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## Stability Indicating Spectrophotometric and Chemometric Methods for Determination of Aripiprazole in Presence of its Degradation Products, A Comparative Study

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**Abstract:** Simple, accurate, selective and validated stability indicating UV spectrophotometric univariate and multivariate methods were developed for determination of Aripiprazole in presence of its alkaline and oxidative degradation products. The developed univariate methods; derivative ratio spectra-zero crossing, successive derivatives of ratio spectra and mean centering of ratio spectra. The first one used the amplitude of the first derivative ratio signals at 303.0 nm, the second method depended on the successive derivative of ratio spectra in two steps and measuring the absorbance of Aripiprazole at 281.0 nm and the third one measured the mean centered values at 294.0 nm. Two chemometric multivariate methods were applied; principal component regression (PCR) and partial least-squares regression (PLS). The selectivity of the proposed methods was confirmed using laboratory-prepared mixtures. The obtained results were statistically compared with those obtained with the manufacturer HPLC method, showing no significant difference with in accuracy and precision. These methods could be applied as stability indicating methods for the determination of Aripiprazole in presence of its degradation products, in bulk powder or in pharmaceutical formulations.

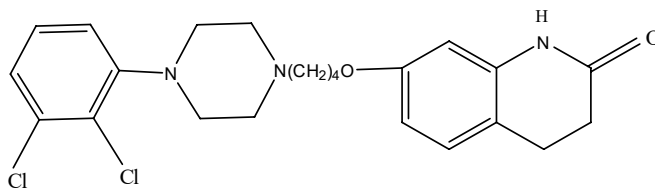
**Keywords:** Aripiprazole, degradation, stability-indicating, spectrophotometry, chemometry.

### Introduction

A stability-indicating procedure is defined as a procedure that allow the selective determination of a drug substance in the presence of its degradation and/or reaction products <sup>1</sup>. Aripiprazole (ARI) (Fig. 1) is, 7-(4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy)-3,4-dihydro-2(1*H*) quinolinone, molecular formula: C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> and molecular weight: 448.39. It acts as a partial dopamine D<sub>2</sub>-, partial serotonin (5-HT<sub>1A</sub>) receptor agonist and (5-HT<sub>2A</sub>) receptor antagonist <sup>2,3</sup>.

It is used in the management of schizophrenia <sup>4</sup>. The literature review showed stability-indicating HPLC methods <sup>5-7</sup>, spectrophotometry <sup>8-11</sup>, chromatography <sup>12-14</sup> and voltammetric methods <sup>15, 16</sup> for determination of ARI in formulations and biological fluids. The use of spectrophotometric methods for resolution of mixtures of two or more compounds having overlapped spectra was an interesting and challenging issue for analytical chemists due to its low cost, short time consuming and did not require prior separation. To our knowl-

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**Fig. 1.** Chemical structure of Aripiprazole

edge, there is no reported stability indicating spectrophotometric and chemometric methods for determination of ARI in presence of its degradation products.

## Experimental

### Apparatus

Shimadzu UV 1800 double beam spectrophotometer (Japan) using UV-Probe 2.32 system software.

Matlab<sup>®</sup> version 7.9 and PLS Toolbox 2.0 software.

Perkin Elmer 1600 USA IR-spectrometer; sampling was under-taken as potassium bromide discs.

Electron impact MS spectra were recorded using shimadzu QP-5050 spectrometer.

## Chemicals and reagents

### Pure sample

Aripiprazole (purity 99.87 %) was kindly supplied by Bristol-Myers Squibb Company, Cairo, Egypt.

### Pharmaceutical dosage form

Aripiprex<sup>®</sup> tablets (B.N. 60365) by El Andalous medical company, Egypt. Each tablet was labeled to contain 10.0 mg of Aripiprazole.

## Chemicals and reagents

Methanol of analytical grade (S.d. fine-chem limited - Mumbai), sodium hydroxide flakes (Central Drug House-LTD), hydrochloric acid 30-34 % and hydrogen peroxide 30 % (ADWIC, Egypt).

## Standard solutions

### ARI standard solutions

Stock standard solution (0.5 mg mL<sup>-1</sup>) of ARI was prepared in methanol. The working standard solution (0.1 mg mL<sup>-1</sup>) was prepared by dilution from the stock solution with methanol.

## Procedures

### Preparation of degradation products of ARI

#### Alkaline degradation

It was prepared by weighing 10.0 mg of pure ARI, transferred into a conical flask and heated with 10 mL 5 M NaOH for 48 h in a thermostatic oven at 80°C. The resulting solution was cooled, neutralized with HCl using digital pH-meter then transferred quantitatively into 100-mL volumetric flask and completed to the mark with methanol to obtain concentration (0.1 mg mL<sup>-1</sup>). The prepared solution was tested for complete degradation by TLC silica plates using toluene: methanol: 1,4-dioxane:dimethylamine in a ratio of (5: 3: 6: 2, by volume) as a mobile phase and detecting the spots at 220 nm, Fig. 2. The prepared alkaline degradation product (ALD) (Fig. 3 (a)) was subjected to IR and mass spectrometry to confirm its structure.

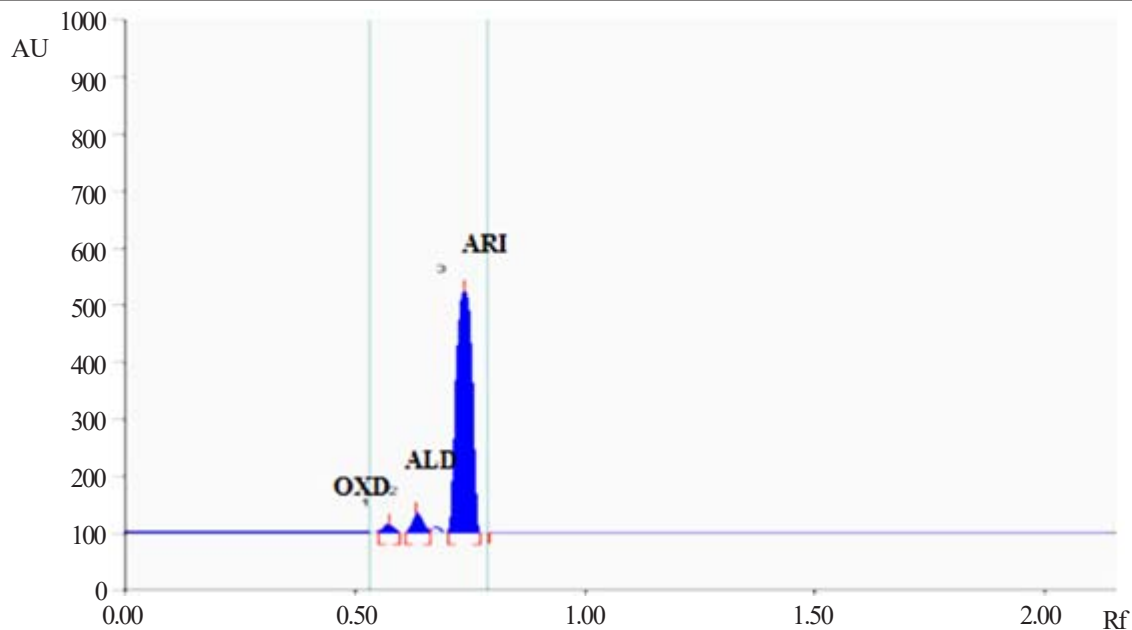
#### Oxidative degradation

It was prepared by weighing 10.0 mg of ARI than adding to the weighed amount 10 mL 3 % H<sub>2</sub>O<sub>2</sub> for 5 h in a thermostatic oven at 70°C. The solution was evaporated to remove the excess H<sub>2</sub>O<sub>2</sub>, cooled, quantitatively transferred into 100-mL volumetric flask and completed to the mark with methanol (0.1 mg mL<sup>-1</sup>). The solution was tested for degradation using the same previous TLC system. The prepared oxidative degradation product (OXD) (Fig. 3 (b)) was subjected to IR and mass spectrometry to confirm its structure.

