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BILAYER TABLET OF ROSUVASTATIN CALCIUM AND FENOFIBRATE: AN ASSESSMENT PRIOR TO FORMULATION DESIGN

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ABSTRACT

A simple, specific and accurate HPLC method was developed for the estimation of Rosuvastatin Calcium (RSTCa) and Fenofibrate (FB) in combination. The separation of two drugs using steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µ*m*),with mobile phase containing Acetonitrile: Methanol: phosphoric acid (50:25:25v/v) was used and eluents were monitored at 286nm. The retention times of RSTCa and FB were 2.45±0.03 and 5.856±0.03min, respectively and both the drugs showed good linearity with a correlation coefficient (R) of 0.9999 and 0.9997 for RSTCa and FB, respectively. The proposed methods have been successfully applied to pharmaceutical formulation and were validated according to ICH guidelines and method showed good precision with percent relative standard deviation less than 2%. The proposed method was accurate and precise for the HPLC estimation of RSTCa and FB in bulk and pharmaceutical dosage forms.

KEYWORDS: Rosuvastatin Calcium, Fenofibrate**,** HPLC estimation, Validation, precision.

INTRODUCTION

RSTCa (Rosuvastatin Calcium) is an anti-hyperlipidemic. It acts by 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibition mainly in the hepatocyte cell of the liver. RSTCa is available as the immediate release formulation which releases the content within 60 minutes. The rate of the release is greater than the rate of the absorption by the carrier on the hepatocyte. So the drug goes systemic circulation produce the unwanted effect drug. Therefore if the rate of release of RSTCa in such a way that it will result in very low systemic concentration and in turn reduce systemic side effect. The drug will remain expose to liver longer period of time and will be more effective than the conventional dosage form. It will improve the effectiveness and reduced the incidence of the side effect of the RSTCa.[1,2,3]

FB (Fenofibrate) is official in Indian Pharmacopoeia. It is chemically Propane-2-yl-[4-(4- chlorobenzoyl) phenoxy]-2-methyl propanate It is the lipid regulating drug. FB increases lipolysis and elimination of triglyceride- rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). Literature survey revealed the various analytical methods such as validated spectrophotometric determination of FB in formulation. Three simple spectrophotometric methods for FB in tablet formulation has been reported for estimation of FB from its formulation. Development and validation of HPLC method for the estimation of FB. In present study an attempt has been made to develop simple, precise, accurate HPLC methods for the simultaneous determination of RSTCa and FB in bulk and in dosage form.

MATERIALS AND METHODS

Materials

Pharmaceutical grade RSTCa and FB were obtained as a gift samples by MSN House, Plot No. C-24, Industrial Estate, Sanath Nagar, Hyderabad, Telangana, India and Plot No 545, Shanti Nagar, Shanti Nagar, Nagpur, Maharashtra, India. These samples were used without further purification and certified to contain 99.65% w/w and 99.89 % w/w, respectively on dried basis. Rozavel-FLS containing 10 mg of RSTCa and 80 mg FB was obtained from a Hetero Pharmacy, Hyderabad. Methanol (HPLC grade), Acetonitrile (HPLC grade), water for HPLC, were purchased from RANKEM Chemicals Limited, MERK Chemicals Limited.

HPLC Method

LC system used consisted of pump (model Shimadzu; LC–2010HT ATvp solvent deliver module) with universal loop injector (Rheodyne 7725 i) of injection capacity 20µL. Detector consists of UV-Visible detector SPD-10 Avp, Shimadzu; the column used stainless steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µ*m*), at 30^0ctemperature.

Different mobile phases were tested in order to find the best conditions, for separating both the drugs simultaneously. The optimal composition of mobile phase was determined to be Acetonitrile: Methanol: phosphoric acid (50:25:25v/v). The flow rate was set to 5ml/min and HPLC detection was carried out at 286nm.

Table.1: Chromatographic Conditions of the given experiment.

Column	**Stainless steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µ*m)***
Detector	Variable
Wavelength	286nm
Injection volume	20 µl
Flow rate	5ml/min
Temperature	30^0C
Run time	15 min
Mobile phase	Acetonitrile: Methanol: phosphoric acid (50:25:25)

Preparation of Standard Stock Solution

Accurately weighed quantities of 5mg and 10mg of RSTCa and FB were dissolved in sufficient quantity of mobile phase in a 10ml volumetric flask. The volume was adjusted up to the mark with mobile phase to obtain the stock solution of 400µg/ml to 1200µg/ml and 40 to 120 µg/ml concentrations respectively.

