ORIGINAL ARTICLE

Method development of ramipril and atorvastatin calcium capsule by using simultaneous equation method and absorbance ratio method

J. S. Rajawat, P. Dadeech, A. D. Ankalgi, M. S. Ranawat, M. S. Panwar[1]

Department of Pharmaceutics, B.N. College of Pharmacy, Udaipur, Rajasthan, [1]Department of Pharmaceutical Chemistry, Mandsaur Institute of Pharmacy, Mandsaur, Madhya Pradesh, India

Ramipril is an angiotensin-converting enzyme inhibitor and atorvastatin calcium is inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase used in the treatment of hypertension. Simple, precise, rapid and selective simultaneous equation and Q-analysis methods have been developed for the simultaneous determination of ramipril and atorvastatin from combined capsule dosageforms. The methods involve solving of simultaneous equations and Q-value analysis based on measurement absorptivity at 210.030 and 246.828 nm, respectively. Linearity lies between 2 and 25 mcg/ml for both drugs.

Key words: *Absorbance ratio method, atorvastatin, ramipril, simultaneous equation*

INTRODUCTION

Ramipril is a prodrug belonging to the angiotensin-converting enzyme used in the treatment of hypertension, congestive heart failure, and nephropathy. Chemically it is 1-(2-[1-ethoxy-1-oxo-4-phenylbutan-2-ylamino] propanoyl) octahydrocyclopenta (b) pyrrole-2-carboxylicacid [Figure 1]. Atorvastatin calcium is a competitive inhibitor of 3-hydroxy-3-methylglutaryl- CoA reductase used as anticholesteremic agent. Chemically it is 7-(2-[4-fluorophenyl]-5-isopropyl-3-phenyl-4-[phenylcarbamoyl] 1H- pyrrol- 1- yl)- 3,5-dihydroxyheptanoic acid [Figure 2]. The review of the literature revealed that no precise, cost-effective and accurate method is yet reported for the simultaneous estimation of both the drugs in combined dosage forms. This paper describes two simple, rapid, accurate, reproducible, and economical methods for the simultaneous estimation of ramipril and atorvastatin calcium in commercial formulation (polyatorva) by using ultraviolet-visible spectrophotometer.[1-3]

EXPERIMENTAL

Preparation of standard solution

Accurately weighed ramipril and atorvastatin calcium (10 mg) was transferred into 100 ml volumetric flask, volume make up to 100 ml by methanol. The final solution contained 100 μg/ml of the drug.

Selection of sampling wavelength

The spectra of two drugs ramipril and atorvastatin calcium were present in Figure 3, wavelengths for the simultaneous analysis of two drugs were selected. From this spectrum, it was observed that wavelength that could be utilized were 210.030 nm and 246.828 nm, respectively. Linearity was observed for ramipril and atorvastatin calcium in the concentration range of 2-25 μg/ml.

Method-1 simultaneous equation method

Determining absorptivity of the drugs and framing simultaneous equations

The absorptivity of ramipril and atorvastatin calcium were determined at two selected wavelengths. The absorptivity values of two drugs are used for framing the simultaneous equation.[3-4] The absorptivity values with respect to four independent estimations are, as;

- Absorptivity of ramipril at 210.030 nm (ax_1) = 0.2458

Address for correspondence:
Prof. J. S. Rajawat,
Department of Pharmaceutics, B.N. College of Pharmacy,
Udaipur - 313 002, Rajasthan, India.
E-mail: jeetu_rajawat@yahoo.co.in

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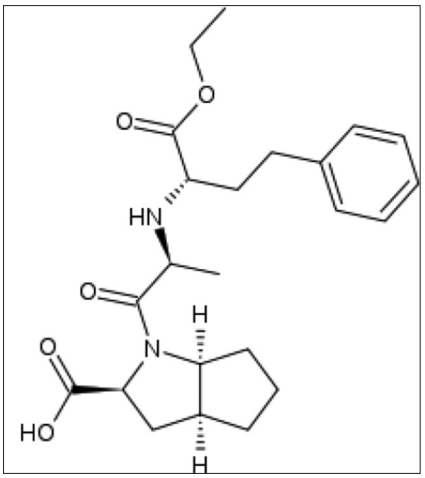