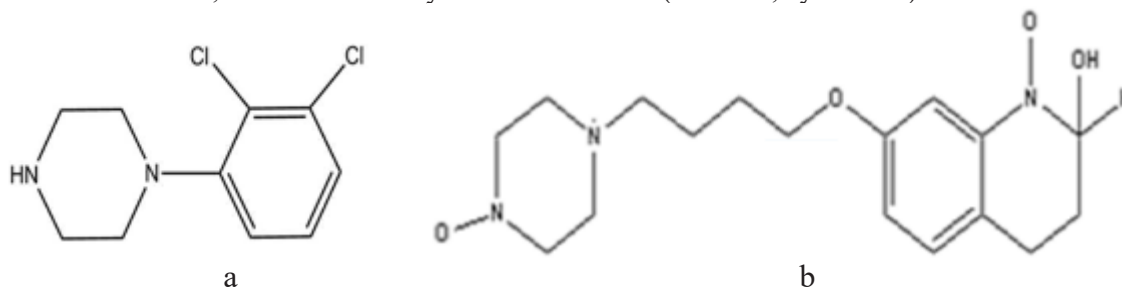
## Construction of calibration curves

### Spectrophotometric methods

Different volumes (0.2-2.8 mL) were transferred from the working solution of ARI into a series of 10 mL-volumetric flasks and diluted with methanol to obtain a concentration range of (2.0-28.0 µg mL<sup>-1</sup>). The absorption spectra of the prepared solutions were measured at (200-400 nm).



**Fig. 2.** TLC densitogram of ARI, ALD and OXD mixture ( $10.0 \mu\text{g spot}^{-1}$ , each), using toluene: methanol: 1,4-dioxane:dimethylamine in a ratio of (5: 3: 6: 2, by volume) at 220 nm



**Fig. 3.** Chemical Structures of (a) alkaline and (b) oxidative degradation products of Aripiprazole

#### Derivative ratio spectra-zero crossing (DRZC)

The absorption spectra of pure ARI and OXD and their ternary mixture with ALD, were divided by a standard of  $6.0 \mu\text{g mL}^{-1}$  ALD (the divisor) and then the first derivative ( $D^1$ ) of the ratio spectra was plotted. In the ternary mixture, the concentrations of ARI were proportional to the first derivative ratio signals at 303.0 nm (zero-crossing point with  $D^1$  of OXD/ALD). Calibration graph was obtained by measuring the first derivative ratio amplitudes at 303.0 nm against the concentrations of ARI and by using ALD as a divisor.

#### Successive derivative of ratio spectra (SDR) <sup>17</sup>

The zero order absorption spectra of different concentration of pure ARI were divided by the spectrum of  $8.0 \mu\text{g mL}^{-1}$  of OXD and the ratio spectra were obtained. First derivatives of this

ratio spectra were obtained with  $\Delta\lambda = 10$  and scaling factor 10. These vectors are divided by the first derivative of the ratio spectra ( $10.0 \mu\text{g mL}^{-1}$  of ALD /  $8.0 \mu\text{g mL}^{-1}$  of OXD) and the second ratio spectra were obtained. First derivative of these second vectors were obtained using  $\Delta\lambda = 10$  and scaling factor 10. The calibration curve of ARI was constructed by plotting the amplitude of the resulting spectra at 281.0 nm against the corresponding concentration.

#### Mean centering of ratio spectra method (MCR)

By the aid of Matlab software, the ratio spectra of pure ARI using ( $8.0 \mu\text{g mL}^{-1}$  of OXD) as a divisor were mean centered. Those MC vectors were divided by the mean centered vector of ( $10.0 \mu\text{g mL}^{-1}$  of ALD/ $8.0 \mu\text{g mL}^{-1}$  of OXD), and then those second ratio spectra were mean centered

again. The calibration curve was constructed by plotting mean centered values at 294.0 nm for ARI against its corresponding concentration.

### Chemometric methods

A five-level, five-factor calibration design was used. The absorption spectra of the prepared mixtures (mixtures of ARI, OXD and ALD) were recorded at 200-400 nm and transferred to Matlab® for subsequent manipulation. Twelve mixtures were chosen to build the calibration set, while seven mixtures were chosen randomly to be used as the validation set. The region below 220 nm was rejected, and then mean center the data.

### Application to laboratory prepared mixtures

Eight mixtures of ARI, ALD and OXD were prepared with different ratios. Their spectra were measured from 200 to 400 nm and stored. The proposed methods were applied and the concentration of ARI was calculated.

### Application to pharmaceutical formulation

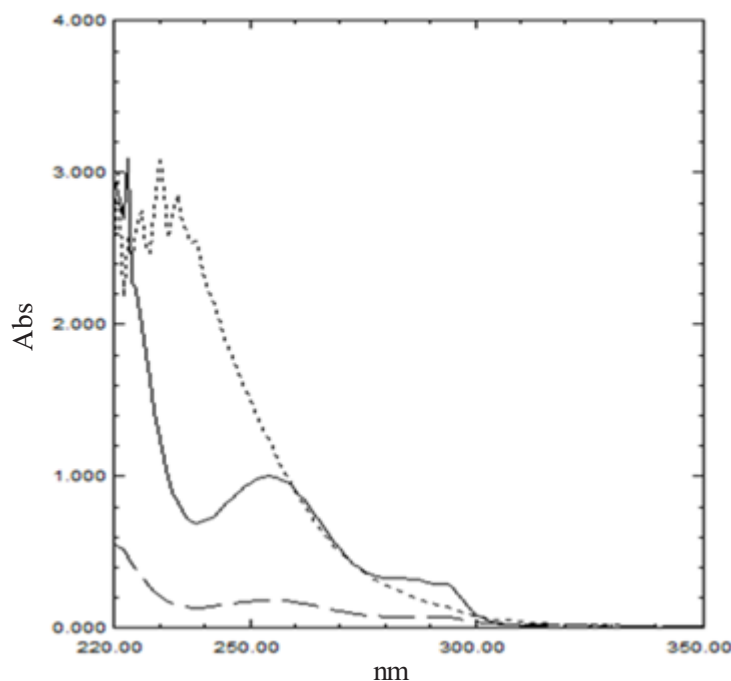
A portion of ten powdered tablets claimed to contain 10.0 mg of ARI was accurately weighed,

transferred into 250-mL beaker and 70 mL of methanol was added, stirred magnetically for about 30 min, filtered into a 100-mL volumetric flask, and the volume was completed with methanol to provide a concentration of  $(0.1 \text{ mg mL}^{-1})$ . The working solution was prepared; by transferring 0.5 mL from the stock  $(0.1 \text{ mg mL}^{-1})$  into 10-mL volumetric flask, and complete the volume with methanol  $(5.0 \text{ } \mu\text{g mL}^{-1})$ . When carrying out the standard addition technique, different known concentrations of standard ARI were added to the pharmaceutical formulation. The resulting mixtures are analyzed by the previously mentioned procedures.

