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SIMULTANEOUS UV SPECTROPHOTOMETRIC ESTIMATION OF PRAVASTATIN AND COENZYME Q10 IN THEIR FORMULATED COMBINED DOSAGE FORMS AND SYNTHETIC MIXTURE

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Abstract

A Pravastatin and reproducible spectrophotometric method, requiring no prior separation, has been developed for the estimation of Pravastatin and Coenzyme Q10 in combined dosage form. First order derivative spectroscopy method was adopted to eliminate spectral interference, using 236 nm and 288 nm as zero using points for Pravastatin and Coenzyme Q10 respectively. Methanol: IPA (50:50% v/v): Isopropyl Alcohol (50:50% v/v) was used as a solvent. The results of analysis have been validated statistically and recovery studies confirmed the accuracy of the proposed method.

INTRODUCTION

Pravastatin is (1S,3R,7S,8S,8aR)-8-{2-[(4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7 dimethyl-1,2,3,7,8,8ahexahydronaphthalen-1-yl2,2-dimethylbutanoate. PRAVASTATIN is a selective and competitive inhibitor of 3-hydroxy-3- methylglutaryl -coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to Mevalonate, a precursor of cholesterol[1]. PRAVASTATIN is a member of the class of Statins, used to treat hypercholesterolemia and related conditions and to prevent cardiovascular disease. It increases the number of hepatic LDL (Low Density Lipoprotein) receptors on the cell surface to enhance uptake and catabolism of LDL. Secondly, PRAVASTATIN inhibits hepatic synthesis of VLDL (Very Low Density Lipoprotein), which reduces the total number of VLDL and LDL particles[2]. Coenzyme Q10 is a 2-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)3,7,11,15,19,23,27,31,35,39Decamethyl2,6,10,14,18,22,26,30,34,38tetracontadecaen-1yl]5,6-dimethoxy-3methyl2,5cyclohexadiene-1,4-dione. Coenzyme Q10 is nutrient or dietary supplement with Pravastatin. It's mainly used in cardiovascular disease, Neurodegenerative disease, Diabetics, Cancer, Asthma Migraine, Immune disorders, HIV/AIDS, Male fertility. A daily dosage up to 3600mg was found to be tolerated by healthy as well as unhealthy person[3-6].

Pravastatin has a side effect of myopathy and Rhabdomyolosis. Number of clinical trial supports this and also it is supported by the official USFDA Site. This side effect is due to PRAVASTATIN block HMGCO A reductase because in synthetic pathway of cholesterol one side chain from fernesyl PP which is converted in to decaprinyl PP which combines with the 4-OH benzoate forms endogenous Coenzyme Q10. So PRAVASTATIN block not only Cholesterol synthesis but also coenzyme Q10 so side effect of PRAVASTATIN due to Coenzyme Q10 block so it has been prove that giving Coenzyme Q10 as a adjuvant with the PRAVASTATIN decrease the Myopathy and rhabdomylosis[3-6].

A detailed survey of analytical literature for PRAVASTATIN revealed several methods based on varied techniques, viz, HPLC[7-12],

LCMS[13-14] Spectrophotometry[15, 16] and High-Performance Thin- Layer Chromatography (HPTLC) [17, 18] and similarly, a survey of the analytical literature for COQ10 revealed several methods based on HPLC[19-25], spectroflorymetry[26] and Ampherometry[27] for determination in pharmaceuticals in combination with other drugs were reported.

The combination of this both drug are still under clinical trials and hence till date we have not come as COQ10s any reported method for Simultaneous estimation of the Pravastatin and coenzyme Q10 during our continues reference work.

MATERIALS & METHODS

Materials

Reference Standards of PRAVASTATIN and COQ10 were obtained as gift samples from the Astrone Pharmaceuticals Ltd., Ahmedabad and West Coast pharma Ltd., Ahmedabad, respectively. All other reagents were of analytical grade for Spectrophotometric method.

