SIMULTANEOUS ESTIMATION OF CHLORTHALIDONE AND METOPROLOL SUCCINATE IN COMBINED PHARMACEUTICAL DOSAGE FORM BY UV SPECTROSCOPY

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Abstract
A simple, rapid and specific UV spectroscopic method with good sensitivity was developed and validated for the simultaneous determination of Chlorthalidone and Metoprolol Succinate in combined pharmaceutical dosage form. In Methanol the $\lambda_{max}$ of Chlorthalidone and Metoprolol Succinate were fixed as 219 and 229 nm respectively using a Shimadzu UV-Visible spectrophotometer. In this proposed method both drugs obeyed linearity within the concentration range of 2-10 µg/ml and 10-20 µg/ml for Chlorthalidone and Metoprolol Succinate respectively. The low RSD values indicate good precision and high recovery values indicate accuracy of the proposed method. The proposed method has been applied to the determination of drugs in commercial formulations. Assay results were in good agreement with label claim. The method was validated as per ICH guidelines. The developed method was simple, accurate, precise, specific, sensitive and reproducible which can be efficiently and easily applied to pharmaceutical dosage forms.

Keywords: Chlorthalidone, Metoprolol Succinate, simultaneous estimation, methanol.
INTRODUCTION

Chlorthalidone (CLR) is chemically 2-chloro-5-(1-hydroxy-3-oxo-2, 3dihydro1Hisoinol-1-yl) benzene-1-sulfonamide (Molecular Formula C₁₄H₁₂CIN₂O₄S) a monosulfonamyl diuretic, differs from other thiazide diuretics in that a double ring system is incorporated into its structure. Chlorthalidone is used alone or with atenolol in the management of hypertension and edema. Chlorthalidone inhibits sodium ion transport across the renal tubular epithelium in the cortical diluting segment of the ascending limb of the loop of Henle. By increasing the delivery of sodium to the distal renal tubule, Chlorthalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism. It is soluble in acetonitrile and methanol. Metoprolol Succinate (MET) is chemically 1-(isopropylamino)- 3- [p-(2-methoxyethyl) phenoxy] - 2-propanol succinate.(Molecular Formula C₁₅H₂₅NO₃) a competitive, beta1-selective (cardioselective) adrenergic antagonist, is similar to atenolol in its moderate lipid solubility, lack of intrinsic sympathomimetic activity (ISA), and weak membrane stabilizing activity (MSA). Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta (1)-adrenergic receptors in the heart. Beta (1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure. Soluble in water, ethanol and methanol. For this combination literature survey revealed that there are a very few methods available for individual and simultaneous estimation of Chlorthalidone and Metoprolol succinate. The present work aims at developing a simple, sensitive, accurate and precise method for the effective quantitative estimation of Chlorthalidone and Metoprolol succinate as Active Pharmaceutical Ingredient (API) as well as in pharmaceutical preparations without the interference of other constituents in the preparation. In summary, the primary objective of the proposed work is to develop a simple, sensitive and accurate method for the determination of Chlorthalidone and Metoprolol succinate in combination dosage form by UV-Spectrophotometry [1-18].

MATERIALS AND METHODS

INSTRUMENT SPECIFICATIONS: UV Spectrophotometer, Shimadzu, model 1800

CHEMICALS AND REAGENTS: Methanol obtained from local market, manufactured pure chlorthalidone and metoprolol succinate were obtained as gift sample from Aurobindo Pharma, Hyderabad. The tablet dosage form VINICOR-D 50 (claim: 50mg metoprolol and 12.5mg chlorthalidone) was procured from local market.
PREPARATION OF STANDARD STOCK SOLUTIONS
The 10 mg of standard chlorthalidone and metoprolol succinate were weighed accurately and transferred into two different 100 ml volumetric flasks. Both the drugs were dissolved in methanol and diluted up to the mark by using the solvent methanol to obtain a final concentration of 100μg/ml. The resulting solution was used as a working standard solution. The aliquot portions of stock solution of chlorthalidone and metoprolol succinate were diluted approximately with methanol to obtain concentration of 10mcg/ml of each drug. These solutions were scanned in the range of 200-400 nm in 1cm cell against blank. From the overlain spectra the wavelength selected for the estimation are 219nm and 229nm for chlorthalidone and metoprolol succinate respectively.

PREPARATION OF SAMPLE SOLUTIONS
For the preparation of sample solution 20 tablets were taken and weighed, their mean weight was determined and finely powdered. An equivalent weight (10mg) of the tablet powder was weighed. It contains 2.5mg of chlorthalidone and 10mg of metoprolol succinate. So 7.5mg of API of chlorthalidone was added to make both drugs 10 mg (standard addition method). This powder was transferred into 10 ml volumetric flask, and dissolved in methanol. This solution was sonicated for 15 min. and filtered through whatman filter paper. From the filtrate 0.1 ml was taken and made up to 10 ml with methanol to give 10mcg/ml of both drugs. This solution was scanned over the range of 200-400 nm, using two sampling wavelengths 219nm and 229nm determined the concentration of these drugs in tablet formulation.