### Results and discussion

The aim of this work was the development of specific, accurate stability indicating spectrophotometric methods for the determination of ARI in presence of its alkaline and oxidative degradation products in laboratory mixtures and in pharmaceutical formulation without interference from excipients.

The zero-order absorption spectra of ARI, ALD and OXD showed severe overlap, Fig. 4, so different manipulating techniques have been applied;



**Fig. 4.** Zero order absorption spectra of Aripiprazole (—), alkaline (---) and oxidative degradation products (····), ( $10.0 \text{ } \mu\text{g mL}^{-1}$ , each) using methanol as a blank

derivative ratio spectra zero-crossing (DRZC), successive derivative of ratio spectra (SDR), mean centering of ratio spectra (MCR) and two chemometric techniques in order to resolve the overlap.

### Structure elucidation of degradation products of Aripiprazole

The proposed structures of the alkaline and oxidative degradation products of ARI were identified by IR and LC/MS techniques. The spectral data of degradation products were compared with that of ARI. The two degradation products were pharmacologically inactive due to the absence of quinolinone ring for the alkaline degradation product and presence of N-oxide in the oxidative degradation product.

The IR-spectrum of alkaline degradation product (ALD) exhibited the disappearance of the peak corresponding to the ether group present in ARI at  $1270\text{ cm}^{-1}$ , which clearly elucidated the breakdown of the ether bond as shown in Fig. 5 and Fig. 6(a). The mass spectrum of intact ARI and ALD product showed a molecular ion at  $447\text{ m/z}$  and at  $283.63\text{ m/z}$ , respectively which indicated the breakdown of the ether bond of ALD, Fig. 7 and Fig. 8(a) which confirm the reported structure of the alkaline degradation product <sup>7</sup>.

The IR-spectrum of the oxidative degradation product (OXD) exhibited the appearance of two peaks at  $1457$  and  $1551\text{ cm}^{-1}$  characteristic to (-NO) group and appearance of broad peak at  $3397.9\text{ cm}^{-1}$  which was characteristic to (OH) group which were absent in the pure drug. The peak of the ether group of the pure ARI drug was still present at  $1270\text{ cm}^{-1}$  as shown in Fig. 6(b). The mass spectrum showed a molecular ion at  $383.74\text{ m/z}$ , as shown in Fig. 8(b), while that of pure drug was at  $447\text{ m/z}$ . The isotopic ratio of two chlorine atoms that appeared in the fragmentation pattern of the mass spectrum of pure ARI (triplet form) didn't appear in that of OXD, so that this difference supported the suggested structure of the oxidative degradation product.

### Spectrophotometric methods

#### *Derivative ratio spectra - zero crossing (DRZC)*

In this method, the absorption spectra of ARI and OXD in methanol recorded between 200-400 nm and were divided by the spectrum of  $6.0\text{ }\mu\text{g mL}^{-1}$  ALD. The resulting ratio spectra were smoothed at  $\Delta\lambda = 10.0\text{ nm}$  and their first derivative were plotted with intervals of  $\Delta\lambda = 10\text{ nm}$  and scaling factor of 10 as shown in Fig. 9. The concentrations of ARI in the ternary mixture were determined by measuring the first derivative ratio signals at  $303.0\text{ nm}$ .