Preparation of Standard Solution

Pravastatin

Accurately weight 20mg dissolve in 80ml of Solvent mixture Methanol:IPA (50:50%v/v): IPA (50:50%v/v) and sonicate for 15min and make up the volume with solvent mixture up to 100ml. From this the working standard solutions containing 40µg/mL of PRAVASTATIN was prepared from above stock by diluting with the same diluents.

Coenzyme Q10

Accurately weight 25mg dissolve in 40ml of Solvent mixture methanol: IPA (50:50 % v /v): IPA (50:50 % v/v) sonicates for 15min and make up the volume up to 50ml with solvent mixture. From this the working standard solutions containing 50 µg/mL of COQ10 was prepared from above stock by diluting with the same diluents.

Selection of Analytical wavelength

Solution of PRAVASTATIN (10 µg/ml) was prepared in methanol: IPA (50:50 %v/v): IPA (50:50 %v/v) and spectrum was recorded between 200-400 nm. First-derivative spectrum for above concentration was obtained. Similarly, Solution of COQ10 (10 µg/ml) was prepared in methanol: IPA (50:50%v/v) and spectrum was recorded between 200-400 nm and first derivative spectrum was obtained. The overlain

derivative spectrum of PRAVASTATIN (10 µg/ml) and COQ10 (10 µg/ml) show the zero using point (ZCP) 236 nm and 288 nm, respectively, which were selected for measurement of PRAVASTATIN and COQ10 respectively.

Preparation of calibration curve

Pravastatin

From the working standard solution pipette out 0.5,1.0,1.5,2.0,2.5,3.0 ml in separate 10ml volumetric flask and make up the volume with solvent mixture to obtain the concentration of Pravastatin 2,4,6,8,10,12 µg/mL.

Coenzyme Q10:

From the working standard solution pipette out 1,2,3,4,5,6 ml in separate 10ml volumetric flask and make up the volume with solvent mixture to obtain the concentration of COQ10 is 5,10,15,20,25,30 µg/mL.

The samples were scanned between 200-400 nm using SCHIMADZU UV/Visible double beam spectrophotometer (UV-1800) with 1cm matched quartz cells. And spectrums were converted into first order derivative form. Absorbances of PRAVASTATIN and COQ10 solutions were measured at 236nm nm and 288 nm, respectively using first order derivative spectrophotometric method. The graph of absorbance versus respective concentration was plotted.

Methods

Twenty tablets were accurately weighed and average weight per tablets was calculated. Powder equivalent to 10 mg PRAVASTATIN and 20 mg COQ10 was accurately weighed and transferred to a 100 ml volumetric flask containing methanol:IPA (50:50%v/v):IPA (50:50%v/v) (80 ml). The flask was sonicated for 5 min. The flask was shaken and the volume was diluted to the mark with methanol:IPA (50:50%v/v):IPA(50:50%v/v). The above solution was filtered through Whatman filter paper no. 41. The aliquot 10 ml was transferred to 100 ml volumetric flask and volume adjusted to the mark with methanol:IPA (50:50%v/v):IPA (50:50%v/v). The first derivative response of this solution was measured at 236 nm and 288 nm for quantification of PRAVASTATIN and COQ10, respectively. First order derivative absorbances at these wavelengths were substituted in regression equation

representing the calibration curves for PRAVASTATIN and COQ10, with correction for dilution, to calculate the amounts of drug present.

RESULTS AND DISCUSSION

Selection of wavelength for Simultaneous estimation of PRAVASTATIN and COQ10

UV spectra of PRAVASTATIN partially overlaps that of PRAVASTATIN so, absorbance effect of COQ10 is suppressed in the mixture. Therefore Simultaneous estimation in zero order spectra was not successful. So it was thought of interest to develop the first order derivative spectrophotometric method for Simultaneous estimation of PRAVASTATIN and COQ10 from formulated tablet dosage form. Individual first order derivative spectra were recorded for both drugs and zero crossing points were selected (Figure 4). First order derivative spectrum for PRAVASTATIN was taken and it showed zero crossing point 288 nm, was selected for determination of COQ10 in the mixture. Simaltailarly, first order derivative spectrum for COQ10 was taken and it showed zero COQ10sing point 236 nm, was selected for estimation of PRAVASTATIN in mixture since it showed adequate absorbance at this wavelength.

