successfully applied to pharmaceutical formulations because no interferences from tablet excipients were found. The proposed methods were found to be simple, sensitive, accurate, precise, rapid and economical for the routine quality control application of Dronedarone in pharmaceutical formulations.

Keywords: Dronedarone, Multaq, Derivative spectrophotometry - Zero order, First order, Second order and third order derivative spectrum, Validation – Linearity, Accuracy, LOD, LOQ.

INTRODUCTION

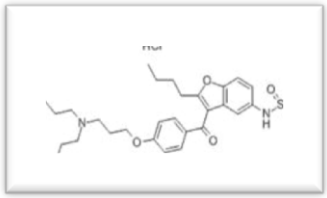

Fig.1 Structure of Dronedarone hydrochloride

Dronedarone is a drug mainly for the indication of cardiac arrhythmias, chemically as N-(2-Butyl-3-(p-(3(dibutylamino) propoxy) benzoyl) -5-benzofuranyl) methane sulfonamide and its structural formula is $C_{31}H_{44}N_2O_5S$ [1]. The arrhythmatous condition needs to be controlled, as humans cannot withstand this rapid and chaotic beating of the heart. A new investigational drug like Dronedarone is being used. Dronedarone is the most recent anti-arrhythmic drugs (AAD). It was approved by USFDA and is available in the USA as Multaq tablets (400 mg). In Dronedarone, the iodine moieties are not present, reducing toxic effects on the thyroid and other organs. A methyl sulfonamide group is added to reduce solubility in fats and hepatic impairment. Dronedarone displays amiodarone like class III anti-arrhythmic activity in vitro and in clinical trials. The drug also appears to exhibits activity in each of the four Vaughan-Williams anti-arrhythmic classes. Dronedarone falls under the category of multiple ion channel blocker. It mainly targets the re-polarization currents, making them less active and hence pro-longing the action potential duration (APD). Dronedarone also exhibits anti adrenergic activity, thus reducing the pace of the pacemaker. Dronedarone has been proven to be a safe and efficacious AAD, evidenced by both animal and human studies. These studies showed that there was prolongation of the APD and absence of QT interval prolongation with long term administration of the drug. Also there was reduced thyroid hormone receptor expression. Dronedarone is significantly safer and effective in maintaining the sinus rhythm and reducing the ventricular pro-arrhythmias, justifying it for the long term treatment of atrial fibrillation compared to other anti-arrhythmic drugs. As per literature there were some methods related to analyse Dronedarone with HPTLC, HPLC, UV-spectrophotometer [2-8], but so far, no derivative spectrophotometric method has been reported for the estimation of Dronedarone from pharmaceutical dosage form with. This paper deals with validation and development of a method by derivative spectrophotometry for the assay of Dronedarone from its bulk drug and in pharmaceutical dosage forms.

EXPERIMENTAL

Instrumentation

A Lab India model 3200 double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV win system software (UV win version 3000). Digital analytical balance branded Afcoset model: ER200A, an ultrasonic bath (Enertech, Mumbai, India).

Materials and methods

Dronedarone was a gift sample by Dr. Reddy's Laboratories, Hyderabad, India and was used without further purification. All chemicals and reagents used were of analytical grade and were purchased from Merck Chemicals, India.

Preparations of the standard solution:

The standard solutions were prepared by accurately weigh and transfer 10mg of Dronedarone working standard into a 100mL volumetric flask add about 70mL of Methanol and sonicate to dissolve it completely and make volume up to the mark with the same solvent, the stock standard solution of Dronedarone was prepared as 100µg/ml and kept stored in dark glass flasks. Working standard solutions were prepared from the stock standard solutions. A calibration graph was constructed in the range of 3, 5, 7.5, 10, 12.5, 15

and 20 µg/ml for Dronedarone (n=6). For quality control samples containing concentration 4, 9, 17.5 µg/ml of Dronedarone, the stock solution was diluted with methanol.

Procedure for pharmaceutical preparations:

The average tablet mass was calculated from the mass of 10 tablets of brand MULTAQ, which was composed of Dronedarone and some common excipients. They were then finely ground; homogenized powder was weighed accurately equivalent to 10 mg of tablet powder Dronedarone and transfer into a 50 ml brown measuring flask and diluted to scale with methanol. The mixture was sonicated for at least 20 min to aid dissolution and then filtered through a Whattmann's No 42 paper. Approximate dilutions were made at concentrations of 5 and 15µg/ml with methanol. Zero-, first, second and third-order derivative spectra were recorded against methanol.

DEVELOPMENT OF THE METHOD

The derivative wavelength difference (Δλ) depends on the measuring wavelength range and n values (smoothing factor). Generally, the noise decreases by increasing Δλ. Optimal wavelength range should be chosen since the broad peaks become sharper, the ratio of signal/noise elevates and the sensitivity of the method increases by controlling the degree of low pass filtering or smoothing. Therefore, a series of *n* values (*n*=1-9) were tested in the first-, second- and third-order derivative spectra of Dronedarone in methanol. Optimum results were obtained in the measuring wavelength range 240-310 nm, *n*=5 (Δλ=17.5 nm) for first-, second- and third-order derivative spectrophotometric methods.