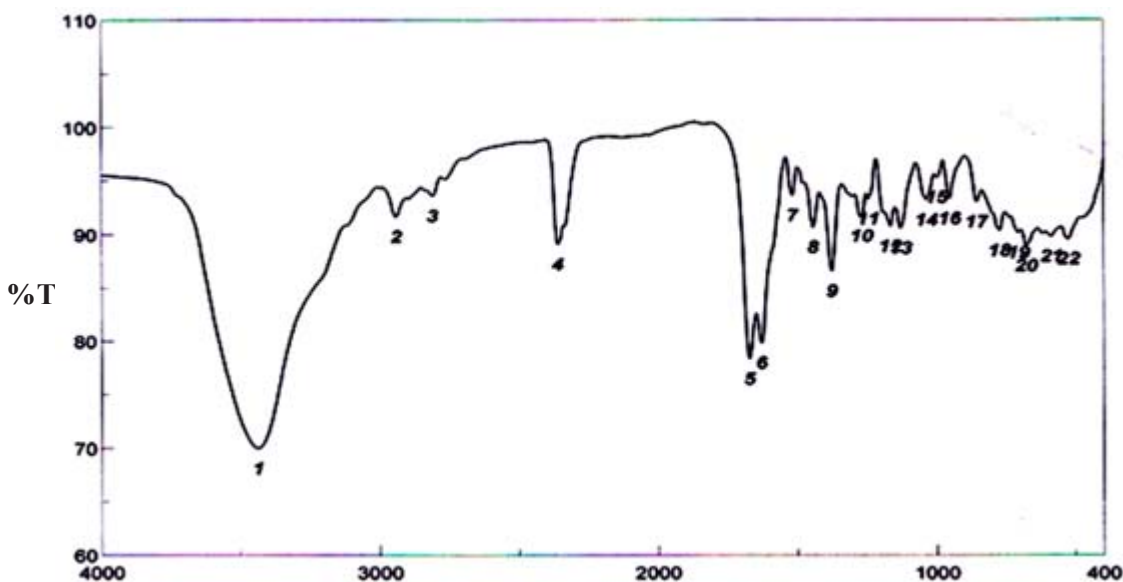


Fig. 5. IR spectrum of intact Aripiprazole

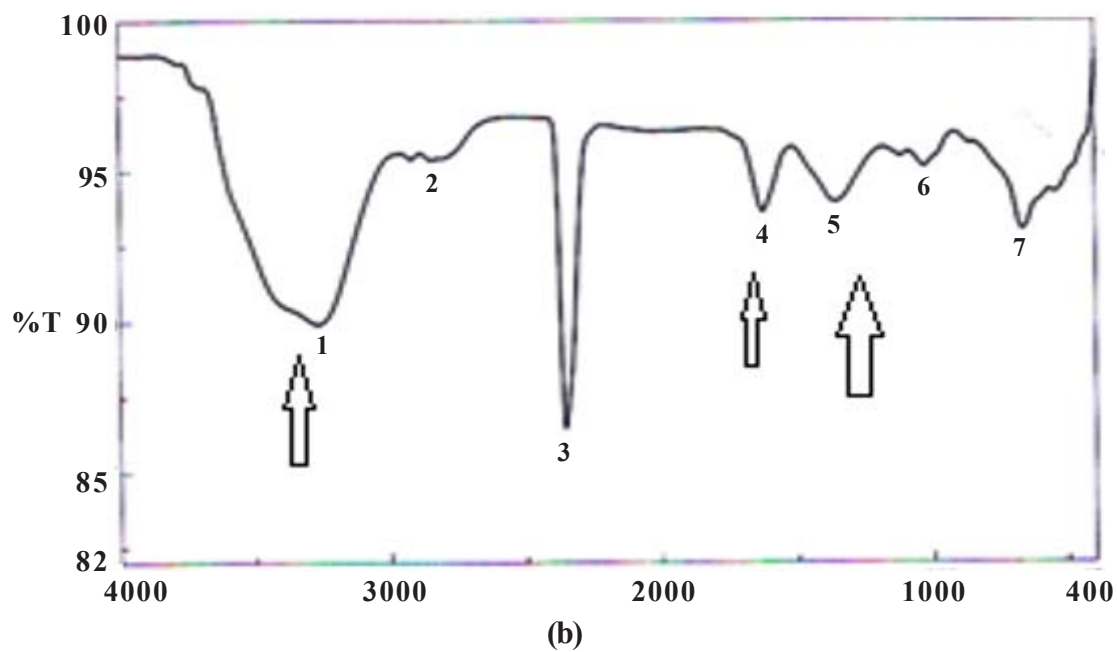
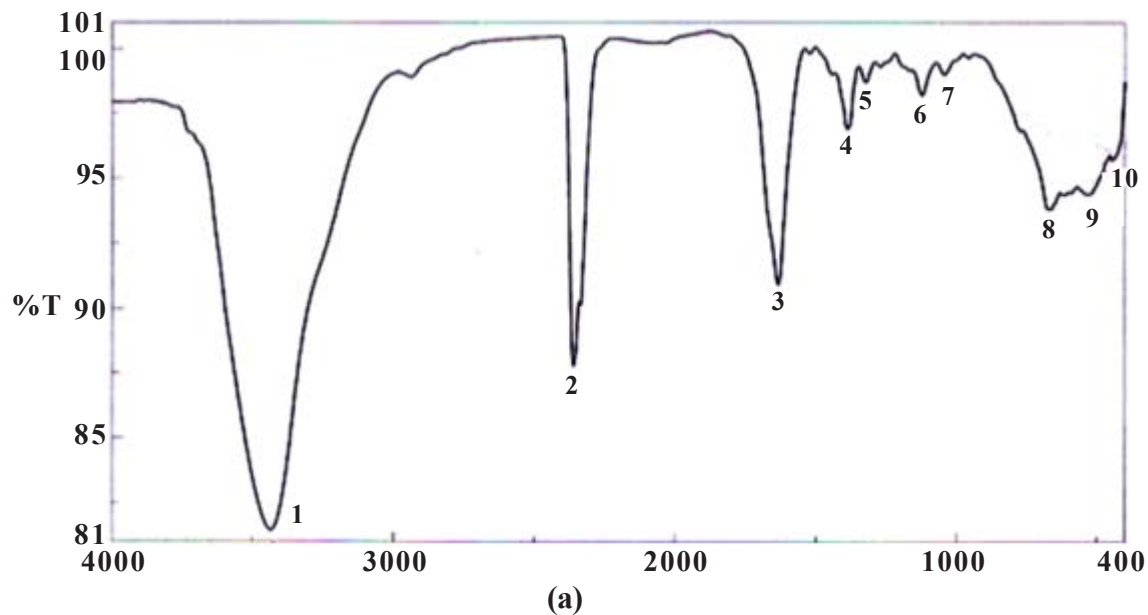


Fig. 6. IR spectrum of (a) alkaline and (b) oxidative degradation products of Aripiprazole

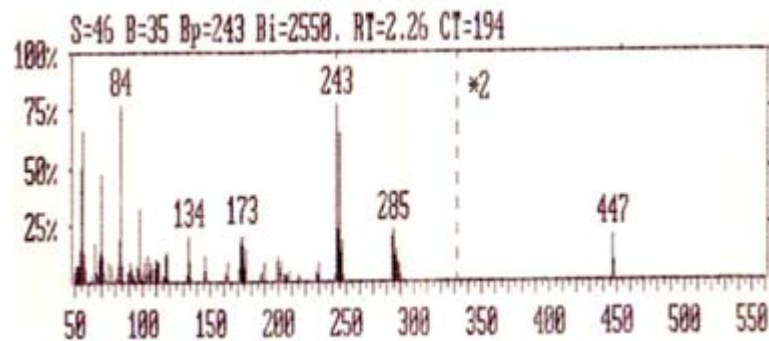


Fig. 7. Mass spectrum of intact Aripiprazole

**Successive derivative of ratio spectra (SDR)**

For determination of ARI, The absorption spectra of different concentrations of ARI were divided by  $8.0 \mu\text{g mL}^{-1}$  of OXD and first derivative of the ratio spectra was then obtained. Then these vectors were divided by  $(10.0 \mu\text{g mL}^{-1}\text{ALD}/8.0 \mu\text{g mL}^{-1}\text{OXD})$  to obtain the second ratio spectra. The concentration of ARI was determined by measuring the amplitude at  $281.0 \text{ nm}$  as shown in Fig. 10.

**Mean centering of ratio spectra (MCR)**

This method reduced the manipulating steps and therefore the signal-to-noise ratio was enhanced.

The ratio spectra of  $(\text{ARI} / 8.0 \mu\text{g mL}^{-1}\text{OXD})$  were mean centered in the wavelength range of  $(220\text{-}360 \text{ nm})$  and divided by the mean centered of  $(10.0 \mu\text{g mL}^{-1}\text{ALD} / 8.0 \mu\text{g mL}^{-1}\text{OXD})$ . The obtained second ratio spectra were mean centered. The spectra from  $(200\text{-}220 \text{ nm})$  were eliminated as it affected the linearity of MC curve. The concentration of ARI was determined by measuring the MC amplitude at  $294.0 \text{ nm}$  corresponding to a maximum wavelength as shown in Fig. 11.