Validation of the proposed Method

The method is validated as per ICH (International conference on harmonization) Guidelines as follows:

Linearity and Range

The linearity range for both PRAVASTATIN and COQ10 was found to be in the range of 2-12 µg/ml and 5-30 µg/ml respectively (Figure 5). Correlation co-efficient for calibration curve of PRAVASTATIN and COQ10 was found to be 0.999 and 0.999 respectively.

The regression line equation for COQ10 and PRAVASTATIN are as following,

$Y_{Pravastatin} = 0.004x + 0.0006$..... (1)

$Y_{coq10} = 0.001x + 0.0006$..... (2)

Accuracy (% Recovery)

1) In Tablet:

The accuracy of the method was determined by calculating recoveries of PRAVASTATIN and COQ10 by the standard addition method in tablets. Known amount of standards of COQ10 (4, 8, 12 µg/ml) and PRAVASTATIN (2, 4 and 6 µg/ml) were spiked to a prequantified sample (4 and 8 µg/ml for PRAVASTATIN and COQ10,

respectively) and the mixtures were analyzed again. The amounts of PRAVASTATIN and COQ10 were determined by measuring the absorbances and by fitting these values into the regression equation of the calibration plots. The % recovery was found in the range of 98.92-99.46 % for PRAVASTATIN (Table 2) and 99.43-100.5 % for COQ10 (Table 3).

2) In synthetic mixture:

The accuracy of the method was determined by calculating recoveries of PRAVASTATIN and COQ10 by the standard addition method in synthetic mixture. Synthetic mixture was prepared by 20 mg and 40 mg of PRAVASTATIN and COQ10 and 5 mg of Talc and Mg stearate and MCC as a diluents up to the 500 mg. Known amount of standards of COQ10 (4, 8, 12 µg/ml) and PRAVASTATIN (2, 4 and 6 µg/ml) were spiked to a prequantified sample (4 and 8 µg/ml for PRAVASTATIN and COQ10, respectively) and the mixtures were analyzed again. The amounts of PRAVASTATIN and COQ10 were determined by measuring the absorbances and by fitting these values into the regression equation of the calibration plots. The % recovery was found in the range of 99.75 - 100.23% for PRAVASTATIN (Table 4) and 99.71-100.5 %for COQ10 (Table 5).

Precision

Repeatability

The repeatability of measurement of absorbance was checked by repeatedly measuring (n = 7) absorbance of same concentration of PRAVASTATIN (12 µg/ml) and COQ10 (30 µg/ml). The relative standard deviations for the same are 0.72 for PRAVASTATIN; and 1.34 for COQ10, respectively (Table 6).

Intermediate precision

The Intermediate precision of the proposed method was assessed by estimating the corresponding responses (n = 3) for 5 different concentrations (2, 4, 6, 8, 10, 12 µg/ml) for PRAVASTATIN and (5, 10, 15, 20, 25, 25, 30 µg/ml) for COQ10 on the same day (Intraday) (Table 7), and on the different days (Interday) (Table 8). The results are reported in terms of relative standard deviation.

LOD and LOQ

The limits of detection (LOD) and quantification (LOQ) were calculated from the standard deviation (SD) of y-intercepts and slope (S) of the calibration plots using

equations LOD = 3.3 × SD/S and LOQ = 10 × SD/S as per International Conference on Harmonization (ICH) guidelines. The detection and quantification limits obtained by this method were 0.30 and 0.92 µg for PRAVASTATIN; while 0.32 and 0.99 µg for COQ10, respectively, which indicates the sensitivity of the method (Table 9).