Figure 2(a) presents the overlay of UV spectra of Dronedarone in methanol gives two characteristic maxima at 274 and 280 nm. These two shouldered peaks were separated by using derivative spectrophotometer. Figure 2(b-d) presents the overlay of first-, second- and third-order ultraviolet spectra of Dronedarone standard samples in methanol, respectively. As demonstrated in the Figure 2b, the spectra present characteristic a maximum and two minima. Maximum is represented at 262 and minima are shown at 276 and 283 nm. As demonstrated in the Figure 2c, the spectra present characteristic two minima and two maxima. Maxima are represented at 279 and 287 nm and minima are shown at 278 and 284 nm. As demonstrated in the Figure 2d, the spectra present characteristic two minima and a maximum. Maximum is represented at 278 nm and minima are shown at 277 and 284 nm.

As no difference was observed between spectra of Dronedarone standard and tablet solutions and in the maxima and minima wavelengths of all spectra, it was suggested that the developed methods allowed complete elimination of the background absorption due to the tablet excipients at the chosen wavelengths in zero-, first-, second- and third-order derivative spectra of Dronedarone.

VALIDATION OF THE PROPOSED METHODS

The proposed method is validated according to the International Conference on Harmonization (ICH) guidelines [9].

Linearity and Range

For quantitative analysis of Dronedarone, the calibration curves were plotted for each spectrophotometric method over the concentration ranges cited. The peak to zero method for calibration curve in the first-, second- and third-order derivative spectrophotometric methods were used. The linearity ranges of all spectrophotometric methods were found to be 3.0-20μg/ml (Figures 2(a-d). The statistical parameters and regression equations which were calculated from the calibration curves along with the standard error of the slope and the intercept are given in Table 1.

Specificity

Comparison of the zero-, first-, second- and third-order derivative spectrum of Dronedarone in standard drug and formulation (MULTAQ tablet) solutions show that the wavelength of maximum and minimum absorbance did not changed. According to the results obtained, the zero-, first-, second- and third-order derivative spectrophotometric methods are able to access the Dronedarone in presence of excipients and hence, methods can be considered specific.

Precision & Accuracy

The precision of the analytic methods were determined by repeatability (within-day) and

intermediate precision (between-day). Three different concentrations which were quality control samples (4.0, 9.0, 17.5µg/ml) were analyzed six time in one day for within-day precision and once daily for three days for between-day precision. Repeatability was ≤2.23 %, ≤3.12 %, ≤3.81 % and ≤3.24 % (n=6) and intermediate precision was ≤3.39%, ≤3.93 %, ≤3.92 % and ≤4.24 % (n=6) for zero-, first-, second- and third-order derivative spectrophotometric methods, respectively (Table 2). Within and between-day accuracy of zero-, first-, second- and third-order derivative spectrophotometric methods showed acceptable relative error values were ≤0.25 %, ≤3.25 %, ≤4.00 %, ≤5.25 %, ≤1.44 %, ≤4.25 %, ≤5.25 % and ≤5.50 % (n=6), respectively (Table 2).

Recovery

To determine the accuracy of the zero-, first-, second- and third-order derivative spectrophotometric methods and to study the interference of formulation additives, the recovery was checked as three different concentration levels (5.0, 10, 15 µg/ml) and analytical recovery experiments were performed by adding known amount of pure drugs to pre-analyzed samples of commercial dosage form (Multaq tablet). The percent analytical recovery values were calculated by comparing concentration obtained from the spiked samples with actual added concentrations. The recoveries of zero-, first-, second- and third-order derivative spectrophotometric methods were 99.6 %, 100.3 %, 101.2 % and 100.2 (Table 3).

Sensitivity

Limits of detection (LOD) and Limit of quantification (LOQ)

The LOD and LOQ of Dronedarone by the proposed methods were determined using calibration standards. LOD and LOQ values were calculated as **3.3 σ/S and 10 σ/S,** respectively, where S is the slope of the calibration curve and σ is the standard deviation of y-intercept of regression equation (n=6) (Table 1).

Degradation studies

To evaluate the stability of Dronedarone, standard solutions were prepared separately at concentrations covering the low, medium and higher ranges of calibration curve for different temperature and times. These solutions were stored at room temperature, refrigeratory (4°C) and frozen (-20°C) temperature for 24 h and 72h. Stability measurements were carried out with zero-, first-, second- and third-order derivative spectrophotometric methods. The results were evaluated comparing these measurements with those of standards and expressed as percentage deviation and Dronedarone was found as stable at room temperature, 4 and -20°C for at least 72hr. were shown in table 4.