The international conference on Harmonization (ICH) guidelines<sup>1</sup> for method validation was followed for validation of the spectrophotometric

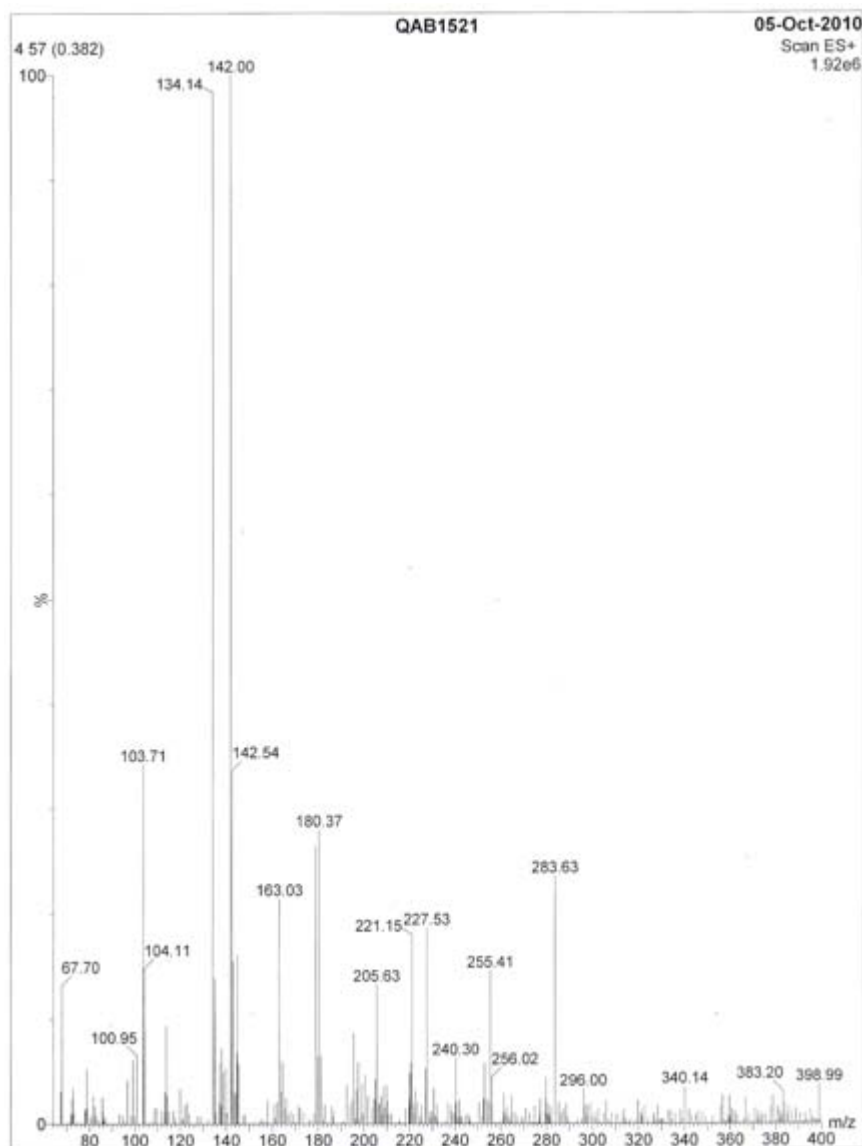


Fig. 8a

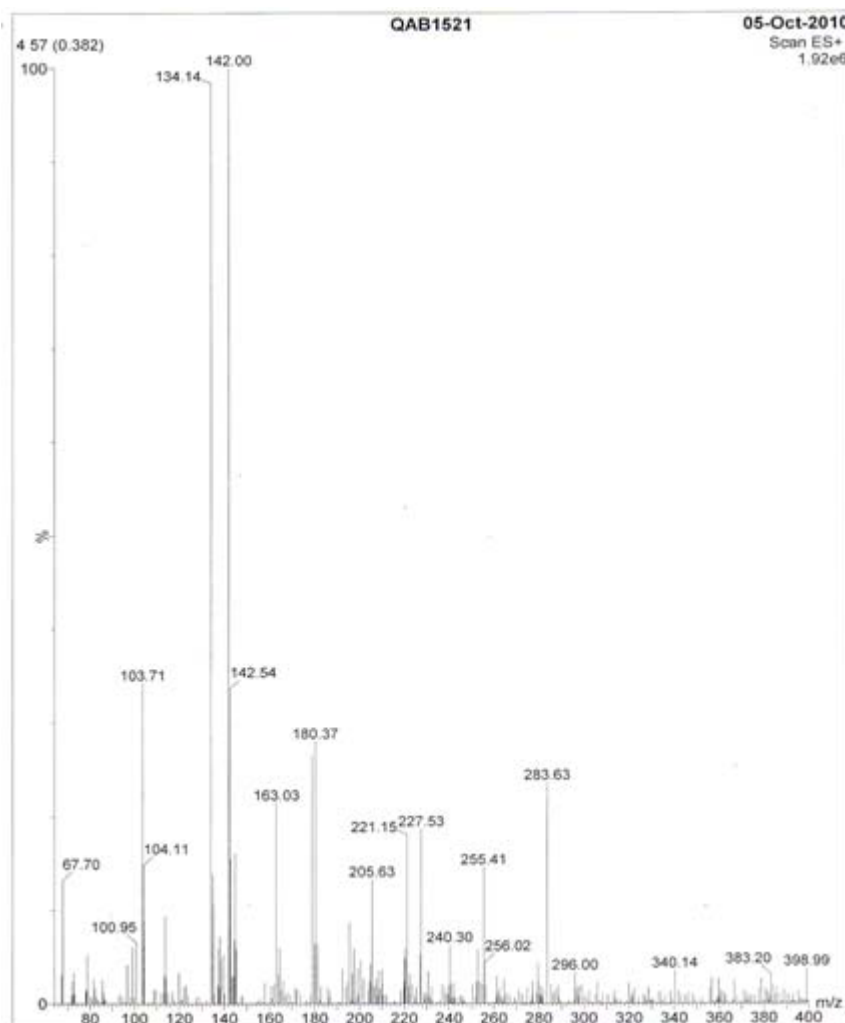


Fig. 8b

**Fig. 8.** Mass spectrum of (a) alkaline and (b) oxidative degradation products of Aripiprazole

methods of analysis.

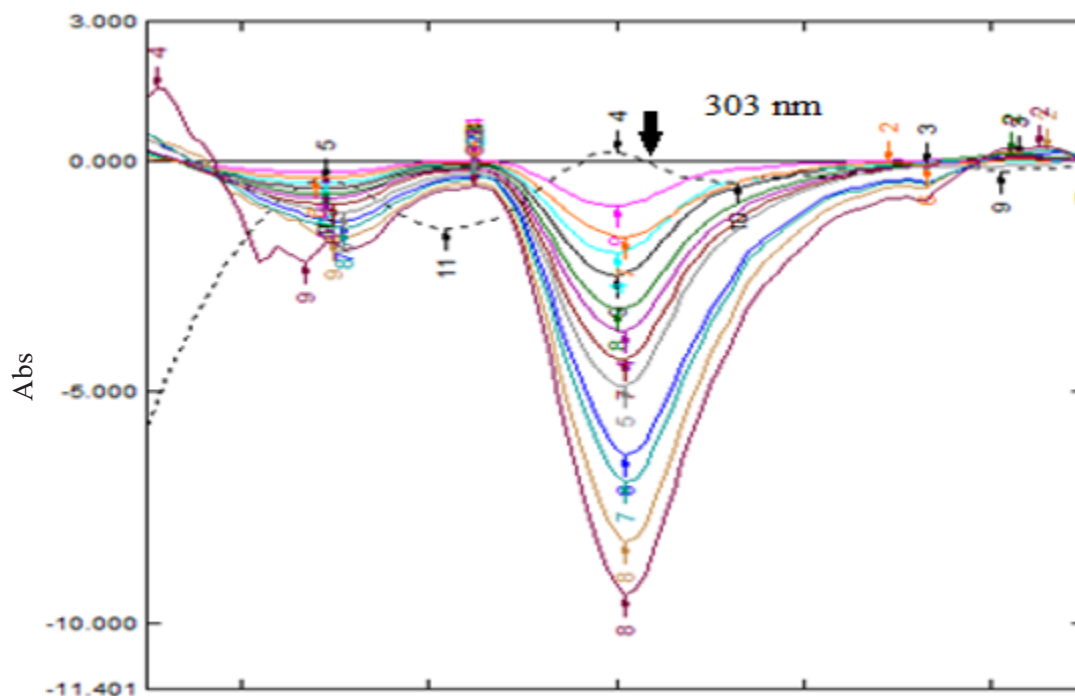
The statistical parameters of the regression equations and the concentration ranges were shown in (Table 1). The selectivity of the proposed procedures was assessed by the analysis of laboratory prepared mixtures containing different ratios of the ARI, ALD and OXD, where satisfactory results were obtained, as shown in (Table 2).