Simultaneous estimation of PRAVASTATIN and COQ10 in pharmaceutical dosage form

The proposed method was applied to analyze the combined formulated dosage form of PRAVASTATIN and COQ10. Formulated preparation was analyzed by the proposed method. The amount of PRAVASTATIN and COQ10 was found to be 99.5 and 98.5 % of the labeled amount respectively. Thus, the developed first order derivative spectrophotometric method is Simple, rapid, precise, accurate and economical. It can be applied for routine analysis of PRAVASTATIN and COQ10 combined dosage forms.

CONCLUSION

The proposed first order derivative Spectrophotometric method is accurate, Simple, rapid and selective for Simultaneous estimation of PRAVASTATIN and COQ10 in formulated tablet dosage form and synthetic mixture.

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Table 1.

Linear Regression data of the calibration plots for PRAVASTATIN and COQ10 (n=3)

Parameter	PRAVASTATIN	COQ10
Linearity range (µg/ml)	2-12	5-30
Correlation coefficient (r)	0.999	0.999
Slope	0.004	0.0006
Intercept	0.001	0.0006

Table 2.

Results of recovery studies for PRAVASTATIN in tablets (n=3)

Amount of PRAVASTATIN in sample (µg/ml)	Amount of Std PRAVASTATIN added (µg/ml)	Total amount of PRAVASTATIN (µg/ml)	Spicked amount of PRAVASTATIN (µg/ml) (n=3)	% Recovery Mean (n=3)
4	2	6	1.98	99.46
4	4	8	3.95	98.92
4	6	10	5.96	99.60

Table 3.

Results of recovery studies for COQ10 in tablets (n=3)

Amount of COQ10 in sample (µg/ml)	Amount of Std COQ10 added (µg/ml)	Total amount of COQ10 (µg/ml)	Spicked amount of COQ10 (µg/ml) (n=3)	% Recovery Mean ± SD
8	4	12	4.02	100.50
8	8	16	7.96	99.58
8	12	20	11.93	99.43

Table 4.

Results of recovery studies for PRAVASTATIN in Synthetic mixture (n=3)

Amount of PRAVASTATIN in sample (µg/ml)	Amount of Std PRAVASTATIN added (µg/ml)	Total amount of PRAVASTATIN (µg/ml)	Spicked amount of PRAVASTATIN (µg/ml) (n=3)	% Recovery Mean (n=3)
4	2	6	2.00	100.23
4	4	8	3.99	99.75
4	6	10	6.00	100.6

Table 5.

Results of recovery studies for COQ10 in synthetic mixture (n=3)

Amount of COQ10 in sample (µg/ml)	Amount of Std COQ10 added (µg/ml)	Total amount of COQ10 (µg/ml)	Spicked amount of COQ10 (µg/ml) (n=3)	% Recovery Mean ± SD
8	4	12	4.02	100.50
8	8	16	8.03	100.40
8	12	20	11.96	99.71

Table 6.

Repeatability data for COQ10 and PRAVASTATIN

Concentration(µg/ml)		% C.V. (n=7)	
COQ10	PRAVASTATIN	PRAVASTATIN	COQ10
30	12	0.72	1.34

Table 7.

Intraday precision data for PRAVASTATIN and COQ10

Concentration (µg/ml)		% C.V. (n=3)	
PRAVASTATIN	COQ10	PRAVASTATIN	COQ10
2	5	1.05	0.95
4	10	1.23	1.25
6	15	1.2	1.62
8	20	1.2	1.68
10	25	0.62	1.37
12	30	0.67	1.11

Table 8.
Interday Precision data for PRAVASTATIN and COQ10

Concentration (µg/ml)		% C.V. (n=3)	
PRAVASTATIN	COQ10	PRAVASTATIN	COQ10
2	5	1.20	1.91
4	10	1.55	1.83
6	15	1.37	1.85
8	20	1.55	1.88
10	25	0.73	1.91

Table 9.
LOD and LOQ

PRAVASTATIN	**COQ10**
LOD=3.3 x (SD/Slope)	LOD=3.3 x (SD/Slope)
LOD=3.3x (0.000333/0.0036)	LOD=3.3x (0.000099/0.001)
LOD=0.30µg/ml	LOD=0.32µg/ml
LOD=10 x (SD/Slope)	LOD=10 x (SD/Slope)
LOD=10x (0.000333/0.0036)	LOD=10x (0.000099/0.001)
LOD=0.92µg/ml	LOD=0.99µg/ml

Table 10.