LIST OF TABLES

Table 1: R**egression analysis of Dronedarone by the proposed methods**

Method	Range (µg/ml)	Linear regression	Intercept	Slope	R^2	LOD	LOQ
Zero-order Spectrophotometric Method	3.0-20	A 274nm = 0.0079x-0.0043	0.0036	0.0019	0.9940	0.80	2.42
First-order Spectrophotometric Method	3.0-20	1st order 262nm= 0.0147x+0.0017	0.0061	0.0032	0.9983	0.73	2.21
		1st order 276nm= 0.0277x+0.0011	0.0043	0.0060	0.9980	0.72	2.18
		1st order 283nm= 0.0516x-0.0061	0.0142	0.0109	0.9985	0.70	2.12
Second-order Spectrophotometric Method	3.0-20	2nd order279nm= 0.0017x+0.001	0.0002	0.0004	0.9963	0.78	2.36
		2nd order287nm= 0.0019x+0.0003	0.0004	0.0003	0.9914	0.52	1.58

		2^{nd}order278nm= 0.0026x-0.0006	0.0005	0.0005	0.9968	0.63	1.92
		2^{nd}order284nm= 40.0016x-0.0009	0.0006	0.0003	0.9966	0.62	1.88
	3.0-20	3^{nd}order278nm= 0.0032x+0.0021	0.0089	0.0007	0.9916	0.72	2.18
Third-order							
Spectrophotometric		3^{nd}order277nm= 0.0062x+0.0014	0.0049	0.0012	0.9975	0.64	1.94
Method							
		3^{nd}order284nm= 0.008x-0.0019	0.0152	0.0015	0.9918	0.62	1.88

Table 2: **Precision and accuracy of Dronedarone by the proposed methods**

Method	**Wavelength**	**Added**	**Within-day**			**Between-day**		
		(μg/ml)	**Found (μg/ml)**	**RSD % RSD**	**Accuracy Precision**	**Found (μg/ml)**	**RSD % RSD**	**Accuracy Precision**
Zero-order		4.0	4.01±0.049	0.25	1.22	3.98±0.088	-0.50	2.21
Spectrophotometric	^{A}274 nm	9.0	9.02±0.192	0.22	2.13	9.13±0.285	1.44	3.12
Method		17.5	17.54±0.391	0.23	2.23	17.61±0.597	0.63	3.39
	^{1D}262 nm	4.0	4.02±0.052	0.50	1.29	4.08±0.093	2.00	2.28
		9.0	9.11±0.198	1.22	2.17	9.16±0.281	1.78	3.07
First-order		17.5	17.56±0.409	0.34	2.33	17.51±0.503	0.06	2.87
		4.0	4.11±0.089	2.75	2.17	4.14±0.118	3.50	2.85
Spectrophotometric	^{1D}276 nm							
		9.0	9.13±0.209	1.44	2.29	9.11±0.274	1.22	3.01
Method								
		17.5	17.66±0.551	0.91	3.12	17.67±0.694	0.97	3.93
	^{1D}283 nm	4.0	4.13±0.088	3.25	2.13	4.17±0.129	4.25	3.09
		9.0	9.11±0.179	1.22	1.96	9.16±0.271	1.78	2.96
		17.5	17.61±0.503	0.63	2.86	17.58±0.569	0.46	3.24
	^{2D}279 nm	4.0	3.97±0.078	-0.75	1.96	4.08±0.093	2.00	2.28
		9.0	9.13±0.275	1.44	3.01	9.12±0.289	1.33	3.17
		17.5	17.44±0.499	-0.51	2.87	17.63±0.517	0.74	2.93
Second-order	^{2D}287 nm	4.0	4.16±0.948	4.00	2.28	4.21±0.135	5.25	3.21
		9.0	9.22±0.292	2.44	3.17	9.31±0.356	3.44	3.82
Spectrophotometric								
		17.5	17.71±0.674	1.20	3.81	17.68±0.695	1.09	3.92
Method								
	^{2D}278 nm	4.0	4.20±0.091	5.00	2.17	4.17±0.135	4.25	3.24
		9.0	9.18±0.174	2.00	1.89	9.21±0.348	2.33	3.78
		17.5	17.61±0.532	0.63	3.02	17.78±0.686	1.60	3.86
	^{2D}284 nm	4.0	3.95±0.090	-1.25	2.28	4.13±0.127	3.25	3.08
		9.0	8.87±0.165	-1.44	1.86	9.21±0.274	2.33	2.98
		17.5	17.36±0.415	-0.80	2.39	17.75±0.579	1.43	3.26
	^{3D}278 nm	4.0	4.21±0.133	5.25	3.16	3.87±0.127	-3.25	3.28
		9.0	9.17±0.297	1.89	3.24	9.31±0.375	3.44	4.03
Third-order		17.5	17.86±0.511	2.06	2.86	17.68±0.568	1.03	3.21

Spectrophotometric	^{3D}277 nm	4.0	4.16±0.091	4.00	2.19	4.22±0.144	5.50	3.41
Method		9.0	9.32±0.176	3.56	1.85	9.38±0.259	4.22	2.76
		17.5	17.70±0.5661	1.14	3.20	17.81±0.725	1.77	4.07
	^{3D}284 nm	4.0	3.84±0.076	-4.00	1.98	4.03±0.084	0.75	2.08
		9.0	9.23±0.256	2.56	2.78	9.31±0.361	3.44	3.88
		17.5	17.86±0.5372	06	3.01	17.69±0.750	1.09	4.24