Figure 1: Ramipril

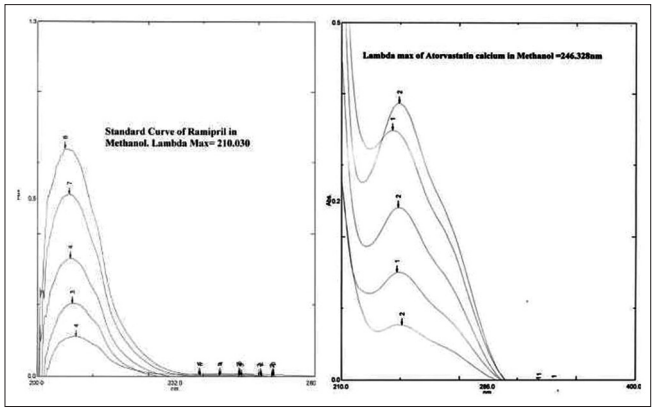

Figure 3: Ultraviolet spectra of ramipril and atorvastatin calcium

- Absorptivity of ramipril at 246.828 nm (ax_2) = 0.0117
- Absorptivity of atorvastatin calcium at 246.828 nm (ay_1) = 0.2738
- Absorptivity of atorvastatin calcium at 210.030 nm (ay_2) = 0.1495.

Set of two simultaneous equations for simultaneous estimation of ramipril and atorvastatin calcium using these absorptivity values are as:

$$A_1 = 0.2458C_x + 0.117 \times C_y \quad (1)$$

$$A_2 = 0.2738C_x + 0.1495C_y \quad (2)$$

Where,
C_x and C_y are concentrations of ramipril and atorvastatin in g/1000 ml in the sample solution.

A_1 and A_2 are the absorbances of the mixture at 210.030 and 246.828 nm, respectively.

The concentration of C_x and C_y can be calculated from the above-framed equations.

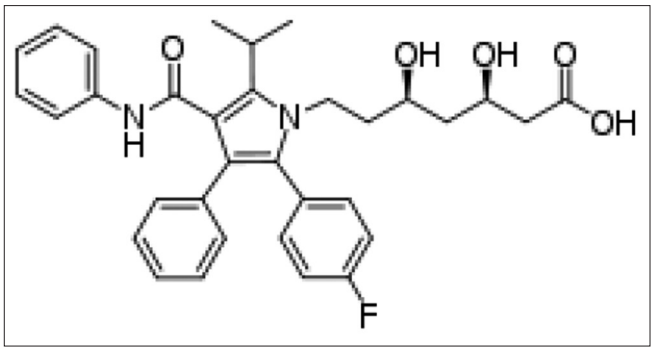

Figure 2: Atorvastatin Calcium

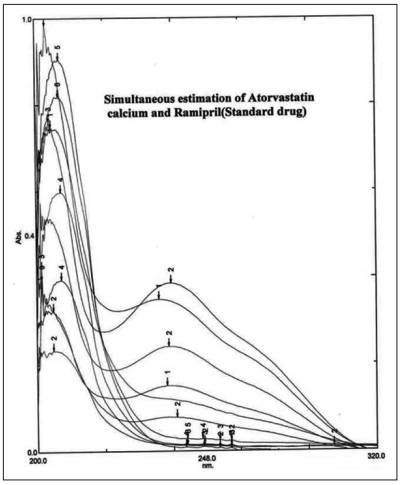

Figure 4: Ultraviolet spectra of atorvastatin calcium and ramipril using mixed standard (simultaneous equation)

Standardization of the method by analysis of laboratory prepared sample

To check the validity of above framed equations four mixed standards were prepared using pure sample of two drugs. The absorbance of these mixed standards were measured at respective wavelengths and compared with absorbance calculated using above framed equations. The concentrations of two components of mixed standards were calculated using above framed equations. The results of validation studies are reported in Table 1.