Results of Assay of formulated tablet dosage forms

	mg/tablet	Assay(n=5)	
PRAVASTATIN	COQ10	PRAVASTATIN	COQ10
20	40	99.5	98.5

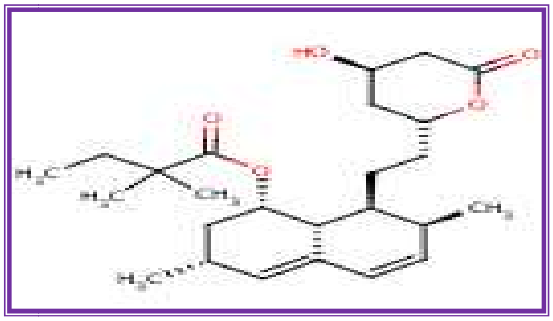

Figure 1. Chemical Structure of Pravastatin

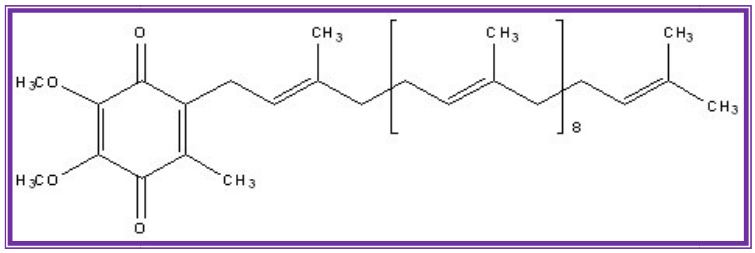

Figure 2. Chemical Structure of COQ10uvastatin Calcium