The proposed spectrophotometric methods were applied for the determination of ARI in its pharmaceutical formulation (Aripiprex<sup>®</sup> tablets). The recovery results, shown in Table 3, were satisfactory and with good agreement with the labeled amount. The validity of the methods was assessed by applying the standard addition technique (Table

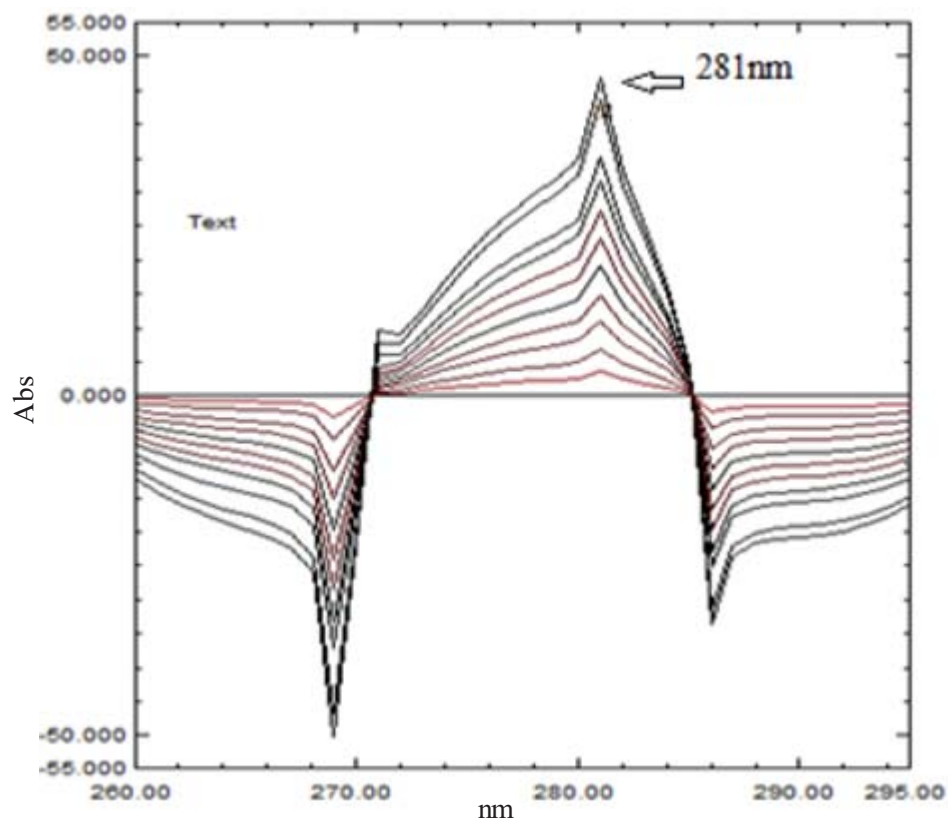
3). It showed that the developed methods were accurate and specific for determination of ARI in presence of excipients.

### Chemometric methods

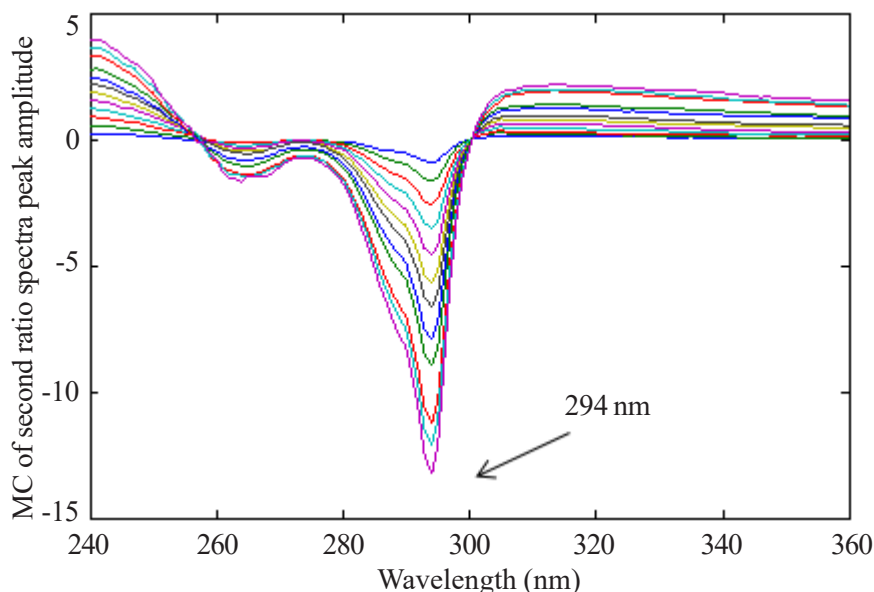
The calibration set was obtained by using the absorption spectra of twelve mixtures of ARI and its degradation products, listed in Table 4. The leave one out cross validation was applied and RMSEP values were used as diagnostic tools for examining the errors in the predicted concentrations. The maximum number of factors to calculate the optimum RMSEC was selected to be 7 (half the number of samples + 1). Five factors were found suitable for PCR model and four factors for PLS model as shown in Fig. 12. To vali-



**Fig. 9.** First derivative of the ratio spectra of ARI (4.0-28.0  $\mu\text{g mL}^{-1}$ ) and OXD (...) (10.0  $\mu\text{g mL}^{-1}$ ), using 6.0  $\mu\text{g mL}^{-1}$  of ALD as a divisor



**Fig. 10.** Successive derivative ratio spectra of ARI (2.0-24.0  $\mu\text{g mL}^{-1}$ ), with  $\Delta\lambda = 10$  and scaling factor 10



**Fig. 11.** The mean centered vectors of the second ratio spectra obtained for ARI in the range of (2.0-26.0  $\mu\text{g mL}^{-1}$ )

**Table 1.** Validation parameters obtained by applying the proposed spectrophotometric methods, for determination of Aripiprazole