Assay

Twenty tablets containing RSTCa (10mg) and FB (80mg) were taken and crushed to fine powder. Then powder equivalent to 10mg to FB was taken in 10ml volumetric flask and dissolved in mobile phase. It was sonicated for 5-10min. Solution was filtered through whatmann filter paper. From 1000µL of filtrate was further diluted with the mobile phase toget a solution containing 100µg/ml. From the above solution each 4.8ml was taken which contains 6µg/ml of RSTCa and 48 µg/ml of FB. The solution was injected three times into the column. The amount present in the each tablet was calculated by comparing the areas of standards with the test samples.

VALIDATION OF THE METHOD

Linearity

The linearity responses in the concentration range of 40-120µg/ml and 400-1200µg/ml for RSTCa and FB were determined and the data was given in Table 2.

Precision

Precision was measured in terms of repeatability of application and measurement. Study was carried out by injecting six replicates of the standard concentrations of10µg/ml and 80µg/ml for RSTCa and FB. The precision values were given in Table 4.

Accuracy

Accuracy of the method was ascertained by performing recovery studies. Recovery studies were carried out by addition of standard drug solution to pre-analysed tablet sample solution at three different concentrations levels (80%,100%, and 120%) within the range of linearity. Results of recovery studies were shown in Table 5.

System suitability

System suitability was carried out by injecting10µg/ml and 80µg/ml of RSTCa and FB at different injection volumes 10-50µg/ml within crement of injection volumes, the %RSD fortailing factor and theoretical plate number was less than 1% and is satisfactory.

LOD and LOQ

The LOD and LOQ values were determined by formulae LOD = 3.3 σ/m and LOQ = 10 σ/m(where, σ is the standard deviation of the responses and m is the mean of the slope ofthe calibration curve)

