J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 48(3): 803-810, 2024
Doi: 10.33483/jfpau.1441955

ORIGINAL ARTICLE / ÖZGÜN MAKALE

THE SIMULTANEOUS SPECTRAL DETERMINATION OF CANDESARTAN CILEXETIL AND HYDROCHLOROTHIAZIDE IN TABLETS USING THE TRIVARIATE CLASSICAL LEAST SQUARES METHOD

ÜÇ DEĞİŞKENLİ KLASİK EN KÜÇÜK KARELER YÖNTEMİ KULLANILARAK TABLETLERDE KANDESARTAN SİLEKSETİL VE HİDROKLOROTİAZİDİN EŞZAMANLI SPEKTRAL TAYİNİ

Asiye ÜÇER[1,2], Özgür ÜSTÜNDAĞ[2], Uğur SAKLI[2], Erdal DİNÇ[2]*

[1]Ankara Yıldırım Beyazıt University, Faculty of Pharmacy, Department of Analytical Chemistry, 06010, Etlik, Ankara, Türkiye
[2]Ankara University, Faculty of Pharmacy, Department of Analytical Chemistry, 06560, Yenimahalle, Ankara, Türkiye

ABSTRACT

Objective: *Candesartan cilexetil (CDS) is a member of the sartan group of drugs and is widely used to lower blood pressure. Hydrochlorothiazide (HCT) is the most commonly used diuretic group of drugs and is prescribed together with candesartan cilexetil in cases where blood pressure cannot be reduced. Pharmaceutical preparations containing these two active compounds in combination are preferred today to provide a more effective pharmacological effect. Therefore, it is of great importance to determine the quantities of these combined pharmaceutical preparations with new analytical methods that are fast, easy, and sensitive in quality control and routine analysis. In this study, a new trivariate classical least squares calibration method (TCLS) was developed for the simultaneous quantification of candesartan cilexetil (CDS) and hydrochlorothiazide (HCT) in binary mixtures and commercial tablets without using a preliminary separation step.*

Material and Method: *CDS and HCT compounds were kindly donated by National Pharm Ind., Turkey. HPLC-grade methanol (J.T. Baker, Netherlands) was used as a solvent for the spectrophotometric analysis. In the application of the TCLS method, the determination and quantification of CDS and HCT were carried out using UV spectrophotometric measurements with 1 cm quartz cells in the 200-310 nm spectral region (slit range 2 nm). The newly developed TCLS method was tested using a validation set consisting of eight synthetic mixture solutions within the working ranges of 4.0-20.0 µg/ml for CDS and HCT. Simultaneous quantification analyses of CDS and HCT were performed on ATACAND PLUS® Tablet supplied by Astra Zeneca İlaç Ltd Şti.*

Result and Discussion: *The method is based on the application of TCLS to the absorbance measurements at three different wavelength points (223.5, 240.0, and 268.5 nm). The absorptivity values ($\mu g^{-1}mlcm^{-1}$) of pure CDS and pure HCT were $6.67x10^{-2}$, $2.76x10^{-2}$, $2.33x10^{-2}$, and $11.41x10^{-2}$, $0.46x10^{-2}$, $6.42x10^{-2}$ at the selected wavelengths, respectively. Recovery values and relative standard deviation values were calculated as 97.2% and 1.61% for CDS and 99.7% and 3.67% for HCT, respectively. This method was successfully applied to the spectrophotometric quantitative analysis of tablets containing CDS and HCT, and then, a good agreement was reported.*

* **Corresponding Author / Sorumlu Yazar:** Erdal Dinç
e-mail / e-posta: dinc@ankara.edu.tr, **Phone / Tel.:** +903122126805

Submitted / Submitted : 23.02.2024
Accepted / Kabul : 22.04.2024
Published / Yayınlanma : 10.09.2024

Keywords: *Angiotensin II receptor antagonists, candesartan cilexetil, hydrochlorothiazide, quantitative tablet analysis, trivariate classical least squares method*