Parameters	DRZC	SDR	MCR
Calibration range ( $\mu\text{g mL}^{-1}$ )	4.0-28.0	2.0-24.0	2.0-26.0
Slope	0.327	2.015	0.528
Intercept	-0.665	-1.045	-0.608
Correlation coefficient (r)	0.9992	0.9997	0.9995
Accuracy (Recovery % $\pm$ SD) <sup>a</sup>	99.65 $\pm$ 1.13	98.94 $\pm$ 0.75	99.73 $\pm$ 0.62
LOD ( $\mu\text{g mL}^{-1}$ ) <sup>b</sup>	1.07	0.63	0.83
LOQ ( $\mu\text{g mL}^{-1}$ ) <sup>c</sup>	3.34	1.91	1.95
Precision (RSD % <sup>a</sup> )			
Intraday	1.43	0.65	1.16
Interday	1.67	0.97	1.38

<sup>a</sup> Three replicate were used for determination;

<sup>b</sup> LOD = (S.D of the response/slope)  $\times$  3.3

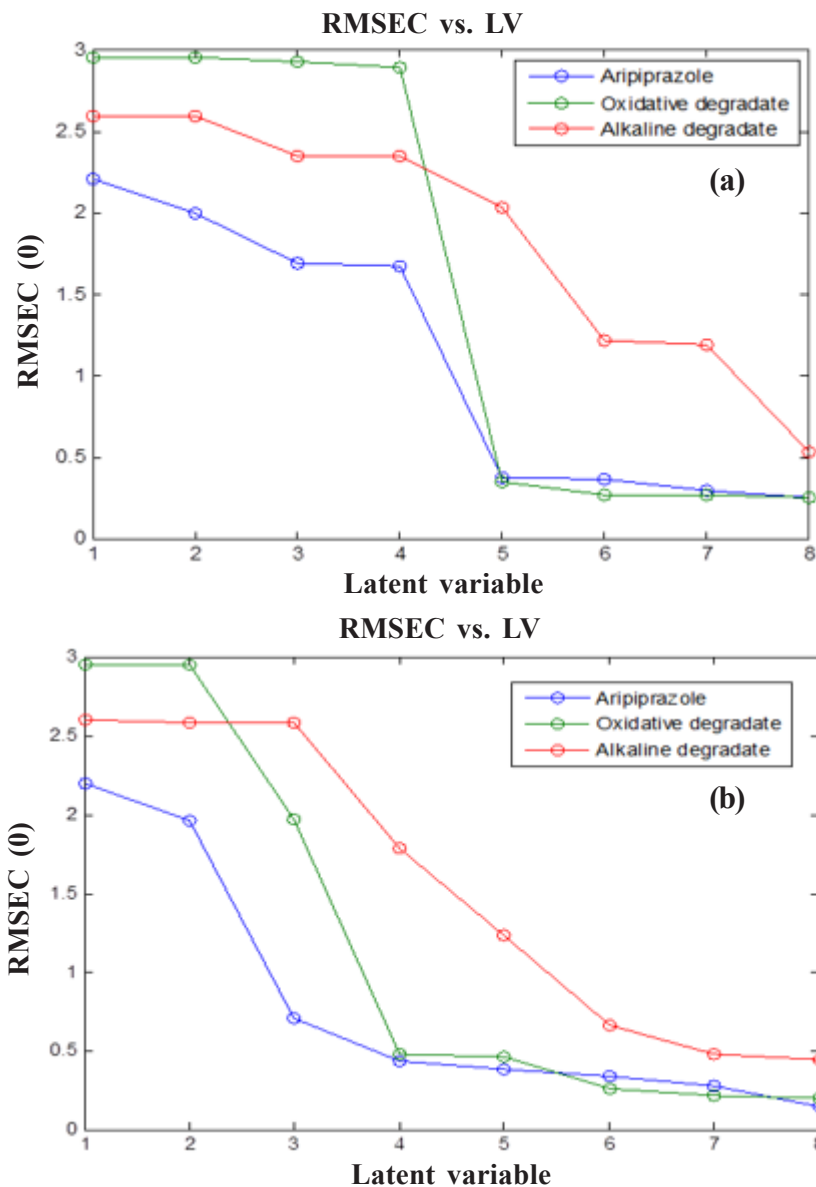
<sup>c</sup> LOQ = (S.D of the response/slope)  $\times$  10

date the prediction ability, a validation set was used, Table 5. The proposed procedures were also applied for the determination of ARI in pharmaceutical preparation without interference from excipients. The validity of the proposed procedures was confirmed by applying the standard addition technique. The results obtained were listed in Table 6. The predicted concentrations were plotted against the actual concentration values, Fig. 13. The residuals were plotted against the actual concentration values of the validation set, Fig. 14. The

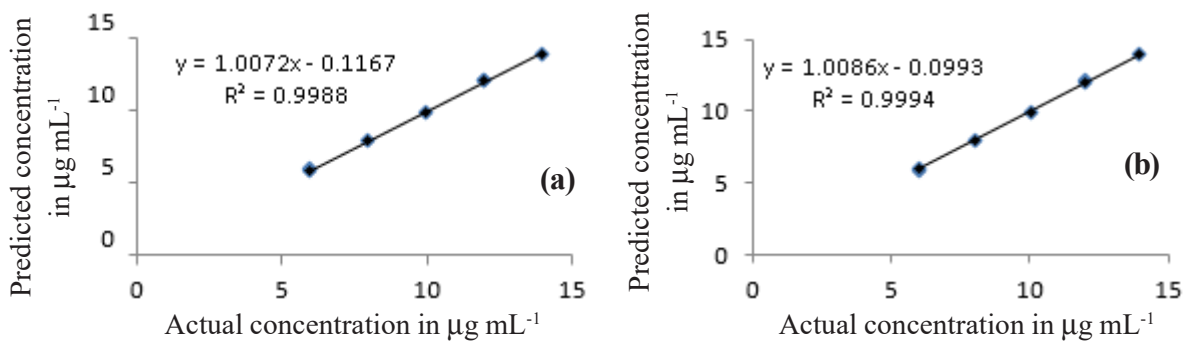
results obtained by applying the diagnostic tools were listed in Table 7, indicating the good predictive abilities of both models.

#### Statistical comparison

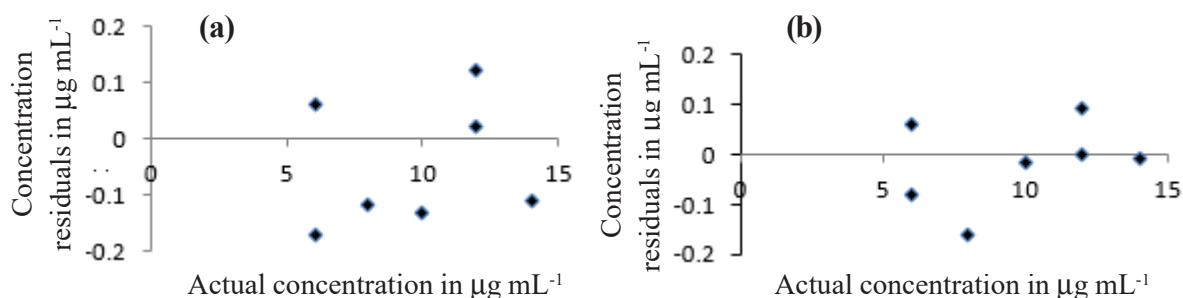
The statistical comparison <sup>18</sup> of the results obtained by applying the proposed methods versus the manufacturer HPLC method for determination of ARI in pharmaceutical preparation was shown in Table 8. It was concluded that with 95 % confidence, there was no significant difference