Table 3: **Recovery values of Dronedarone in pharmaceutical preparations**

Commercial Preparation	**Method**	**Wave length (nm)**	**Amount Added (μg/ml)**	**Amount Found (μg/ml)**	**(%) Recorvery**	**(%) R.S.D**
Multaq tablet (2μg/ml)	Zero-order Spectrophotometric Method	^{A}274 nm	5	4.97±0.113	99.4	2.27
			10	9.98±0.316	99.8	3.17
			15	14.93±0.318	99.5	2.13
	First-order Spectrophotometric Method	^{1D}283 nm	5	4.92±0.146	98.4	2.96
			10	10.17±0.294	101.7	2.89
			15	15.93±0.289	100.9	1.91
	Second-order Spectrophotometric Method	^{2D}278 nm	5	5.13±0.115	102.6	2.24
			10	10.17±0.312	101.7	3.07
			15	14.91±0.428	99.4	2.87
	Third-order Spectrophotometric Method	^{3D}284 nm	5	4.89±0.138	97.8	2.82
			10	10.14±0.421	101.4	4.15
			15	15.18±0.541	101.2	3.56

Table 4: **Degradation studies of Dronedarone in a solution**

Stability (%)		**Room temperature stability (Recovery%RSD)**		**Refrigerator stability +4°C (Recovery % RSD)**		**Frozen stability - 20°C (Recovery % RSD)**	
Wave length(nm)	Added (μg/ml)	24 h	72 h	24 h	72 h	24 h	72 h
A_{274} nm	5	99.1±0.578	99.3±0.582	101.2±0.639	102.2±1.961	101 .1±4.479	102.2±1.817
	10	98.1±0.017	100.4±0.187	99.4±0.077	98.7±0.162	102 .3±0.086	98.2±0.742
	20	100.3±0.078	102.4±0.432	102.8±0.215	102.1±0.059	99.5±0.127	101.0±0.087
$1D_{283}$ nm	5	98.5±0.453	98.7±0.113	102.9±0.074	98.7±3.206	100. 1±1.025	98.6±0.264
	10	100.2±0.087	101.5±0.084	98.7±4.517	100.9±2.024	9 9.3±0.095	98.7±0.221
	20	102.6±1.597	102.1±0.088	103.0±1.218	99.1±1.234	1 02.2±0.086	101.2±0.098
$2D_{278}$ nm	5	99.6±2.541	101.2±2.564	101.1±1.968	104.6±1.310	10 1.1±2.895	99.7±1.747
	10	101.3±1.876	102.1±2.135	98.87±0.148	103.5±0.093	102.5±0.083	100.4±1.319
	20	99.5±0.724	101.3±2.523	102.0±0.150	98.7±1.028	98 .0±0.677	99.7±1.537
$3D_{284}$ nm	5	99.8±2.541	101.2±2.564	101.1±1.988	104.2±1.302	10 1.2±2.865	99.8±1.776
	10	101.2±1.876	102.1±2.135	98.8±0.158	103.1±0.092	1 02.5±0.076	100.2±1.317
	20	99.6±0.744	101.2±2.523	102.0±0.130	98.9±1.028	98 .4±0.687	99.7±1.593

