Plant Archives Volume 20 No. 2, 2020 pp. 5158-5162 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

ION PAIR EXTRACTION OF CARVEDILOL AND LOSARTAN IN PHARMACEUTICAL SAMPLES

Qasim Mzban[1], Sarmad Bahjat[2] and Mohammed Jasim M. Hassan[1]*

[1*]Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, IRAQ.
[2]Department of Chemistry, College of Education Ibn Al Haitham, Baghdad University, IRAQ.

Abstract

A sensitive, rapid, accurate and simple method for estimating carvedilol and losartan in pharmaceutical samples was developed. This approach has been based upon the formation of ionic complexes of drugs with eriochrome black-T in an acidic medium at pH=2 succeeded with extraction in the chloroform. The linear relationship of carvedilol and losartan with eriochrome black-t has been 25 - 250 mg / mL. The evolving method was found to be accurate and accompanied by validation of the statistical verification of analytical data. The suggested approach was applied with success to the analysis of pharmaceuticals samples

Key words: Carvedilol, Losartan, Eriochrome black-T and Spectrophotometric method.

Introduction

Carvedilol can be defined as a racemic mix of (±)-1-(9H-carbazol-4yloxy)-3-[[2-(omethoxyphenoxy) ethyl]amino]-2propanol (Fig. 1). It is a lipophilic vasodilating non cardio selective-blocker, lacking the intrinsic sympathomimetic activities, thereby, it has enhanced tolerability in comparison to the older-blockers (McTavish *et al*., 1993; Toda and therapeutics, 2003). The absorption of the carvedilol happens rapidly after being orally administered and is metabolized extensively in liver (Stafylas *et al*., 2008). The "traditional"-blockers of the older generation selectively. Losartan, with an IUPAC name chemically it is2-n-butyl-4chloro-hydroxy-methyl-1-((2c(1Htetrazol-5yl)(biphenyl-4yl) methyl) imidazole potassium salt, it is a strong, non-peptide, angiotensin II receptor antagonist that affect renin-angiotensin system, used mainly for the treatment of hypertension (Howland *et al*., 2006). Several reported approaches were described for determining the LOS in its tablet. Those approaches such as spectrophotometry (Lande *et al*., 2000; Darwish, 2005). Losartan potassium can be described as one of the competitive AT-1 angiotensin II receptor antagonist, which is helpful for the maintenance of the constant blood pressure in spite of the variations in a hydration state of a person, the intake of the sodium as well as other physiological aspects. In addition to that, the Angiotensin II carries out regulatory tasks of the inhibition of the sodium excretion by kidneys, inhibiting norephedrin re-uptake and stimulation of the bio-synthesis of the aldosterone (Lifshitz *et al*., 2004)

Several methods such as RPHPLC (Kardani *et al*., 2013), spectrophotometry (Theivarasu *et al*., 2010), gas chromatography-mass spectrometry (Manohar *et al*., 2013), Extractive spectrophotometric (Verma and Syed, 2007), liquid chromatography (Zarghi *et al*., 2007) and HPLC (Galanopoulou *et al*., 2008; Sripalakit *et al*., 2010) in biological samples have been reported. A new simple, sensitive ultraviolet spectrophotometric approach was developed for estimating the carvedilol in the pharmaceutical dose forms without the necessity of sample pretreatment. The suggested approach has been developed and validated based on the parameters of the validation. Several reported approaches were described for determining the LOS in its tablet. Those approaches such as the spectrophotometry (Darwish, 2005; Lande *et al*., 2000), Spectrofluorimetry (Bebawy *et al*., 2005), HPLC (Furtek *et al*., 1992; Obando *et al*., 2008; Ali and Rasheed, 2020b; Ali and Rasheed, 2020a; Abdulla and

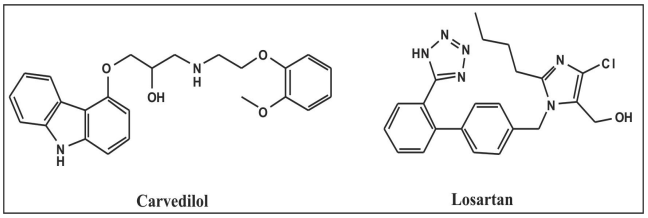

Fig. 1: Chemical structures of the carvedilol and losartan.