ÖZ

Amaç: *Kandesartan sileksetil (CDS), sartan ilaç grubuna ait olup, kan basıncını düşürmek amacıyla yaygın olarak kullanılmaktadır. Hidroklorotiazid (HCT) en sık kullanılan diüretik ilaç grubudur ve kan basıncının düşürülemediği durumlarda kandesartan sileksetil ile birlikte reçete edilir. Bu iki aktif bileşiğin kombinasyon halinde bulunduğu farmasötik preparatlar, günümüzde daha etkili bir farmakolojik etki sağlamak amacıyla tercih edilmektedir. Bu nedenle, bu kombine farmasötik preparatların miktarlarının, kalite kontrol ve rutin analizlerde hızlı, kolay ve hassas yeni analitik yöntemlerle belirlenmesi büyük önem taşımaktadır. Bu çalışmada, ikili karışımlarda ve ticari tabletlerde kandesartan sileksetil (CDS) ve hidroklorotiyazidin (HCT) bir ön ayırma adımı kullanılmadan eş zamanlı ölçümü için yeni bir üç değişkenli klasik en küçük kareler kalibrasyon yöntemi (TCLS) geliştirildi.*

Gereç ve Yöntem: *CDS ve HCT bileşikleri National Pharm Ind., Türkiye tarafından bağışlanmıştır. Spektrofotometrik analiz için solvent olarak metanol (J.T. Baker, Hollanda) kullanıldı. TCLS yönteminin uygulanmasında CDS ve HCT'nin belirlenmesi ve nicelendirilmesi, 200-310 nm spektral bölgede (slit aralığı 2 nm) 1 cm'lik kuvars hücrelerle UV spektrofotometrik ölçümler kullanılarak gerçekleştirildi. Yeni geliştirilen TCLS yöntemi, CDS ve HCT için 4.0-20.0 µg/ml çalışma aralıklarında sekiz sentetik karışım çözeltisinden oluşan bir doğrulama seti kullanılarak test edildi. Astra Zeneca İlaç Ltd Şti tarafından sağlanan ATACAND PLUS® Tablet üzerinde CDS ve HCT'nin eş zamanlı miktar tayini analizleri yapıldı.*

Sonuç ve Tartışma: *Yöntem, TCLS'nin üç farklı dalga boyu noktasında (223.5, 240.0 ve 268.5 nm) absorbans ölçümlerine uygulanmasına dayanmaktadır. Saf CDS ve saf HCT'nin absorptivite değerleri ($\mu g^{-1}mlcm^{-1}$) seçilen dalga boylarında sırasıyla $6.67x10^{-2}$, $2.76x10^{-2}$, $2.33x10^{-2}$ ve $11.41x10^{-2}$, $0.46x10^{-2}$, $6.42x10^{-2}$ idi. Geri kazanım değerleri ve bağıl standart sapma değerleri CDS için sırasıyla %97.2 ve %1.61, HCT için ise %99.7 ve %3.67 olarak hesaplandı. Bu yöntem, CDS ve HCT içeren tabletlerin spektrofotometrik kantitatif analizine başarıyla uygulandı ve ardından iyi bir uyum olduğu bildirildi.*

Anahtar Kelimeler: *Anjiyotensin II reseptör antagonistleri, hidroklorotiyazid, kandesartan sileksetil, kantitatif tablet analizi, üç değişkenli klasik en küçük kareler yöntemi*

INTRODUCTION

Angiotensin II receptor antagonists are a group of drugs, also known as the sartan family, used in the treatment of hypertension [1]. Angiotensin II, which is the basic peptide of the renin-angiotensin system, which has important physiological effects on blood pressure regulation and water and salt homeostasis, plays a key role in the cardiovascular system by playing an important role in the development of physiopathological events such as hypertension, heart and kidney failure, and atherosclerosis. Candesartan cilexetil (CDS) (see Figure 1a) is a member of this group of medicines. It helps reduce blood pressure by relaxing and widening blood vessels. Candesartan can be used to treat hypertension, left ventricular hypertrophy, isolated systolic hypertension, and diabetic nephropathy, and is also used as an alternative agent in the treatment of heart failure, myocardial infarction, systolic dysfunction, and coronary artery disease [2,3]. Hydrochlorothiazide (HCT) (see Figure 1b) belongs to a group of medicines called 'diuretics'. It is used to treat swelling due to hypertension and fluid accumulation, as well as to treat renal tubular acidosis and diabetes insipidus, and to reduce the risk of kidney stones in those with high calcium levels in the urine [4]. It helps remove water and salts such as sodium from the body through urine. This causes blood pressure to decrease. These two active ingredients are prescribed in cases where blood pressure cannot be reduced with candesartan cilexetil (CDS) or hydrochlorothiazide (HCT) alone.