FIGURES

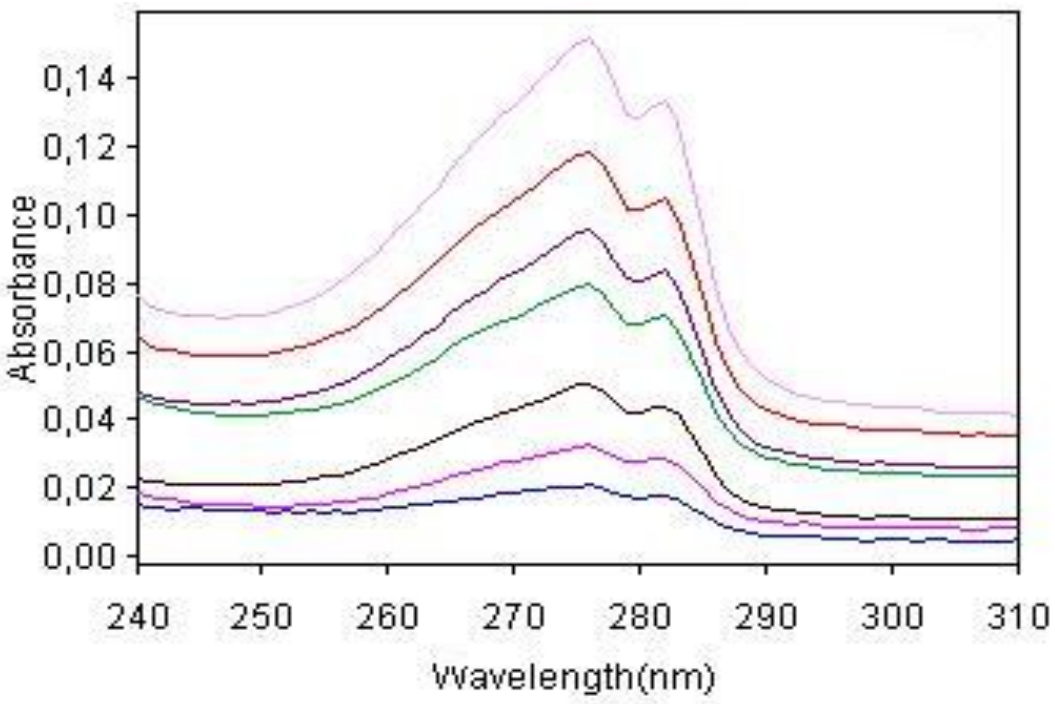

Figure 2(a): Spectrum of obtaining calibration graph point: Zero-order

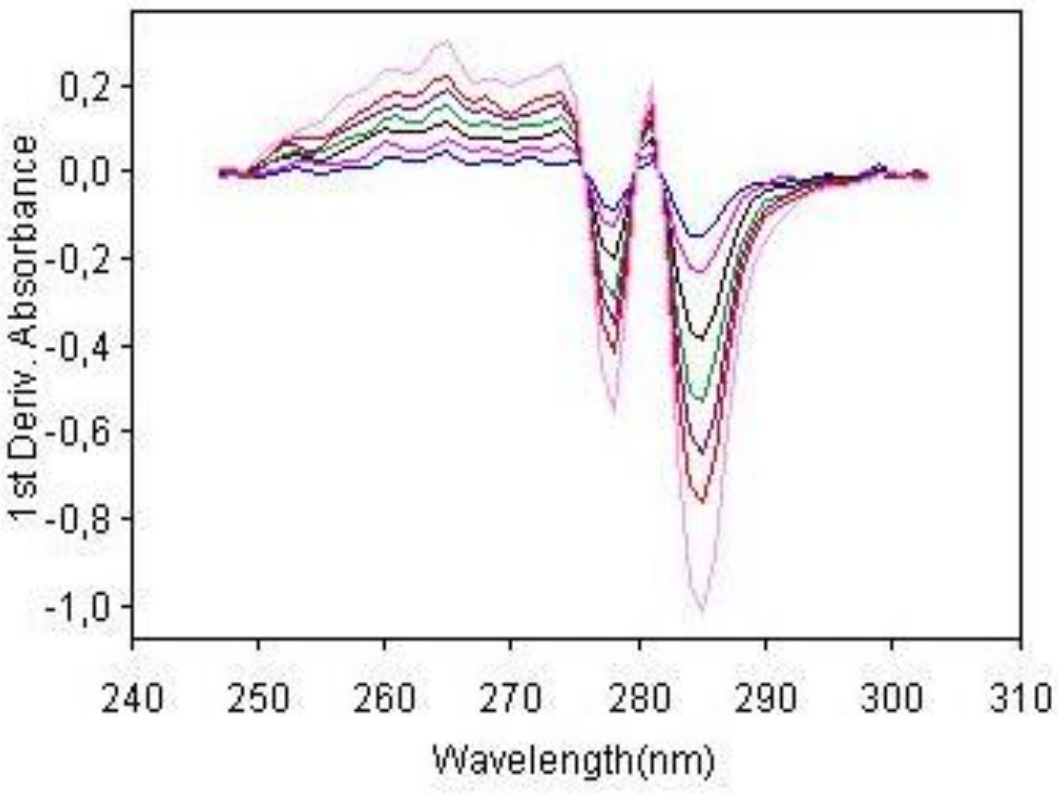

Figure 2(b): Spectrum of obtaining calibration graph point: First-order

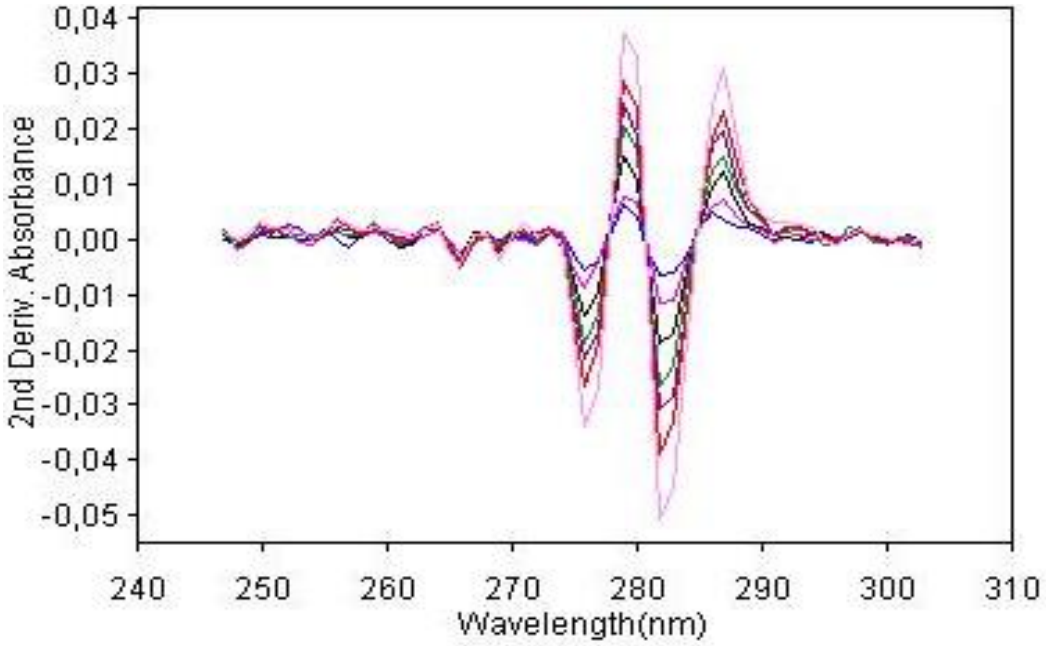

Figure 2(c): Spectrum of obtaining calibration graph point: Second –order

