Determination celiprolol hydrochloride drug by used zero, first, second and third order derivative and peak area spectrophotometry method in its pure form and in pharmaceutical tablets

Mohanad H Halboos¹, Aayad Ammar Sayhood² and Tamara Ala'a Hussein²

¹Department of Ecology, Faculty of Science, University of Kufa, Najaf, Iraq
²Department of Basic Sciences, Faculty of Dentistry, University of Kufa, Najaf, Iraq

Email: muhaned.halbus@uokufa.edu.iq

Abstract. An easy, specified, accurate, precise and reproducible quantitative analyses for determination of celiprolol hydrochloride drug by used zero, first, second and third order derivative and peak area spectrophotometry method. The suggest methods determined the drug in the concentration range (0.5-30) μg.mL⁻¹ at 286.6 nm for 0th order, at 306.6 and 272.2 nm for 1st order, at 319.2, 289.8 and 250.2 nm for 2nd order and at 325.6, 304.8, 242.2 and 219.6 nm for 3rd order derivative spectrophotometry, respectively. The peak area spectrophotometry method also used in the same range for determining celiprolol hydrochloride, at (284.4-379.2) and (248.6-284.4) nm for 1st order, at (306.4-372.2), (271.2-306.4) and (239.4-271.2) nm for 2nd order, and at (318.6-363.8), (290.4-318.6), (233.2-250.4) and (210.8-233.2) nm for 3rd order, respectively. The accuracy and precision of the methods used was calculated and the results were highly satisfactory. The limit of detection (LOD) and limit of quantification (LOQ) was calculated for the suggested methods, Where (LOD) was within range (0.0124-0.0632) μg.mL⁻¹, and (LOQ) within range (0.0415-0.1632) μg.mL⁻¹. The methods were successful in application when estimating celiprolol hydrochloride drug on some pharmaceutical tablets available in the local markets.

Keywords: Celiprolol hydrochloride, derivative spectrophotometry, peak area spectrophotometry method.

Introduction:

Celiprolol hydrochloride, Figure (1), 3-[3-Acetyl-4-[(RS)-3-[1,1-dimethylethyl-amino]-2-hydroxypropoxy]phenyl]-1,1-diethylare hydrochloride, (Cel.HCl), is used for β-adrenoceptor antagonist ¹. Cel.HCl is an activity for direct vasodilator and intrinsic sympathomimetic ². It's used for the control of angina pectoris and hypertension ³. Several methods were used for determination Cel.HCl, such as; HPLC ⁴-⁶, Liquid chromatography ⁷,⁸ spectrophotometric ⁹-¹⁴, fluorometric ¹⁵, potentiometric ¹⁶, voltammetry ¹⁷,¹⁸.
By looking at previous studies, we found that the derivative was not used in conjunction with the peak area to estimate celiprolol hydrochloride drug. In this paper, we proposed a new, simple and inexpensive method and did not need reagents to estimate Cel.HCl drug in its pure form and in pharmaceutical preparations through used zero, first, second and third order derivative and peak area spectrophotometry method.

![Celiprolol hydrochloride structure](image)

**Figure (1): Celiprolol hydrochloride structure**

**Experimental:**

**Instrumentation and materials:**

Shimadzu double beam UV-visible spectrophotometer, model UV-1800 PC with quartz cells of 1.0 cm path length, which connected to a computer have the software UVProbe 2.34 was used for all spectral measurements. Sensitive balance ± 0.0001g (Mettler Toledo/Switzerland). Ultrasonic (Homogenizer/Germany).

The reference standard of celiprolol hydrochloride drug was supplied as a gift sample from the State Company For Drug Industries and Medical Appliance (SDI) Samarra-Iraq.

**Preparation of standard and sample solutions:**

Cel.HCl 100 μg.mL\(^{-1}\) was prepared by dissolving accurate weighted 0.1000 g of pure drug in a small amount of distilled water then quantitatively transfer into a 1000 mL volumetric flask, diluted to the mark with distilled water and stored in a cool dark place (< 25 °C). Working solutions were freshly prepared each day by serial dilutions in the concentration range (0.5-30) μg.mL\(^{-1}\).