It is of great importance to determine the quantities of these combined pharmaceutical preparations, which are preferred today to provide a more effective pharmacological effect, with new analytical methods that are fast, easy, and highly sensitive in quality control and routine analysis. In the literature, chromatographic separation methods such as liquid chromatography (LC) [5], high-performance liquid chromatography or ultra-performance liquid chromatography (HPLC/UPLC) [6-8],

capillary electrophoresis (CE) [9-10] and micellar electrokinetic chromatography [11], which consist of high-tech and expensive equipment for the analysis of complex samples are used. These expensive and complex methods may not always produce the expected results in the analysis processes. In addition, another disadvantage in the application of these methods is that the optimization of experimental conditions and analysis are time-consuming. On the other hand, it is noteworthy that spectrophotometric methods are also used extensively in the literature [12-13]. However, quantitative analysis of combined commercial pharmaceutical preparations is not possible with conventional spectral analysis methods because the active substances give interfering spectra in the same region [14]. In such cases, derivative spectrophotometry and its modified versions were used for a simple and rapid quantitative determination without separation steps [15-19]. However, derivative spectrophotometry requires signal-processing treatments, which need a long analysis period, to get derivative signals of zero-order spectra. Additionally, these conventional derivative methods do not yield successful results in their applications due to their disadvantages such as interference of main peaks and noise peaks, and decrease in signal/noise ratio, especially at high derivative degrees. To eliminate the drawbacks of the spectral derivative methods, numerical methods or multivariate spectral methods, such as direct absorbance measurement techniques based on a set of two or more wavelength points, provide an alternative way to quantitatively resolve complex mixtures containing two or more active compounds.

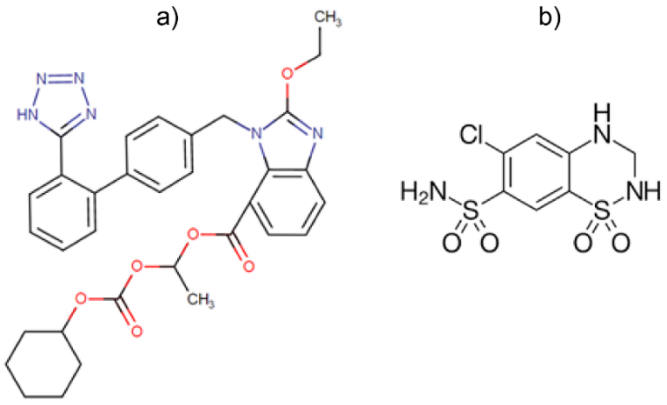

Figure 1. a) Candesartan cilexetil (CDS), **b)** Hydrochlorothiazide (HCT)

In this study, a new TCLS approach was developed, for the first time, for the quantitative analysis of a commercial pharmaceutical tablet consisting of candesartan cilexetil (CDS) and hydrochlorothiazide (HCT). The developed and validated method was successfully applied to both synthetic mixtures and commercial pharmaceutical tablets.

MATERIAL AND METHOD

Apparatus and Software

All UV spectrophotometric data were collected using a Shimadzu UV-1601 (Kyoto, Japan) double-beam UV-VIS spectrophotometer with 1 cm quartz cells. UV absorbance spectra of the samples and standard solutions were plotted in the spectral region of 200-310 nm (slit range 2 nm). After the obtained data were transferred to the Shimadzu UV computer software, the Matlab (MathWorks, Natick, MA, USA) program was used in the application of the TCLS approach to the spectra, statistical analysis, and regression analysis. All graphics and figures were drawn with Matlab. All prepared solutions were filtered with a Sartarius Minisart disposable filter with a pore size of 0.2 µm.