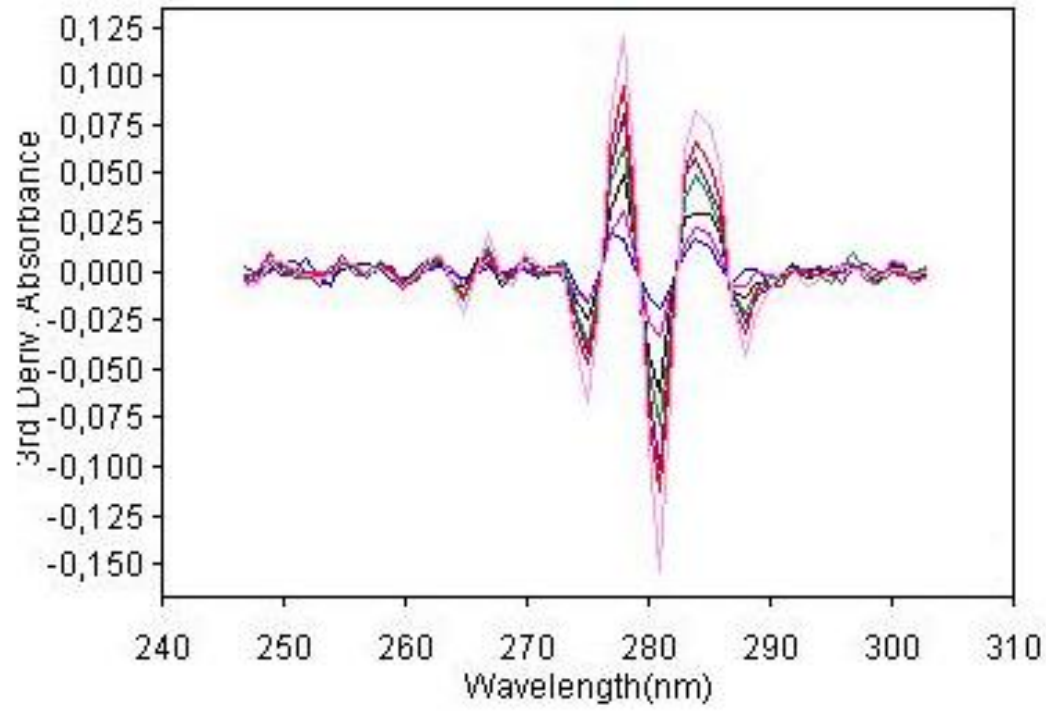

Figure 2(d): Spectrum of obtaining calibration graph point: Third –order

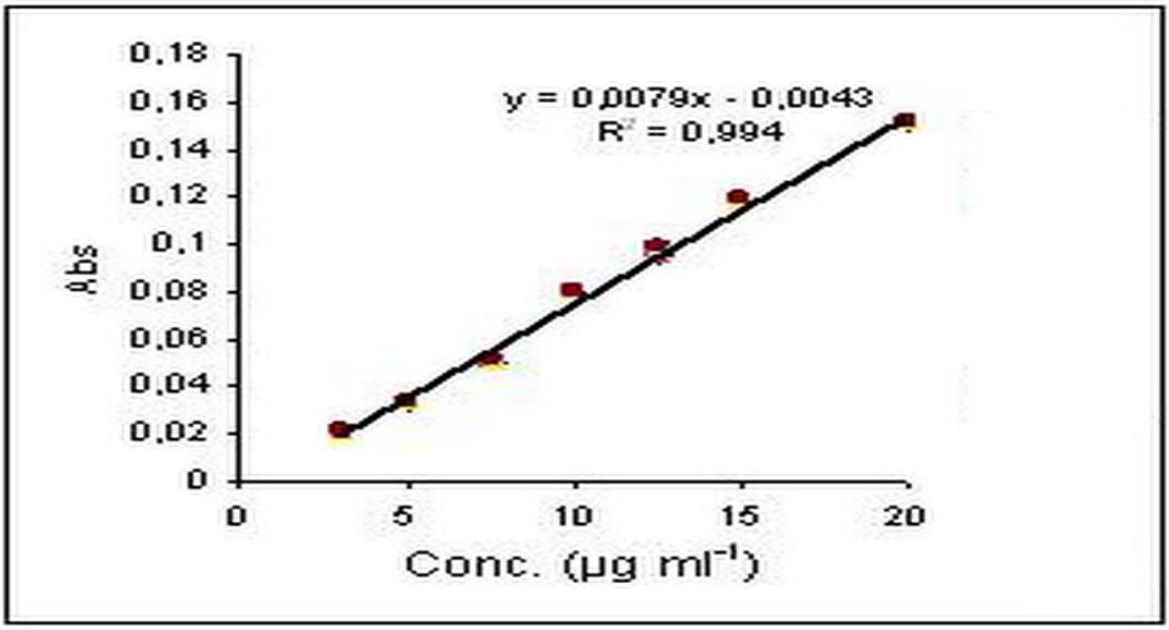

Figure 3(a): Zero-order derivative calibration curves of Dronedarone

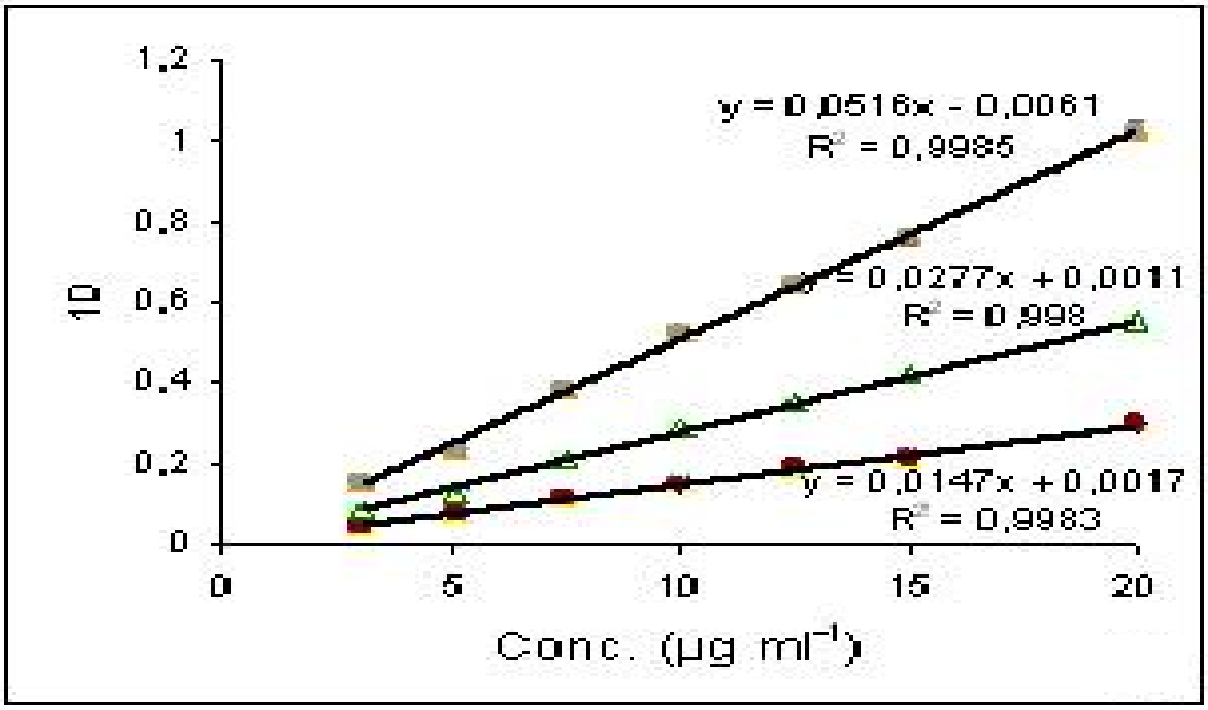

Figure 3(b): First -order derivative calibration curves of Dronedarone

