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Simultaneous Estimation of Metoprolol Succinate and Olmesartan Medoxomil in Pharmaceutical Dosage Form by RP-HPLC

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Abstract

A simple, precise, specific and accurate reverse phase HPLC method has been developed for the simultaneous determination of Metoprolol succinate (METO) and Olmesartan medoxomil (OLME) in tablet dosage form. The chromatographic separation was achieved on inertsil ODS 3V (250 mm×4.6 mm, 5 µm) column using PDA detector. The mobile phase consisting of Buffer (2 ml O-phosphoric acid in 2000 ml milli-Q Water) and Acetonitrile in the ratio of 50:50 (v/v) at a flow rate of 1.0 mL/min was used. And the compounds were detected by a UV-detector at 220 nm at a column temperature of 25 ± 2°C. The retention time and drug content of Metoprolol succinate and Olmesartan medoxomil were 1.6 min, 100.2% and 2.4 min, 100.1%, respectively. The method was validated according to the ICH guidelines with respect to specificity, linearity (r^2=0.999), accuracy (100 to 99.8%), precision and robustness (RSD<2%).

Keywords: Metoprolol succinate; Olmesartan medoxomil; RP-HPLC; Simultaneous determination; Validation

Introduction

Metoprolol succinate (METO) is chemically (RS)-1-(Isopropyl amino)-3-[4-(2-methoxyethyl) Phenoxy] propan-2-ol succinate [1], it is a cardio selective β-blocker and used in the treatment of hypertension, angina pectoris, arrhythmia, myocardial infarction and heart failure [2]. It is official in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP) and United States Pharmacopoeia (USP). IP [3], BP [4] and USP [5] describe potentiometric method for its estimation. Various methods are there for the determination of this drug like UV Spectrophotometric method, HPLC method for determination of Metoprolol, Atenolol and Propranolol in plasma and urine [6,7], Simultaneous determination of Metoprolol succinate and Amlodipine besylate in human plasma by liquid chromatography–tandem mass spectrometry method and its application in bioequivalence study [8], LC-MS method for estimation of Metoprolol succinate and Ramipril [9], HPTLC method for estimation of Metoprolol succinate and Atorvastatin in capsule [10].

Olmesartan medoxomil (OLME) is chemically (5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1*H* imidazole-5-carboxylate [11], is a angiotensin II receptor antagonist for the treatment of hypertension [12]. Various methods are there for the determination of this drug derivative and quantitative analysis of spectrophotometric method estimation of Hydrochlorothiazide and Olmesartan medoxomil in tablets [13], Simultaneous quantitative determination of Olmesartan And Hydrochlorothiazide in human plasma and urine by liquid chromatography coupled to tandem mass spectrometre [14], New RP-HPLC method for the determination of Olmesartan medoxomil in tablet dosage form [15], Development and validation of a reversed phase HPLC method for simultaneous estimation of Olmesartan and Hydrochlorothiazide in combined tablet dosage form [16], HPLC and HPTLC method for quantitation of Amlodipine Besylate and Olmesartan medoxomil in bulk drug and formulation [17], Stability-indicating LC method for the determination of Olmesartan in bulk drug and in pharmaceutical dosage form [18]. The combined dosage forms of METO and OLME are available in the market for the treatment of hypertension. Literature survey does not reveal any simple spectroscopic method for determination of METO and OLME in combined dosage form. The present manuscript describes simple, sensitive, accurate, precise, rapid and economic spectrophotometric method based on simultaneous equations for simultaneous estimation of METO and OLME in tablet dosage form.

Materials and Methods

Instrumentation

HPLC system (Agilent technology) consisting of gradient pump, Auto sampler, column oven and photodiode array detector (PDA, Agilent technology) was employed for analysis. Chromatographic data was acquired using chemstation software.

Reagents and materials

Metoprolol succinate and Olmesartan medoxomil active pharmaceutical ingredient were supplied by Cadila Healthcare Limited (Ahmedabad, India). The commercial fixed dose combination obtained from local market. Acetonitrile (HPLC, Spectrochem Pvt. Ltd., India), Methanol (HPLC, Spectrochem Pvt. Ltd., India), Milli-Q Water.

Chromatographic condition

Inertsil ODS 3V (250 mm×4.6 mm, 5 µm) column was used as a stationary phase. The mobile phase consisting of a mixture of buffer (2 ml O-phosphoric acid in 2000 ml milli-Q Water) and Acetonitrile in the ratio of 50:50 (v/v) was used throughout the analysis. The flow rate of the mobile phase was 1.0 mL/min. Detector signal was monitored at a wavelength of 220 nm. The column temperature was kept 25°C and injection volume was 50 µl.

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Preparation of standard stock solutions

The standard stock solution was prepared by transferring 25 mg Metoprolol succinate and 20 mg Olmesartan medoxomil in a 100 ml volumetric flask. Then each 5 ml solution was diluted in a 50 ml volumetric flask to obtain final standard concentration of Metoprolol succinate and Olmesartan medoxomil 25 µg/ml and 20 µg/ml, respectively.

Preparation of sample solution

Accurately 20 intact tablets were weighed to determine average weight of tablets. Then tablets were finely crushed and tablet powder equivalent to 50 mg Metoprolol succinate and 40 mg Olmesartan was transferred into 200 ml volumetric flask. Then 50 ml diluents was added to flask and sonicated for 40 minute with intermittent shaking. Volume is made up to 200 ml. From that solution 5 ml of sample solution was used and made up volume up to 50 ml using 50 ml volumetric flask using diluents. Then solution was filtered through 0.45 µ PVDF Millipore filter and the final concentration of test sample solution had concentration of Metoprolol succinate and Olmesartan medoxomil 25 µg/ml and 20 µg/ml, respectively.