Chemicals and Reagents

CDS and HCT compounds were kindly donated by National Pharm Ind., Turkey. HPLC-grade methanol (J.T. Baker, Netherlands) was used as a solvent for the spectrophotometric analysis. All

samples were prepared fresh daily and stored in a dark place and a refrigerator during the analysis.

Standard, Calibration, and Validation Solutions

Stock solutions of CDS and HCT were prepared individually by dissolving 25.0 mg of active compounds in methanol in a 100 ml calibrated flask and made up to the mark with methanol. All standard and validation samples were prepared from these stock solutions. In the application of the spectral least squares method, standard solutions were prepared in the concentration range of 6.0-18.0 µg/ml for CDS and the concentration range of 4.0-16.0 µg/ml for HCT. A validation set of eight different concentrations containing these two compounds was prepared within the working ranges of 4.0-20.0 µg/ml for CDS and HCT.

Preparation of Samples

In the first application of the TCLS method in commercial pharmaceutical tablet analysis, ten tablets of ATACAND PLUS® Tablet (Astra Zeneca İlaç Ltd. Şti.) were precisely weighed and the amount corresponding to one tablet was calculated after being thoroughly powdered in a mortar. It was dissolved in methanol in a 100 ml volumetric flask. The solution content was mixed with a mechanical stirrer for 30 min and filtered through a 0.20 µm pore size membrane filter. For the analysis, 1.0 ml of the filtered solution was transferred to a 100 ml volumetric flask and the volume was made up with the same solvent.

TCLS Method and Its Application

Absorption spectra of solutions and binary mixtures prepared at different CDS and HCT concentrations were recorded. Absorptivity (a) values were calculated using absorbances measured at 223.5, 240.0 and 268.5 nm for each of the compounds in the binary mixture. Using the absorptivity (a) value, a system of equations with two unknowns for compounds in a binary mixture can be written as follows:

$$A = a.l.C,\ l\ (optical\ path\ lenght) = 1.0\ cm \quad (1)$$

Where a denote absorptivity, A denote absorbance, and C denote concentration (µg/ml).

$$A_1 = a_1C_1 + \beta_1C_2 \quad (2)$$

$$A_2 = a_2C_1 + \beta_2C_2 \quad (3)$$

$$A_3 = a_3C_1 + \beta_3C_2 \quad (4)$$

Where A_1, A_2 and A_3 denotes the absorbances of solutions of synthetic mixtures of CDS and HCT, and represent the calculated a and β absorptivity values at λ_1, λ_2 and λ_3 for CDS and HCT, respectively. C_1, and C_2 are the concentrations of CDS and HCT, respectively. The subscripts 1, 2 and 3 refer to λ_1 (223.5 nm), λ_2 (240.0 nm) and λ_3 (268.5 nm), respectively.

When written according to the matrix notation given below, the above set of equations (2, 3, and 4) greatly simplifies the matter and easily solves the equations with two unknowns:

$$\begin{bmatrix} A_1 \\ A_2 \\ A_3 \end{bmatrix} = \begin{bmatrix} a_1 & \beta_1 \\ a_2 & \beta_2 \\ a_3 & \beta_3 \end{bmatrix} * \begin{bmatrix} C_1 \\ C_2 \end{bmatrix} \quad (5)$$

Here, the quantification of CDS and HCT was carried out from the concentrations corresponding to the absorbance of the samples in Equation 5 at the wavelengths of λ_1, λ_2 and λ_3.

Based on Equation 5, the concentration of each compound in the binary mixture can be calculated using the multiplication of the inverse of the coefficient matrix by the absorbance measurements of samples.