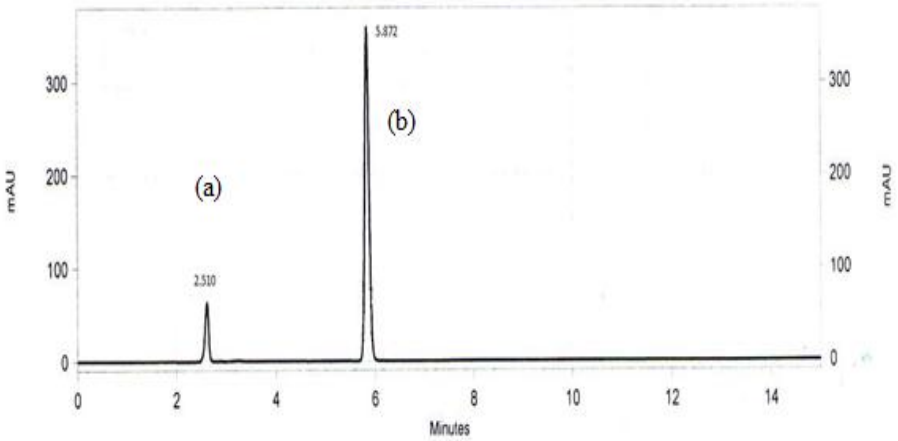

Figure 1: Chromatogram of (a) Rosuvastatin Calcium and (b) FB

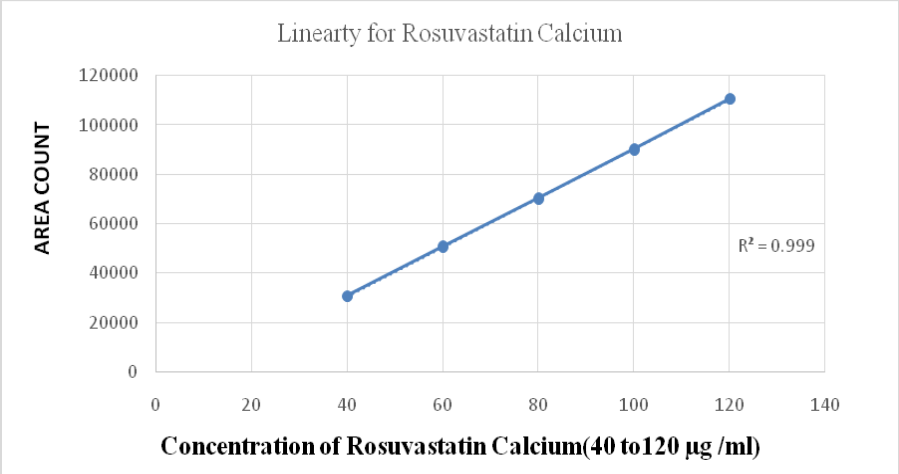

Figure 2: Calibration curve ofRosuvastatin Calcium

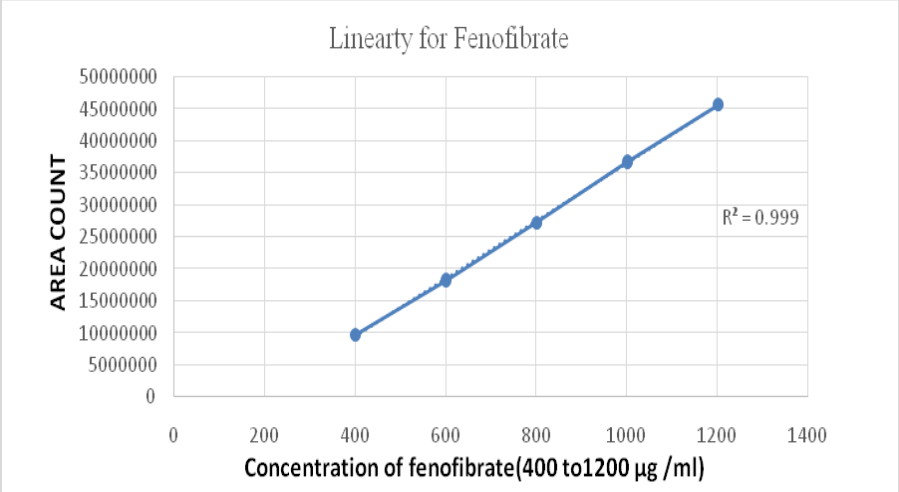

Figure 3: Calibration curve of FB

Table 2. Linearity

Se. No	Rosuvastatin Calcium			FB		
	Conc. (µg/ml)	Retention time (min)	Peak area	Conc. (µg/ml)	Retention time (min)	Peak area
1	40	2.3	30845	400	5.8	9763487
2	60	2.467	50753	600	5.87	18220557
3	80	2.49	70254	800	5.87	27226901
4	100	2.5	90095	1000	5.87	36703491
5	120	2.5	110568	1200	5.87	45579141
CORRELATION (R)	0.9999			0.9997		

Table 3: System suitability studies.

Parameters	Rosuvastatin calcium	FB	Limit
Retention time (min)	2.51	5.87	
Theoretical plates (N)	7930	16628	N > 2000
Tailing factor (T)	1.42	1.52	T of < 2
Resolution (Rs)	3.5		Rs of > 2

Table 4: Precision.

Drugs	Rosuvastatin Calcium	FB
Mean	70503	27498715
Standard Deviation	42622.94	17329052
%RSD	0.604555	0.630177

Table 5: Accuracy

Drugs	Spiked level (%)	Amount taken (µg/ml)	Amount found (µg/ml)	Percent recovery (% w/w)
RSTCa	80	6.5	6.41	99.5
	100	8	8.04	100.15
	120	9.5	9.49	99.89
FB	80	50	49.91	99.99
	100	65	64.95	99.99
	120	75	75.01	99.98

RESULTS AND DISCUSSION

HPLC methods was found to be simple, accurate, economic and rapid for routine simultaneous estimation of RSTCa and FB in bulk and in tablet dosage forms. In HPLC method, HPLC conditions were optimized to obtain an adequate separation of eluted compounds. Mobile phase and flow rate selection was based on peak parameters (height, tailing, theoretical plates), run time etc. The system with Acetonitrile: Methanol: Phosphoric acid (50:25:25 v/v) with 5 ml/min flow rate is quite robust. The optimum wavelength for detection was 286nm at which better detector response for drugs was obtained. The average retention times for RSTCa and FB was found to be 2.45±0.03 and 5.856±0.03min, respectively (Figure 1).

The calibration curve was linear in concentration range of 40–120 µg/ml for RSTCa and 400- 1200 µg/ml for FB. The correlation coefficient was found to be 0.9999 and 0.9997 for RSTCa and FB, respectively(Table 2). The intercept value was found to be 9012.2 for RSTCa and 0.000009 for FB. The slope was found to be 993.94 and 45057 for RSTCa and FB, respectively.

The proposed method was found to be linear. Sample to sample precision and accuracy were evaluated using three samples at three different concentrations, which were prepared and analyzed on same day. Interday variability was assessed using three concentrations analyzed on three different days, over a period of one week. Results revealed the accuracy and reproducibility of the assay. Thus, it was concluded that there was no significant difference on the assay, which was tested on intra-day and inter day basis.

The % R.S.D. values was found to be 0.604555 and 0.630177 for RSTCa and FB respectively(Table 4). These values proposed that HPLC methods provide acceptable intra-day and inter day variation of RSTCa and FB. The % RSD values were found to be less than 2% (Table 4).

Precision is reflected by %RSD as 0.815 for RSTCa and 0.751 for FB which was less than 2.The method was specific since excipients in the formulation did not interfere in the estimation of RSTCa and FB. Accuracy of the method was indicated by the recovery values 98.9-100.7% for RSTCa and FB (Table 5).

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