Thirty tablets each containing 200 mg of celiprolol hydrochloride were weighed and crushed to powder and the mean weight was calculated. Powder equivalent to 100 mg of Cel.HCl was transferred in 1000 ml of volumetric flask. A 100 ml of distilled water was added and sonicated for 20 minutes. Then the solution was filtered and diluted up to the mark with distilled water.

**Results and discussion:**

**Linearity and range:**

Under the experimental conditions qualified, the scheme obtained for zero, first, second and third order and peak area methods spectra noted the linear correlation. The regression analysis was done for the correlation coefficient values, slope and intercept as shown in the figure (2-8).

In figure (2) the spectra of Cel.HCl drug in the concentration range (0.5-30) μg.mL\(^{-1}\) and the calibration curve at 286.4 nm for 0\(^{th}\) order derivative spectrophotometry, the regression equation of calibration curve was \(y = 0.0861x + 0.0231\) (R\(^2\) = 0.9996).
Figure (2): (A); Zero order derivative spectrum of celiprolol hydrochloride. (B); calibration curve for Cel.HCl at 286.4 nm.

In figure (3) the spectra of Cel.HCl drug in the concentration range (0.5-30) μg.mL⁻¹ and the calibration curves at 306.6 and 272.2 nm for 1st derivative spectrophotometry, the regression equations of calibration curves were \( y = -0.0026x - 0.0001 \) (\( R^2 = 0.9995 \)) and \( y = 0.0009x - 0.0002 \) (\( R^2 = 0.9995 \)), respectively.

In figure (4) the peak area of Cel.HCl drug in the concentration 30 μg.mL⁻¹ and the calibration curves at (284.4-379.2) and (248.6-284.4) nm for 1st derivative spectrophotometry, the regression equations of calibration curves were \( y = -0.0825x - 0.003 \) (\( R^2 = 0.9995 \)) and \( y = 0.0216x - 0.0129 \) (\( R^2 = 0.9997 \)), respectively.

Figure (3): (A); First order derivative spectrum of celiprolol hydrochloride. (B); calibration curve for Cel.HCl at 272.2 nm. (C); calibration curve for Cel.HCl at 306.6 nm.
Figure (4): (A); Peak area for first order derivative spectrum of celiprolol hydrochloride. (B); calibration curve for Cel.HCl at (248.6-284.4) nm. (C); calibration curve for Cel.HCl at (284.4-379.2) nm.

In figure (5) the spectra of Cel.HCl drug in the concentration range (0.5-30) μg.mL⁻¹ and the calibration curves at 319.2, 289.8 and 250.2 nm for 2nd order derivative spectrophotometry, the regression equations of calibration curves were $y = 0.0001x - 0.00006$ ($R^2 = 0.9996$), $y = -0.0002x + 0.00005$ ($R^2 = 0.9996$) and $y = 0.00007x + 0.00004$ ($R^2 = 0.9995$), respectively.
Figure (5): (A); Second order derivative spectrum of celiprolol hydrochloride. (B); calibration curve for Cel.HCl at 250.2 nm. (C); calibration curve for Cel.HCl at 289.8 nm. (D); calibration curve for Cel.HCl at 319.2 nm.

In figure (6) the peak area of Cel.HCl drug in the concentration 30 μg.mL⁻¹ and the calibration curves at (306.4-372.2), (271.2-306.4) and (239.4-271.2) nm for 2nd order derivative spectrophotometry, the regression equations of calibration curves were 
y= 0.0026x - 0.0002 (R² = 0.9998), y= -0.0036x + 0.0003 (R² = 0.9997) and y= 0.0012x + 0.0006 (R² = 0.9998), respectively.
In figure (7) the spectra of Cel.HCl drug in the concentration range (0.5-30) μg.mL⁻¹ and the calibration curves at 325.6, 304.8, 242.2 and 219.6 nm for 3rd order derivative spectrophotometry, the regression equations of calibration curves were $y = -0.00008x - 0.000001$ ($R^2 = 0.9994$), $y = 0.00002x - 0.00001$ ($R^2 = 0.9995$), $y = 0.00001x - 0.00003$ ($R^2 = 0.9995$) and $y = -0.00002x + 0.00007$ ($R^2 = 0.9992$).