***Author for correspondence :** E-mail: mjs.uomustansiriyah.edu.iq

Rasheed, 2020; Abbas and Rasheed, 2018; Seubert and Saad Rasheed, 2017; Abbas and Rasheed, 2017a; Abbas and Rasheed, 2017b; Al-Phalahy and Rasheed, 2016; Al-Phalahy *et al*., 2016), HPTLC (Shah *et al*., 2001; McCarthy *et al*., 1998), capillary electrophoresis (Zhang *et al*., 2006; Williams *et al*., 1996) and electro-chemical approaches (Habib *et al*., 2008a; Habib *et al*., 2008b). Square wave voltammetry can be defined as a large-amplitude differential approach where the wave-form which is composed of a symmetric square-wave is applied to working electrodes (Abdelmegied *et al*., 2014; Głodowski *et al*., 1986). The objective of the present work is developing an inexpensive and sensitive spectral approach and give reliable results for estimating carvedilol and losartan in pharmaceutical samples. Because the majority of the earlier approaches include boring sample preparation, difficult reaction conditions and costly tools, which is why, an attempt was made towards developing a simple approach that requires no heating for the production of the colour, as well as low cost. This method was used for an analysis of the quality control of the pharmaceuticals samples of carvedilol and losartan.

Materials and Methods

Instrument

A Single beam spectrophotometer-295 (Lasany-India) with matched quartz cells of (1cm) has been utilized for the purpose of performing all the spectral absorbance measurements. In addition, the pH meter type inoLab7110, WTW-Germany. Electronic balance Mettler AE200, Switzerland.

Reagents and solutions

All of the used chemicals have been of analytical grade, also distilled water used for preparing all the solutions.

1mg/mL standard solution for each of the cited drugs was prepared through dissolving solid material of (100 mg) in methanol (5 ml) as well as diluting with distilled water to (100 ml) in a volumetric flask. Moreover, 0. 1% (w/v) solution of Eriochrome Black-T(EBT) prepared through dissolving the reagent of 100 mg in distilled water of 100 ml. Also, a buffer solution (pH = 2) has been prepared via mixing (13 mL) of the 0.2 M hydrochloric acid solution has been added to 50 mL of the 0.2 M KCL solution.

Table 1: Optimum conditions of the proposed method.

Studied parameter	Carvedilol Losartan
Type of buffer	2 mL KCl–HCl (pH=2)
Amount of reagent	1 mL of 01% of Eriochrome black-T
Type of organic phase	2mL of chloroform
extraction time	2.0 min

General recommended procedure for the determination of carvedilol and losartan

Aliquots related to the standard solution of losartan and carvedilol is in range of (25-250µg/mL) have been transferred into series of calibrated flasks of (20 mL). To each one of the flasks, a (2mL) of the KCl-HCl buffer solution (pH 2) as well as 1.0 mL of the 0.1% Eriochrome black-T solution have been added, while the volume is made to the mark with the distilled water. In addition, each flask's content is after that shaken in (100 mL) separating funnels for a period of 2 mins. with chloroform of 10 ml, while the absorbance related to the created ion pair complex in chloroform layer has been assessed at 520 nm for the two drugs against reagent blank similarly prepared. Furthermore, the calibration curves have been created via plotting the assessed absorbance value against equivalent concentrations of specific drug. Table 1 presents the optimal conditions.

Results and Discussion

When the solution of a drug (carvedilol and or losartan) was mixed with 0.1% Eriochrome black-T solution in acidic buffered medium, a colored solution is formed, which is then extracted into a chloroform layer. The recorded spectrum of the organic phase for the range 380-800 nm shows a maximum at 520 nm for the complexes of both drugs fig. 2.