RESULT VE DISCUSSION

TCLS Method and Its Application

In the spectral analysis of two-component mixture systems, the main problem is the overlapping spectral bands in the working wavelength region as in our study (see Figure 2). To solve this analytical issue, we focused mainly on the development of the new spectral numerical method, which is based on the use of the absorbance measurement at three different wavelength points, for the simultaneous quantitative analysis of two-component mixtures. This article involves verifying the feasibility and validity of a fast, easy, reliable TCLS method for the simultaneous quantification of CDS and HCT in synthetic mixtures and commercial tablets. The UV spectra of standard CDS and HCT solutions and their synthetic mixtures were plotted in the wavelength region of 200-310 nm.

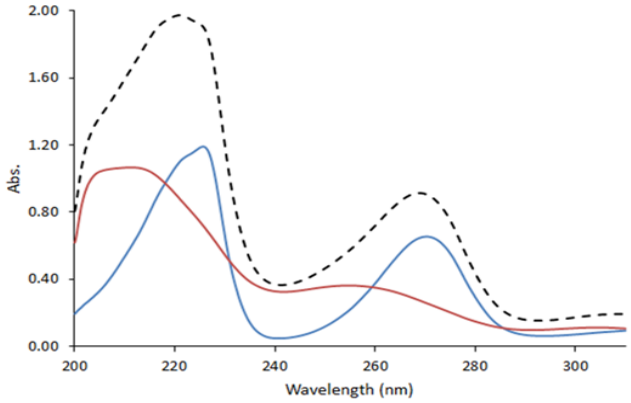

Figure 2. Absorption spectra of 10 µg/ml CDS (———) and 12 µg/ml HCT (———) solutions and commercial tablet solution (– – ·) (in methanol) containing CDS and HCT

The selection of higher sensitive wavelengths is an important parameter for the development of a multivariate spectral method for resolving complex mixtures. In this context, three different wavelengths for CDS and HCT, which correspond to two maxima of wavelength (223.5 and 268.5 nm) and a minimum (240.0 nm) were selected for the application of the new TCLS method to the analysis of CDS-HCT mixtures and pharmaceutical preparations.

In the applied method, the absorbances of the drug standards prepared in the concentration range where Beer's law is valid (6.0-18.0 µg/ml for CDC and 4.0-16.0 µg/ml for HCT) were recorded on the UV spectrophotometer at three different wavelengths (223.5, 240.0 and 268.5 nm). By using the matrix calculation approach explained in the "Experimental Section", the simultaneous quantification of two active substances (CDS and HCT) is possible by direct measurement of absorbances at 223.5, 240.0 and 268.5 nm in the UV spectrum. For both CDS and HCT, the absorptivities of the compounds corresponding to the absorbance values at three wavelengths were calculated using Equation 1. The averages of the calculated absorptivities for each concentration in the calibration set of each compound were presented in Table 1.

Table 1. Calculated absorptivities of CDS and HCT at three different wavelengths

	Absorptivity (a) x 10^{-2}		
λ (nm)	223.5	240	268.5
CDS	6.67	2.76	2.33
HCT	11.41	0.46	6.42

The same spectral procedures were applied to the tablet sample solutions. For the analytical validation of the TCLS method, a validation set consisting of eight synthetic mixture solutions at different concentrations within the 4-20 µg/ml linear working range of CDS and HCT was prepared. The accuracy and precision of the TCLS calibration were tested by analyzing the prepared validation set. Recovery values were found to be 97.2% for CDS and 99.7% for HCT. Relative standard deviation values were calculated as 1.61% for CDS and 3.67% for HCT. The results obtained by applying the TCLS approach to synthetic mixtures are presented in Table 2. As seen in Table 2, the validity of the method was reported with good accuracy and precision.