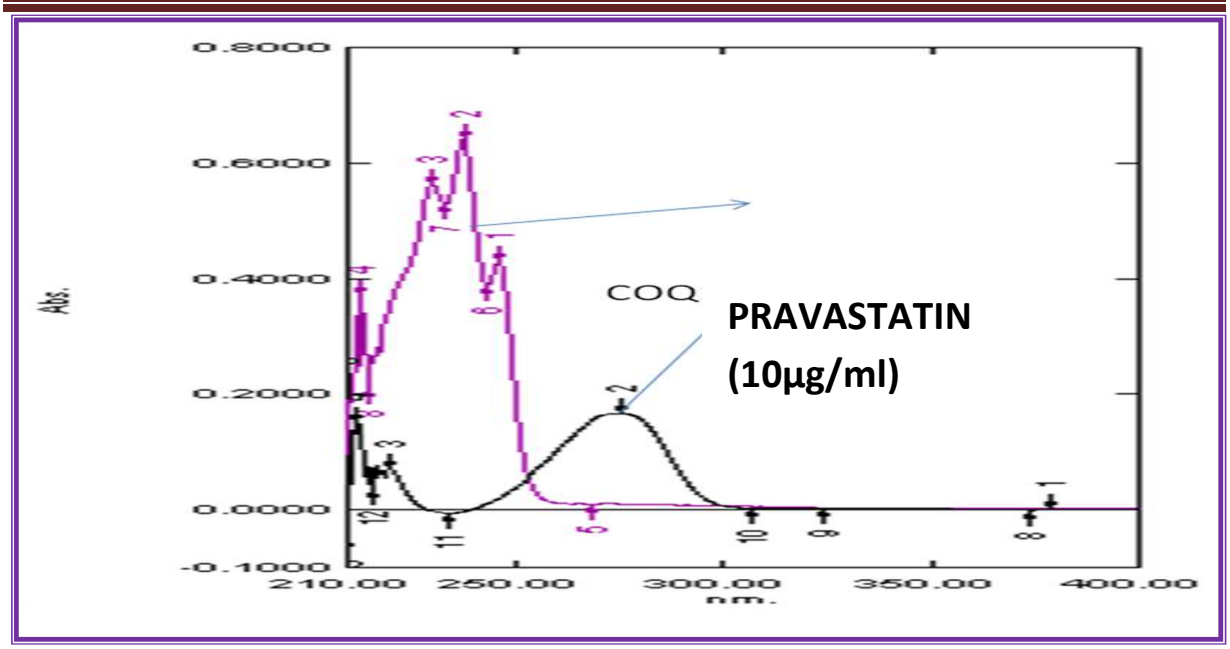

Figure 3. Overlain zero order spectra of PRAVASTATIN (10 µg/ml) and COQ10 (10 µg/ml) in methanol:IPA (50:50%v/v)

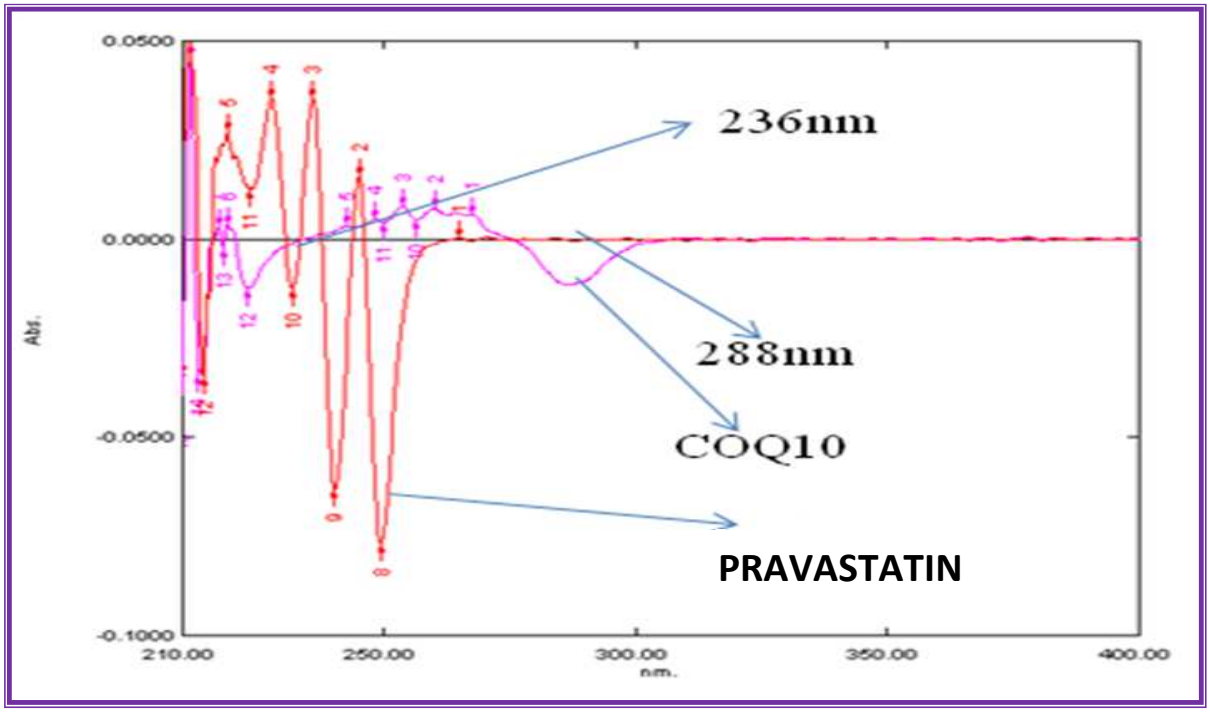

Figure 4. Overlain first order spectra of PRAVASTATIN (10 µg/ml) and COQ10 (10 µg/ml) in methanol:IPA (50:50%v/v)