Figure (7): (A); Third order derivative spectrum of celiprolol hydrochloride. (B); calibration curve for Cel.HCl at 219.6 nm. (C); calibration curve for Cel.HCl at 242.2 nm. (D); calibration curve for Cel.HCl at 304.8 nm. (E); calibration curve for Cel.HCl at 325.6 nm.
In figure (8) the peak area of Cel.HCl drug in the concentration 30 μg.mL⁻¹ and the calibration curves at (318.6-363.8), (290.4-318.6), (233.2-250.4) and (210.8-233.2) nm for 3rd order derivative spectrophotometry, the regression equations of calibration curves were \( y = -0.0003x + 0.0002 \) (\( R^2 = 0.9996 \)), \( y = 0.0004x - 0.0003 \) (\( R^2 = 0.9998 \)), \( y = 0.0001x + 0.00006 \) (\( R^2 = 0.9997 \)) and \( y = -0.0001x - 0.0006 \) (\( R^2 = 0.9996 \)), respectively.

Figure (8): (A); Peak area of third order derivative spectrum of celiprolol hydrochloride. (B); calibration curve for Cel.HCl at (210.8-233.2) nm. (C); calibration curve for Cel.HCl at (290.4-318.6) nm. (D); calibration curve for Cel.HCl at (233.2-250.4) nm. (E); calibration curve for Cel.HCl at (318.6-363.8) nm.
The accuracy:

To investigate the accuracy of the suggested method, recovery investigation was carried out by a standard addition method. The accuracy of the suggested method was evaluated at 60%, 100%, and 140% levels of 10 μg.mL⁻¹ standard solution of Cel.HCl for 0th, 1st, 2nd and 3rd order derivative and peak area method. Five determinations in each level were done, error%, recovery% and RSD% were calculated as shown in table 1.

| Methods          | Sample con.* µg.mL⁻¹ | Standard Added* µg.mL⁻¹ | Found* µg.mL⁻¹ | Error% | Recovery% | R.S.D.% |
|------------------|----------------------|-------------------------|----------------|--------|-----------|---------|
| 0th order derivative | 10.00                | 6.00                    | 16.0255        | 0.1596 | 100.1596  | 0.1394  |
|                  | 10.00                | 10.00                   | 20.0348        | 0.1742 | 100.1742  | 0.2093  |
|                  | 14.00                | 24.0069                 | 0.0290         | 100.0290 | 0.4047   |
| 1st order derivative | 10.00                | 6.00                    | 15.9976        | -0.0145 | 99.9851   | 0.2440  |
|                  | 10.00                | 10.00                   | 20.0301        | 0.15098 | 100.1509  | 0.1720  |
|                  | 14.00                | 23.9605                 | -0.1645        | 99.8354 | 0.0950    |
| 2nd order derivative | 10.00                | 6.00                    | 15.9744        | -0.1596 | 99.8403   | 0.2651  |
|                  | 10.00                | 10.00                   | 20.0348        | 0.1742 | 100.1745  | 0.2167  |
|                  | 14.00                | 23.9744                 | -0.1064        | 99.8935 | 0.2066    |
| 3rd order derivative | 10.00                | 6.00                    | 15.9698        | -0.1887 | 99.8112   | 0.2356  |
|                  | 10.00                | 10.00                   | 20.0255        | 0.1277 | 100.1277  | 0.1759  |
|                  | 14.00                | 23.9790                 | -0.0871        | 99.9128 | 0.2127    |
| Peak Area method | 10.00                | 6.00                    | 15.9651        | -0.2177 | 99.7822   | 0.2218  |
|                  | 10.00                | 10.00                   | 20.0139        | 0.0696 | 100.0696  | 0.1807  |
|                  | 14.00                | 23.9558                 | -0.1838        | 99.8161 | 0.2961    |

*Average of five measurements

The precision:

To investigate the precision of the suggested method, Cel.HCl solutions at 10 μg.mL⁻¹ were analyzed each five times for all for 0th, 1st, 2nd and 3rd order derivative and peak area method. The interday and intraday precision was expressed by RSD as shown in table 2.