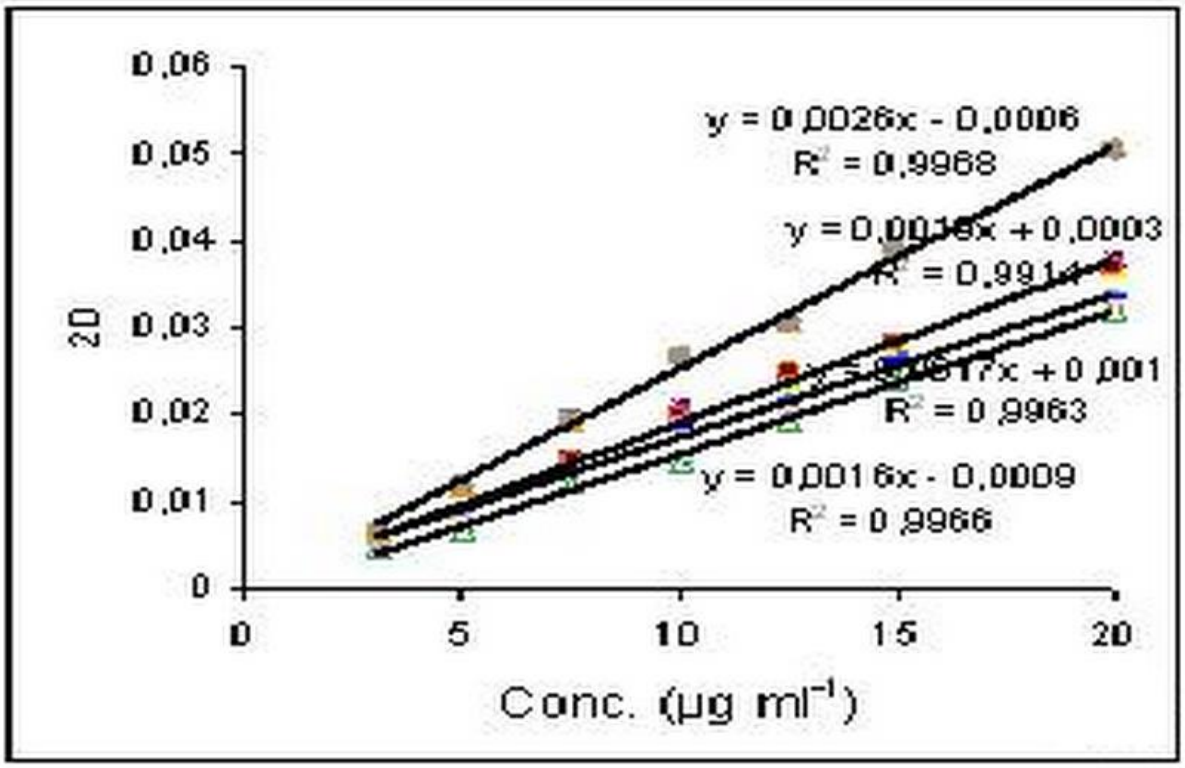

Figure 3(c): Second -order derivative calibration curves of Dronedarone

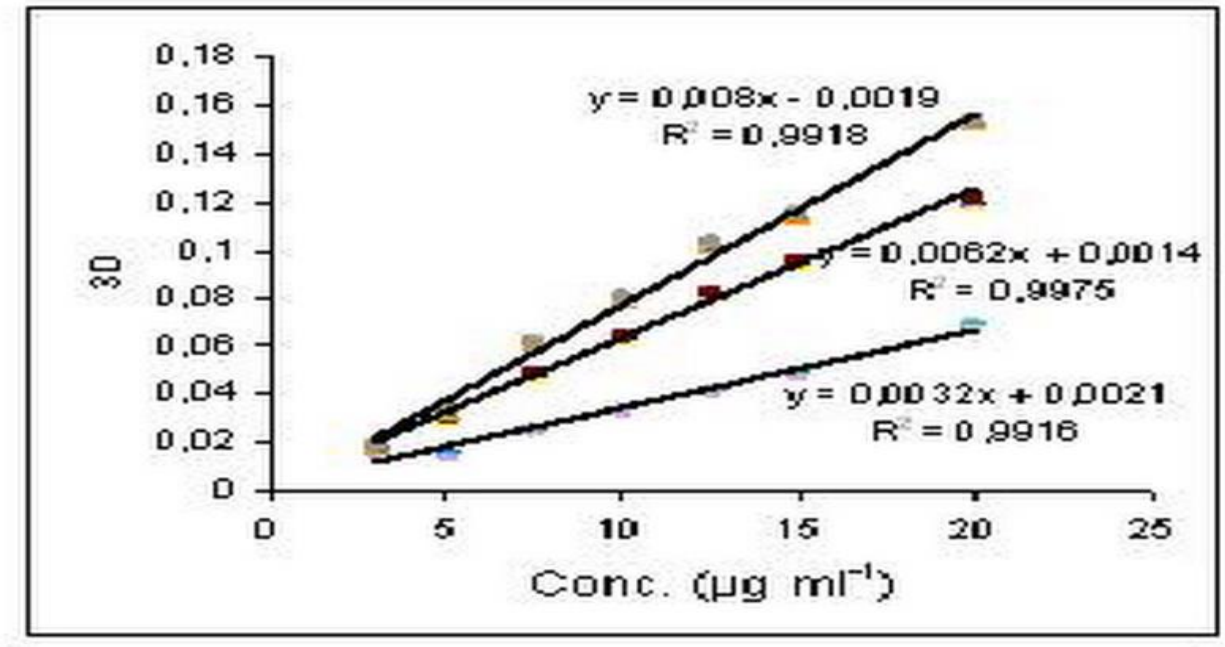

Figure 3(d): Third -order derivative calibration curves of Dronedarone

CONCLUSION

No UV or derivative spectrophotometric methods have been described for the determination of Dronedarone. Therefore simple, fast and reliable derivative spectrophotometric methods were developed for the routine determination of

Dronedarone. The developed methods can be concluded as accurate, sensitive and precise and can be easily applied to the pharmaceutical formulation.

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