VALIDATION OF THE METHOD
1) LINEARITY:
Standard stock solution of Chlorthalidone and Metoprolol Succinate: 100 mg of Chlorthalidone and 100mg of Metoprolol Succinate were accurately weighed and transferred into separate clean and dry 100 ml volumetric flasks, dissolved with sufficient volume of methanol. The volume was then made up to 100 ml with methanol to obtain the concentration of 1000μg/ml (1mg/ml). Working standard solution: 1 ml of the stock solution from each was further diluted up to 10 ml volumetric flask with methanol to get a concentration 100 μg/ml. Serial dilutions of concentration range 2-10 μg/ml were prepared from the working standard solution for Chlorthalidone and 10-20μg/ml for Metoprolol Succinate. These dilutions were scanned at the detection wavelength of 219 nm and 229 nm using methanol as blank. The regression equation, Y- intercept and correlation coefficient were calculated. The linearity was thus determined, and a concentration range was selected.
2) LIMIT OF DETECTION AND LIMIT OF QUANTITATION:
The LOD and LOQ were separately determined based on calibration curve. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines were used to calculate the LOD and LOQ.
I. Formula for LOD (μg/ml);
   \[ \text{LOD} = 3.3 \times \frac{\text{SD}}{S} \]
   Where,
   SD = The standard deviation of the response
   S = The slope of the calibration curve (mean)
II. Formula for LOQ (μg/ml);
   \[ \text{LOQ} = 10 \times \frac{\text{SD}}{S} \]
   Where,
   SD = The standard deviation of the response
   S = The slope of the calibration curve (mean)

3) ACCURACY:
The accuracy of the method was ascertained by carrying out recovery studies using standard addition method. The recovery studies are performed to determine if there was any positive or negative interference from excipients present in the formulation. The percentage recovery results revealed that the values were near to 100%, which indicates that the proposed method is accurate as the results are within the official limits. It also reveals that the commonly used excipients and additives in the formulation were not interfering with the proposed method. (Table no: 2)

4) PRECISION:
The precision of analytical method is expressed as standard deviation or relative standard deviation of a series of measurements. It was ascertained by replicate estimation of drug by the proposed method. (Table no: 3)

RESULTS AND DISCUSSION
Chlorthalidone and Metoprolol Succinate showed maximum absorbance in Methanol at 219 and 229 nm. The proposed method for simultaneous estimation of both the drugs was validated as per the ICH guidelines. The linearity was observed in the concentration range of 2-10 mcg/ml for Chlorthalidone and 10-20 mcg/ml for Metoprolol succinate. The slope, intercept and correlation coefficient values of Chlorthalidone and Metoprolol Succinate are 0.093, 0.004, 0.999 and 0.021,
Amount of drugs estimated by the proposed method was in good agreement with the label claim. The accuracy of the method was assessed by recovery experiments. The precision of the method was studied as repeatability, intra-day and inter-day variations; the %RSD less than 2, indicates proposed method is precise. Recovery was close to 100% for both the drugs.

Table 1: Results of analysis of tablet formulation

<table>
<thead>
<tr>
<th>BRAND</th>
<th>LABEL CLAIM(mg/tablet)</th>
<th>AMOUNT FOUND</th>
<th>%LABEL CLAIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>VINICOR-D 50</td>
<td>Chlorthalidone(12.5mg)</td>
<td>12.6</td>
<td>100.8%</td>
</tr>
<tr>
<td></td>
<td>Metoprolol Succinate (50mg)</td>
<td>49.4</td>
<td>98.8%</td>
</tr>
</tbody>
</table>

Table 2: Results of recovery studies

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>LEVEL</th>
<th>CONCENTRATION</th>
<th>%RECOVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>50%</td>
<td>4mcg</td>
<td>106%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>5mcg</td>
<td>102%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>8mcg</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>10mcg</td>
<td>101%</td>
</tr>
<tr>
<td>Metoprolol Succinate</td>
<td>50%</td>
<td>5mcg</td>
<td>110%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>10mcg</td>
<td>101%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>20mcg</td>
<td>97%</td>
</tr>
</tbody>
</table>

Table 3: Results of precision studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration(mcg/ml)</th>
<th>Absorbance</th>
<th>%RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>10</td>
<td>0.926</td>
<td>0.67%</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.938</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.929</td>
<td></td>
</tr>
<tr>
<td>Metoprol Succinate</td>
<td>10</td>
<td>0.212</td>
<td>1.32%</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.216</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.214</td>
<td></td>
</tr>
</tbody>
</table>

SELECTION OF WAVELENGTH

Fig.1: Overlaid UV spectra of Chlorthalidone and Metoprolol Succinate in methanol
Fig. 2: Overlaid UV spectra of Standard Chlorthalidone (2-10mcg/ml)

Fig. 3: Overlaid UV spectra of Standard Metoprolol Succinate (10-20mcg/ml)

Fig. 4: UV spectrum of Formulation Sample (10mcg/ml)
CONCLUSION

The present study comprises a UV spectroscopic method of analysis for the simultaneous estimation of Chlorthalidone and Metoprolol Succinate in tablet dosage form. From the study of validation parameters, it was observed that the method is specific, accurate, precise and reproducible. The proposed method could be applied to routine analysis in quality control laboratories.

REFERENCES

5. ICH harmonized tripartite guideline, Text on validation of analytical procedures, Recommended for adoption at step 4 of the ICH process by the ICH steering committee.