Validation of the Proposed Method

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines [19].

System suitability

The system suitability test as per method should be performed and checked before performing any parameter (%RSD<2%).

Linearity and range

Linearity was determined at five levels over the range of 20% to 150% of test concentration. A standard linearity solution was prepared to different concentration of 20%, 50%, 80%, 100%, 120%, and 150% of the test concentration. Each linearity solution was injected in duplicate.

Method precision (Repeatability)

Six different test samples were prepared from Metoprolol succinate and Olmesartan tablets. The sample should be prepared under the same condition and of same concentration. Then they were injected by one analyst and analysed on same day.

Intermediate precision (Ruggedness)

Same procedure should be followed as in method precision but on a different day, by a different analyst, different HPLC instrument and different column lot using same lot of sample as specified under precision.

Accuracy

The accuracy of the method was carried out at three levels in the range of 50-150% of the working concentration of sample. Calculated amount of METO and OLME working standards were added in placebo containing volumetric flasks to, prepare 50%, 100% and 150% level of the working concentration. Each level was prepared in triplicate manner and each preparation was injected in duplicate.

Specificity

A blank preparation, standard preparation, placebo preparation, sample preparation of METO and OLME and placebo spiked with targeted concentration of both API were prepared and injected.

Robustness

Change following parameters, one by one and observe their effect on system suitability test and assay. Change flow rate by 10%. (i.e. 0.8 ml/min and 1.2 ml/min). Change the minor components in the mobile phase by ± 2% absolute or ± 30% relatively whichever is lower. Change the column temperature by ± 5°C. (i.e. 35°C and 45°C). Change in mobile phase pH by ± 0.2 unit (i.e. pH 2.8 and pH 3.2).

Result and Discussion

The method has provided adequate separation for Metoprolol succinate and Olmesartan medoxomil from their Dosage Form. Separation was obtained by using Inertsil ODS 3V C-18 (250×4.6 mm), 5 µ column at 25°C temperature and using a mobile phase (2 ml phosphoric acid in 2000 ml milli-Q water) buffer and Acetonitrile is also used to make ratio of Buffer: ACN (50:50) at a flow rate 1.5 ml/min and wavelength for detection was 220 nm. The method is specific for the simultaneous estimation of Metoprolol succinate and Olmesartan medoxomil in solid dosage form. Under these optimized conditions, the analyte peaks were well resolved and free from tailing. The tailing factors were <1.5 for both the peaks. The elution order was METO (RT=1.6 min) and OLME (RT=2.4 min), at a flow rate of +1.0 mL/min. A chromatogram of tablet extract was recorded and shown in figure 1 and system suitability was established by injecting standard solution and results are shown in table 1.

Specificity of the chromatograms were checked for the appearance

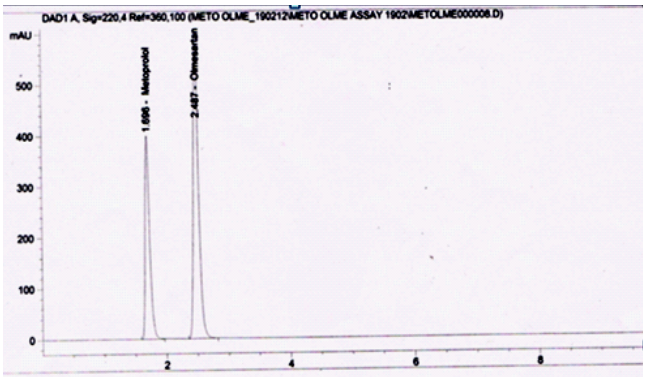

Figure 1: Chromatogram of well separated peak of Metoprolol succinate and Olmesartan medoxomi.

Component	Area	Symmetry	Plate	Resolution	Selectivity
Metoprolol succinate	2019.16	0.7	2875	5.77	1.47
Olmesartan medoxomil	3434.47	0.82	4564		

Table 1: System suitability parameter.

Theoretical (% of target level)	Amount added (actual) (mg)	Amount recovered(mg)	Recovery (%)
Metoprolol succinate			
50	24.8	24.8	100
100	49.70	49.62	99.8
150	74.60	74.35	99.7
Olmesartan medoxomil			
50	19.86	19.86	100
100	40.02	39.98	99.9
150	59.68	59.69	100

Table 2: Accuracy data.

of any extra peaks. No chromatographic interference from the tablet excipients was found. Peak purity was verified by confirming homogeneous spectral data for METO and OLME.

Linearity of METO and OLME showed linearity in the range of 20-75 µg/mL and 8-60 µg/mL, respectively. Linear regression equations and correlation coefficient are y=42.3×-97.659 for METO and y=86.219×-37.465 for OLME and R^2= 0.999 for both METO and OLME.

The accuracy was expressed as the percentage of analytes recovered by the assay method. It was confirmed from results that the method is highly accurate (Table 2).

In Precision, the relative standard deviations (R.S.Ds.) were 0.10% for METO and 0.1% for OLME, which are well within the acceptable limit of 2.0%. The R.S.D's. for intermediate precision were found to be 0.2% for METO and 0.2% for OLME.

In all deliberately varied conditions, the RSD of peak areas of METO and OLME were found to be well within the acceptable limit of 2%. The tailing factor for both the peaks was found to be <1.5.

Conclusion

Proposed HPLC method is specific, accurate and precise for the simultaneous determination of Metoprolol succinate and Olmesartan medoxomil from pharmaceutical dosage form. The described method is suitable for routine analysis and quality control of pharmaceutical preparations containing these drugs either as such or in combination.

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