Procedure for analysis of capsule formulation (polyatorva)

Twenty tablets (Ramipril - 2.5 mg and atorvastatin calcium - 10 mg) were weighed accurately and average weight per capsule was determined. The powder equivalent to 2.5 mg of ramipril and 10 mg atorvastain calcium was weighed and extracted with 40 ml of solvent, sonicated for 10 min. The resultant was filtered through Whatman filter paper number 41 into 100 ml volumetric flask. The filter paper was washed several times with a solvent. The washings were added to the filtrate, and final volume was made up to the mark with the same. Filtrate (0.5 ml) of the sample solution was diluted to 10 ml with solvent. The absorbance of this final dilution was measured at 210.030 nm and 246.828 nm respectively, and concentration of two drugs in

the sample was calculated using above framed simultaneous Equations 1 and 2.

The procedure of analysis for formulation was repeated 5 times with two different formulations and results are reported in Table 2.

Method II: Q-absorbance method (ramipril and atorvastatin calcium)

Determining absorptivity of the drugs and framing equations

The absorptivity of ramipril and atorvastatin were determined at two selected wavelengths. The absorptivity values of two drugs are used for framing the equation. The absorptivity values with respect to four independent estimations are as follows;[5-8]

- Absorptivity of ramipril at 210.030 nm (ax_1) = 0.2458
- Absorptivity of ramipril at 246.828 nm (ax_2) = 0.0117
- Absorptivity of atorvastatin calcium at 246.828 nm (ay_1) = 0.2738
- Absorptivity of atorvastatin calcium at 210.030 nm (ay_2) = 0.1495.

Set of two equations for simultaneous estimation of ramipril and atorvastatin using these absorptivity values are as:

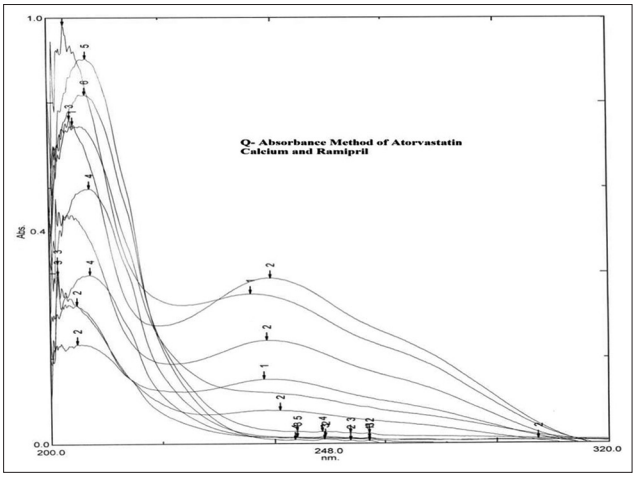

Figure 5: Ultraviolet spectra of atorvastatin calcium and ramipril using mixed standard (Q-method)

$$C_x = (Q_M - Q_Y)\, A_1 / (Q_X - Q_Y)\, a_{x1} \quad (1)$$

$$C_y = A_1 - A_{x1} C_x / A_{y1} \quad (2)$$

Where,

$Q_X = ax_2/ax_1$,

$Q_Y = a_{y2}/a_{y1}$,

$Q_M = A_2/A_1$

C_x and C_y are concentrations of ramipril and atorvastatin calcium in g/1000 ml in the sample solution.

A_1 and A_2 are the absorbances of the mixture at 210.030 and 246.828 nm respectively.

The concentration of C_x and C_y can be calculated from the above-framed equations.[5-8]

Standardization of the method by analysis of laboratory prepared sample

To check the validity of above framed equations three mixed standards were prepared using pure sample of two drugs. The absorbance of these mixed standards was measured at respective wavelengths and compared with absorbance calculated using above framed equations. The concentrations of two components of mixed standards were calculated using above framed equations. The results of validation studies are reported in Table 3.