**Fig. 12.** RMSEC of the calibration set of ARI as a function of latent variables used to construct (a) PCR and (b) PLS calibration models, respectively



**Fig. 13.** Predicted concentration versus actual concentration of ARI in the validation set: using (a) PCR and (b) PLS models



**Fig. 14.** Concentration residuals versus actual concentration of ARI in the validation set: using (a) PCR and (b) PLS models

**Table 2.** Analysis of laboratory prepared mixtures by applying the proposed spectrophotometric methods, for determination of Aripiprazole

Degradates %	DRZC	SDR	MCR
Recovery % <sup>a</sup>			
10	100.65	101.45	99.76
20	100.95	101.34	99.33
30	101.04	102.87	101.65
40	101.48	102.76	100.89
50	102.36	101.52	101.38
60	102.47	103.64	101.47
70	114.88	120.51	118.42

<sup>a</sup> Average of three experiments

**Table 3.** Quantitative determination of ARI in pharmaceutical preparation and application of standard addition technique, by the proposed spectrophotometric methods

Pharmaceutical preparation	Pure added	DRZC ( $\mu\text{g mL}^{-1}$ )	SDR	MCR
Aripiprex <sup>®</sup> tablets		Recovery % $\pm$ SD		
Claimed to contain 5.0 $\mu\text{g mL}^{-1}$ ARI		100.75	101.46	100.49
		$\pm$ 1.36	$\pm$ 0.83	$\pm$ 0.95
		5	100.76	100.32
		10	100.49	100.61
		15	99.73	100.74
		Mean	100.33	100.56
		$\pm$ SD	$\pm$ 0.53	$\pm$ 0.22
				$\pm$ 0.26

<sup>a</sup> Average of three experiments

in accuracy and precision between the results obtained by the proposed methods and the reference HPLC method since the calculated *t* and *F* values were less than the theoretical values.

### Conclusion

The developed spectrophotometric methods; the derivative ratio spectra zero-crossing (DRZC), successive derivative of ratio spectra (SDR) and

**Table 4. Concentrations of ARI, ALD and OXD in the calibration and validation sets**

Mix no.	ARI ( $\mu\text{g mL}^{-1}$ )	ALD ( $\mu\text{g mL}^{-1}$ )	OXD ( $\mu\text{g mL}^{-1}$ )
1	10.0	10.0	10.0
2	6.0	14.0	8.0
3	14.0	8.0	14.0
4	8.0	14.0	10.0
5	12.0	14.0	12.0
6	14.0	12.0	10.0
7	12.0	10.0	14.0
8	10.0	14.0	14.0
9	14.0	14.0	6.0
10	14.0	6.0	12.0
11	6.0	12.0	6.0
12	10.0	6.0	6.0
13*	12.0	6.0	10.0
14*	6.0	10.0	12.0
15*	10.0	12.0	12.0
16*	12.0	12.0	8.0
17*	12.0	8.0	6.0
18*	8.0	6.0	8.0
19*	6.0	8.0	10.0

\* Mixtures of the validation set

**Table 5. Recoveries of ARI in the validation set, by the proposed chemometric methods**

True concentration of ARI ( $\mu\text{g mL}^{-1}$ )	Recovery % <sup>a</sup>	
	PCR	PLS
12.0	101.0	100.77
6.0	101.0	98.72
10.0	98.7	99.84
12.0	100.17	100.56
14.0	99.21	99.95
8.0	98.50	98.23
6.0	97.17	101.55
Mean $\pm$ SD	99.39 $\pm$ 1.31	99.75 $\pm$ 1.06

<sup>a</sup> The average of three separate determinations

mean centering of ratio spectra (MCR), were simple, sensitive and do not require sophisticated techniques or instruments and have the advantage of being simpler than the chemometric methods as they do not require the large number of prepared mixtures. The developed spectrophotometric and chemometric methods can be used as stability indicating alternative methods to chromatography and in routine analysis of ARI in its

dosage form without any preliminary separation steps.

#### Acknowledgment

We thank to October University for Modern Sciences and Arts (MSA) for providing the needed chemicals and instrument for the practical work and Bristol-Myers Squibb Company (Egypt) for the supply of pure standard of Aripiprazole.

**Table 6. Quantitative determination of ARI in pharmaceutical preparation and application of standard addition technique, by the proposed chemometric methods**

Pharmaceutical preparation	Claimed ( $\mu\text{g mL}^{-1}$ )	Found% <sup>a</sup> $\pm$ RSD %		Standard addition technique		
		PCR	PLS	Pure added ( $\mu\text{g mL}^{-1}$ )	Recovery % <sup>b</sup>	
					PCR	PLS
Aripiprex <sup>®</sup> tablets labeled to contain 10.0 mg ARI	7.0	100.76 $\pm$ 0.58	100.38 $\pm$ 0.77	2.0	99.08	100.85
				4.0	100.15	99.41
				6.0	99.63	100.45
	Mean $\pm$ SD				99.6 $\pm$ 0.54	100.23 $\pm$ 0.74

<sup>a</sup> The average of five separate determinations

<sup>b</sup> The average of three separate determinations

**Table 7. Summary of results obtained by applying the diagnostic tools for model validation of the proposed chemometric methods, for determination of ARI**

Validation parameters	PCR	PLS
a) Predicted versus known conc. plot		
1. Slope	1.007	1.008
2. Intercept	0.117	0.099
3. Correlation coefficient (r)	0.998	0.9994
b) RMSEP	0.034	0.016
c) Q <sup>2</sup>	0.9984	0.9992

**Table 8. Statistical comparison between the results obtained, by applying the proposed and the manufacturer HPLC method for determination of ARI in pharmaceutical preparation**

Items	Spectrophotometric			Chemometry		HPLC method <sup>a</sup>
	DRZC	SDR	MCR	PCR	PLS	
Mean	100.75	101.46	100.49	100.09	99.98	99.23
RSD	1.36	0.83	0.95	0.78	0.60	0.74
Variance	1.84	0.68	0.90	0.61	0.36	0.54
n	5	5	5	5	5	5
Student's t-test <sup>b</sup>	1.47	1.92	1.99	0.105	0.401	
	(2.26)	(2.26)	(2.26)	(2.145)	(2.145)	
F- test <sup>b</sup>	3.907	3.497	2.943	1.486	2.482	
	(6.094)	(6.094)	(6.094)	(3.478)	(3.478)	

<sup>a</sup> HPLC method supplied from Bristol-Myers Squibb Company through personal communication; using Hypersil C<sub>18</sub> (250  $\times$  4.6 mm), Mobile phase; methanol: 0.05 M KH<sub>2</sub>PO<sub>4</sub>, pH 3.0 (60: 40, v/v) and UV detection at 254 nm

<sup>b</sup> The values in parentheses are the corresponding theoretical values for t and F at P = 0.05

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