Table 2. Recovery results were obtained by applying the TCLS method to the synthetic mixtures containing different concentrations of CDS and HCT

	Synthetic Mixture (µg/ml)		Found (µg/ml)		Recovery (%)	
No.	CDS	HCT	CDS	HCT	CDS	HCT
1	6	6	5.91	6.10	98.54	101.6
2	10	6	9.72	6.05	97.19	100.8
3	14	6	13.47	6.22	96.21	103.6
4	18	6	17.19	6.27	95.51	104.4
5	8	4	7.99	3.99	99.83	99.8
6	8	8	7.86	7.65	98.28	95.7
7	8	12	7.75	11.38	96.86	94.8
8	8	16	7.63	15.43	95.37	96.5
				Mean	97.2	99.7
				SD	1.57	3.66
				RSD	1.61	3.67

SD: Standard deviation
RSD: Relative standard deviation

The commercial tablet sample was prepared five times as stated in the "Preparation of Samples" subsection. The proposed TCLS approach was applied to the analysis of the tablet samples and then, the amount of CDS and HCT in the commercial pharmaceutical preparation was determined by using the TCLS model based on the absorbance measurements at a set of three wavelengths. The determination results are presented in Table 3. The analysis results showed good agreement with the tablets' label claims. In addition to that, in the TCLS method application providing a low standard deviation and relative standard deviation, a good agreement was reported for the experimental outcomes.

Table 3. Results obtained by the applying TCLS method to the commercial tablet (Label claim in the preparation: 16 mg CDS and 12.5 mg HCT per tablet)

	mg/tablet	
Exp. No.	CDS	HCT
1	16.05	12.40
2	16.11	12.58
3	16.22	12.57
4	16.07	12.39
5	16.30	12.40
Mean	16.1	12.5
SD	0.11	0.10
RSD	0.66	0.78

SD: Standard deviation
RSD: Relative standard deviation

Conclusion

The main aim of this research article was to develop an easy, inexpensive, selective, sensitive, and validated method for the analysis of a commercial pharmaceutical preparation containing CDS and HCT. In this context, the developed TCLS approach was successfully applied to the simultaneous quantification of CDS and HCT in synthetic mixtures and tablets. In the pharmaceutical industry and R&D laboratories, the TCLS method can be used for quality control and routine analysis of binary combined preparations containing CDS and HCT active compounds.

ACKNOWLEDGEMENTS

In this paper study, the method development and its experiment procedures were performed at the Chemometric Laboratory of Faculty of Pharmacy supported by Ankara University Scientific Research Fund (Project No. 10A3336001).

AUTHOR CONTRIBUTIONS

Concept: A.Ü., E.D.; Control: A.Ü, E.D.; Design: A.Ü., Ö.Ü., E.D.; Materials: U.S., E.D.; Sources: A.Ü., Ö.Ü.; Data Collection and/or Processing: U.S., E.D.; Analysis and/or Interpretation: A.Ü., Ö.Ü., E.D.; Literature Review: A.Ü, U.S.; Manuscript Writing: A.Ü., E.D.; Critical Review: A.Ü., Ö.Ü., U.S., E.D.; Other: -

CONFLICTS OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

REFERENCES

1. Burnier, M., Brunner, H.R. (1998). Angiotensin II receptor antagonists in hypertension. Kidney International, 45(68), 107-111. [CrossRef]
2. Gohlke, P., Jürgensen, T., von Kügelgen, S., Unger, T. (1999). Candesartan cilexetil: Development and preclinical studies. Drugs Today (Barc), 35(2), 105-115. [CrossRef]
3. Elmfeldt, D., George, M., Hübner, R., Olofsson, B. (1997). Candesartan cilexetil, a new generation angiotensin II antagonist, provides dose dependent antihypertensive effect. Journal of Human Hypertension, 11(2), 49-53. [CrossRef]
4. Ernst, M.E., Fravel, M.A. (2022). Thiazide and the thiazide-like diuretics: Review of hydrochlorothiazide, chlorthalidone, and indapamide. American Journal of Hypertension. 35(7), 573-586. [CrossRef]
5. Prajapati, S.T., Patel, P.K., Chauhan, V.B., Patel, C.N., Patel, M. (2011). Development and validation of the liquid chromatography-tandem mass spectrometry method for quantitative estimation of candesartan from human plasma. Pharmaceutical methods, 2 (2), 130-134. [CrossRef]
6. Hertzog, D.L., Finnegan J., McCafferty, J.F., Fang, X., Tyrrell, R.J., Reed, R.A. (2002). Development and validation of a stability-indicating HPLC method for the simultaneous determination of Losartan potassium, hydrochlorothiazide, and their degradation products. Journal of Pharmaceutical and Biomedical Analysis, 30, 747-760. [CrossRef]
7. González, L., Alonso, R.M., Jiménez, R.M. (2000). A high-performance liquid chromatographic method for screening angiotensin II receptor antagonists in human urine. Chromatographia, 52, 735-740. [CrossRef]
8. Üstündağ, Ö., Dinç, E. (2021). Continuous wavelet transforms and ultra-performance liquid chromatography applied to the simultaneous quantitative determination of candesartan cilexetil and hydrochlorothiazide in tablet. Monatshefte für Chemie - Chemical Monthly, 152, 1097-1106. [CrossRef]
9. Hillaert, S., Van den Bosshe, W. (2003). Simultaneous determination of hydrochlorothiazide and several angiotensin-II-receptor antagonists by capillary electrophoresis. Journal of Pharmaceutical and Biomedical Analysis, 31, 329-339. [CrossRef]
10. Zhang, M., Wei, F., Zhang, Y.F. (2006) Novel polymer monolith microextraction using a poly(methacrylic