Procedure for analysis of capsule formulation (polyatorva)

Twenty tablets (Ramipril - 2.5 mg and atorvastatin calcium - 10 mg) were weighed accurately, and average weight per capsule was determined. The powder equivalent to 2.5 mg of ramipril and10 mg atorvastatin calcium was weighed and extracted with 40 ml of solvent, sonicated for 10 min. The resultant was filtered through Whatman filter paper number 41 into 100 ml volumetric flask. The filter paper was washed several times with a solvent. The washings were added to the filtrate, and final volume was made up to the

Table 1: Result of validation studies of simultaneous equation method using mixed standards

Concentration (µg/ml)		Absorbance (nm)		Percentage of concentration	
Ramipril	Atorvastatin	210.015	246.828	Ramipril	Atorvastatin
2	8	0.09	0.097	98.87	99.71
4	6	0.167	0.194	99.52	99.79
6	4	0.24	0.281	99.54	99.51
8	2	0.321	0.359	99.71	98.76

Table 2: Results of analysis of commercial formulations

Brand name	Label claim (mg/capsule)		Percentage of label claim estimated*		±SD	
	Ramipril	Atorvastatin	Ramipril	Atorvastatin	Ramipril	Atorvastatin
Polyatorva	2.5	10	98.76	98.88	0.2515	0.2213

*Each value is an average of five determinations. SD: Standard deviation

Table 3: Result of validation studies of Q-absorbance method using mixed standards

Concentration (µg/ml)		Absorbance (nm)		Percentage of concentration	
Ramipril	Atorvastatin	225.264	246.828	Ramipril	Atorvastatin
3	7	0.378	0.582	99.60	98.74
5	5	0.457	0.598	98.35	100.00
7	3	0.561	0.497	99.91	100.00

Table 4: Results of analysis of commercial formulations

Brand name	Label claim (mg/capsule)		Percentage of label claim estimated*		±SD	
	Ramipril	Atorvastatin	Ramipril	Atorvastatin	Ramipril	Atorvastatin
Polyatorva	2.5	10	99.58	99.74	0.3584	0.1784

*Each value is an average of five determinations. SD: Standard deviation

Table 5: Result of recovery studies

Brand name	Label claim (mg/capsule)		Amount of added to final dilution (µg/ml)		Amount of recovered (µg/ml)		Percentage of recovery	
	Ramipril	Atorvastatin	Ramipril	Atorvastatin	Ramipril	Atorvastatin	Ramipril	Atorvastatin
Polyatorva	2.5	10	1	1	0.998	0.990	99.39	98.87
			2	2	1.994	1.980	98.43	99.35
			3	3	2.987	2.981	99.57	99.46

mark with the same. Filtrate (0.5 ml) of the sample solution was diluted to 10 ml with solvent. The absorbance of this final dilution was measured at 210.030 nm and 246.828 nm, respectively, and concentration of two drugs in the sample was calculated using above framed Equations 1 and 2.

The procedure of analysis for capsule formulation was repeated 5 times and results are reported in Table 4.

Recovery studies

Recovery studies were carried out for the formulation by addition of known amount of standard drug solution to preanalyzed capsule sample solution at three different concentration levels. The resulting solutions were analyzed by proposed method. The results of recovery studies were found to be satisfactory and are results are reported in Table 5.

RESULTS AND DISCUSSION

The proposed methods for simultaneous estimation of ramipril and atorvastatin calcium in capsule dosage forms were found to be simple, accurate, economical and rapid. In both the methods, the values of the coefficient of variation were satisfactorily low, and recovery was close to 100% for both the drugs.

CONCLUSION

The proposed method is simple, precise, accurate and rapid for the determination of ramipril and atorvastatin calcium in combined capsule dosage forms. This method can be adopted as an alternative to the existing spectrophotometric methods. Analysis of authentic samples containing ramipril and atorvastatin calcium showed no interference from the common additives and excipients. Hence, recommended procedure is well suited for the assay and evaluation of drugs in pharmaceutical preparations. It can be easily and conveniently adopted for routine quality control analysis.

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