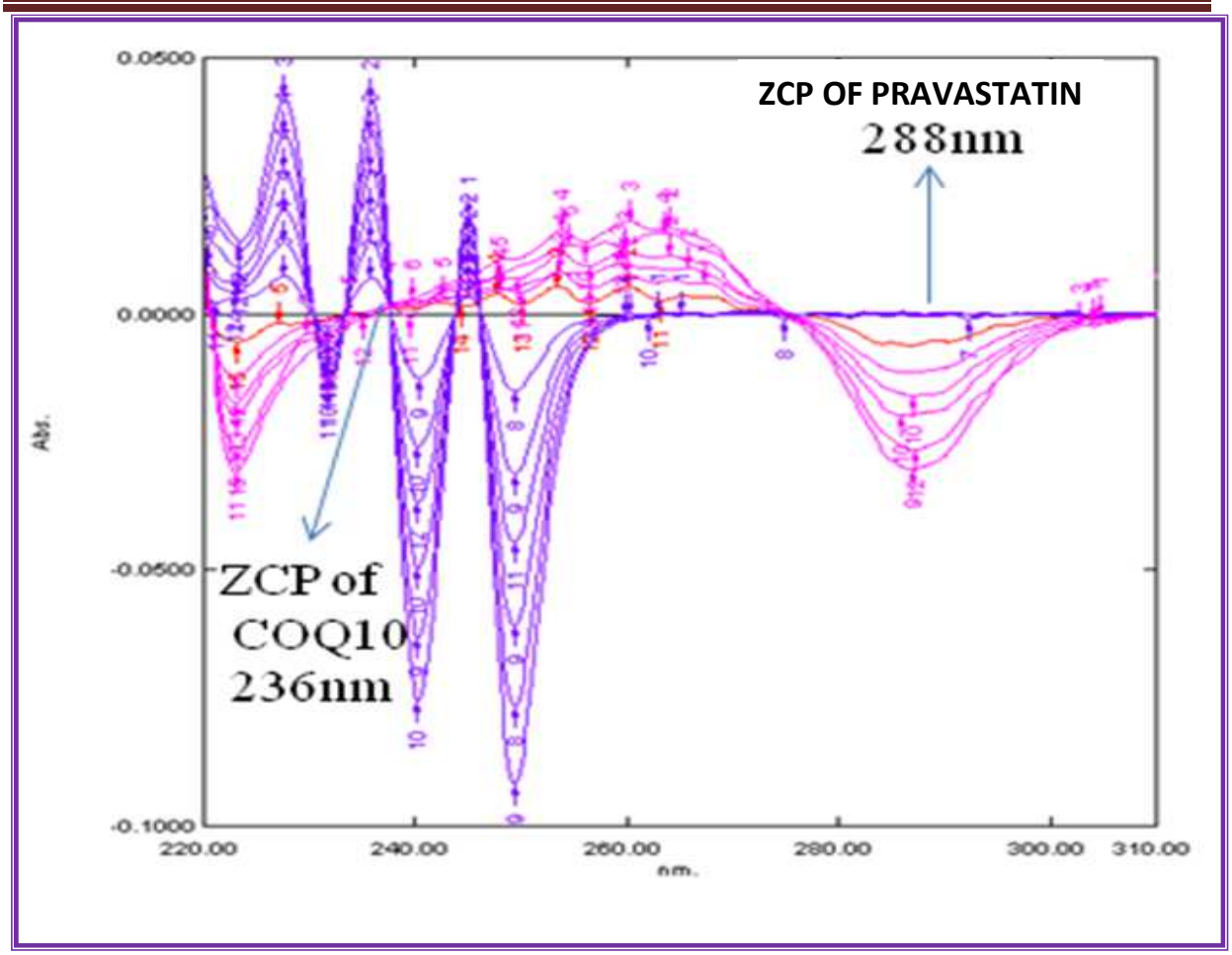

Figure 5. Overlain first order spectra of PRAVASTATIN (2-12 µg/ml) and COQ10 (5-30 µg/ml) in methanol:IPA (50:50%v/v)

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