acid-ethylene glycol dimethacrylate) monolith and its application to simultaneous analysis of several angiotensin II receptor antagonists in human urine by capillary zone electrophoresis. Journal of Chromatography A, 1102, 294-301. [CrossRef]

11. Hillaert, S., De Beer, T.R., De Beer, J.O., Van den Bossche W. (2003). Optimization and validation of a micellar electrokinetic chromatographic method for the analysis of several angiotensin-II-receptor antagonists. Journal of Chromatography A, 984, 135-146. [CrossRef]
12. Lasure, A., Ansari, A., Kalshetti, M. (2020). UV spectrophotometric analysis and validation of acyclovir in solid dosage form. International Journal of Current Pharmaceutical Research,12 (2), 100-103. [CrossRef]
13. Dhole, S.M., Amnerkar, N.D., Khedekar, P.B. (2012). Comparison of UV spectrophotometry and high performance liquid chromatography methods for the determination of repaglinide in tablets. Pharmaceutical Methods, 3 (2), 68-72. [CrossRef]
14. Abdelwahab, N.S. (2016). Spectrophotometric methods for simultaneous determination of Carvedilol and Hydrochlorothiazide in combined dosage form. Arabian Journal of Chemistry, 9, 355-360. [CrossRef]
15. Lastra, O.C., Lemus, I.G., Sánchez, H.J., Pérez, R.F. (2003). Development and validation of an UV derivative spectrophotometric determination of Losartan potassium in tablets. Journal of Pharmaceutical and Biomedical Analysis, 33, 175-180. [CrossRef]
16. Tatar, S., Saglik, S. (2002) Comparison of UV- and second derivative-spectrophotometric and LC methods for the determination of valsartan in pharmaceutical formulation. Journal of Pharmaceutical and Biomedical Analysis, 30, 371-375. [CrossRef]
17. Redasani, V.K., Patel, P.R., Marathe, D.Y., Chaudhari, S.R., Shirkhedkar, A.A., Surana, S.J. (2018). A review on derivative UV-spectrophotometry analysis of drugs in pharmaceutical formulations and biological samples review. Journal of the Chilean Chemical Society, 63(3), 4126-4134. [CrossRef]
18. Mukthinuthalapati, M. A., Kumar, J. S. P. (2015). Simultaneous derivative spectrophotometric determination of candesartan cilexetil and hydrochlorothiazide. Pharmaceutical Methods, 6, 148-151.
19. Belal, T.S., Daabeesb, H.G., Abdel-Khalekb, M.M., Mahrousb, M.S., Khamisb, M.M. (2013). New simple spectrophotometric method for determination of the binary mixtures (atorvastatin calcium and ezetimibe; candesartan cilexetil and hydrochlorothiazide) in tablets. Journal of Pharmaceutical Analysis, 3(2), 118-126. [CrossRef]