The sensitivity:

The limit of detection (LOD) and limit of quantification (LOQ) was calculated for the suggested methods by the equations:

\[
\text{LOD} = 3.3\sigma/\text{Slope}
\]

\[
\text{LOQ} = 10\sigma/\text{Slope}
\]

Where \( \sigma \) is the standard deviation, the summary of the result was shown in table 3.
Table (2): The precision of the suggested method

| Methods                  | Sample con.* µg.mL⁻¹ | R.S.D.% | R.S.D.% |
|--------------------------|----------------------|---------|---------|
|                          |                      | interday precision | intraday precision |
| 0th order derivative     | 10.00                | 0.3695   | 0.2547  |
| 1st order derivative     | 10.00                | 0.3594   | 0.2643  |
| 2nd order derivative     | 10.00                | 0.3479   | 0.2019  |
| 3rd order derivative     | 10.00                | 0.2541   | 0.3651  |
| Peak Area method         | 10.00                | 0.3012   | 0.3197  |

*Average of five measurements

Table (3): Calculates LOD and LOQ for the suggested method

| Methods                  | LOD µg.mL⁻¹ | LOQ µg.mL⁻¹ |
|--------------------------|-------------|-------------|
| 0th order derivative     | 0.0124      | 0.0415      |
| 1st order derivative     | 0.0235      | 0.07846     |
| 2nd order derivative     | 0.0632      | 0.2106      |
| 3rd order derivative     | 0.0487      | 0.1623      |
| Peak Area method         | 0.0379      | 0.1263      |

Analysis of pharmaceutical tablets:

To investigate the accuracy of the suggested method for determination of Cel.HCl in pharmaceutical tablets, three evaluated the concentration of solution of tablets at 10, 15, and 20 µg.mL⁻¹ and determined by 0th, 1st, 2nd and 3rd order derivative and peak area method. Five determinations in each level were done, error%, recovery% and RSD% were calculated as shown in table 4.

Table (4): Analysis of pharmaceutical tablets

| Methods                  | Taken* µg.mL⁻¹ | Found* µg.mL⁻¹ | Error % | Recovery % | R.S.D.% |
|--------------------------|----------------|----------------|---------|------------|---------|
| 0th order derivative     | 10.00          | 10.0534        | 0.5342  | 100.5342   | 0.5753  |
|                          | 15.00          | 15.0197        | 0.1316  | 100.1316   | 0.2408  |
|                          | 20.00          | 20.0209        | 0.1045  | 100.1045   | 0.2298  |
| 1st order derivative     | 10.00          | 10.0301        | 0.3019  | 100.3019   | 0.8005  |
|                          | 15.00          | 14.9965        | -0.0232 | 99.9767    | 0.4291  |
|                          | 20.00          | 19.9953        | -0.0232 | 99.9767    | 0.4291  |
| 2nd order derivative     | 10.00          | 10.0069        | 0.0696  | 100.0696   | 0.9765  |
|                          | 15.00          | 15.0011        | 0.0077  | 100.0077   | 0.4791  |
|                          | 20.00          | 20.0185        | 0.0929  | 100.0929   | 0.3795  |
| 3rd order derivative     | 10.00          | 9.9860         | -0.1393 | 99.86062   | 0.7776  |
|                          | 15.00          | 15.0197        | 0.1316  | 100.1316   | 0.5396  |
|                          | 20.00          | 20.0418        | 0.2090  | 100.2090   | 0.3655  |
| Peak Area method         | 10.00          | 10.0092        | 0.0929  | 100.0929   | 0.9040  |
|                          | 15.00          | 15.0662        | 0.4413  | 100.4413   | 0.3983  |
|                          | 20.00          | 20.0650        | 0.3252  | 100.3252   | 0.3511  |

*Average of five measurements
Conclusion:

The suggest zero, first, second and third order derivative and peak area spectrophotometry method provides easy, specified, accurate, precise and reproducible quantitative analyses for determination of Cel.HCl drug. The methods were validated as per ICH guidelines in terms of specified, linearity, precision, accuracy, limits of detection (LOD), limits of quantification (LOQ) and reproducibility. The suggested method can be used for the routine analysis and the quality control assay of drug in bulk and pharmaceutical preparations.

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