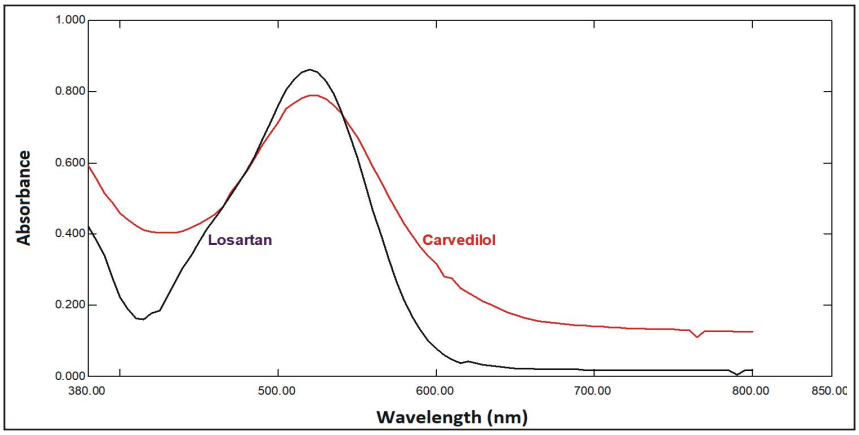

Fig. 2: Absorption spectra of the reaction products of carvedilol and losartan with Eriochrome black-T against their reagent blank.

The newly formed band was due creating ion-pair complex between Eriochrome black-T and the drug. The measured intensity related to this band after extracting the developed complex into an organic solvent (chloroform) found to be increased with increasing the concentration of the cited drug. There are a lot of experimental parameters impacting the extraction and formation of created ion-paired complexes were

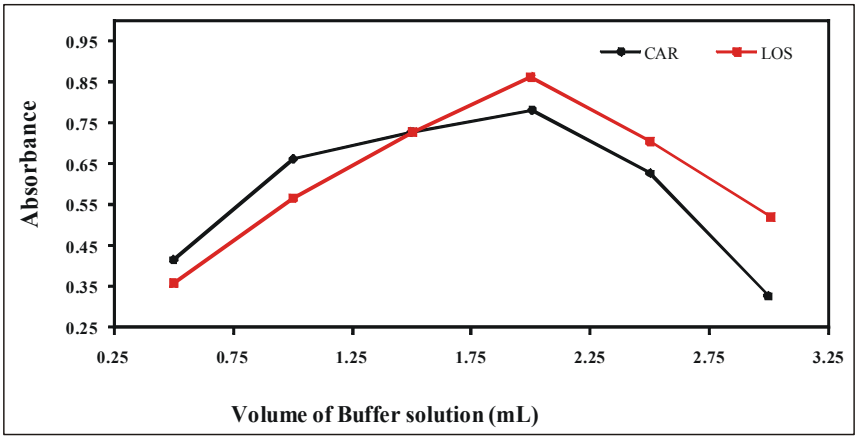

Fig. 3: The effect of the amount of buffer.

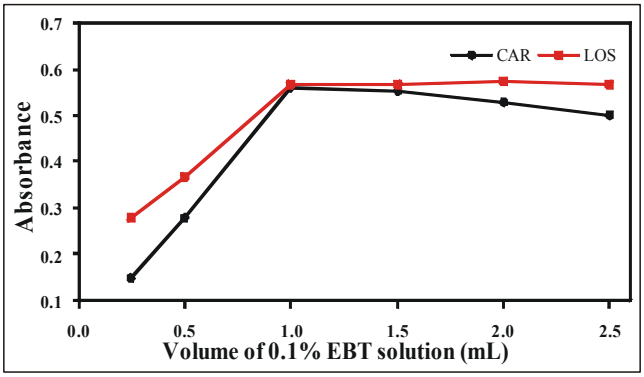

Fig. 4: The effect of the amount of reagent.

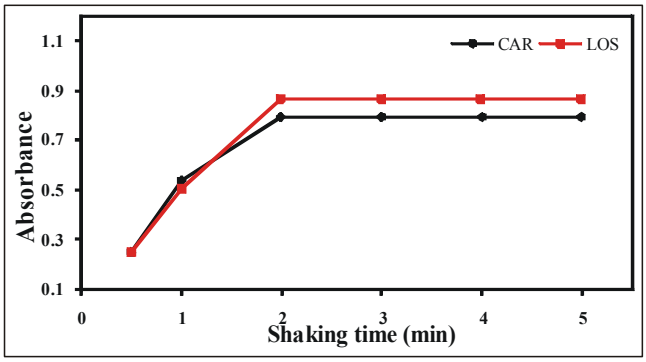

Fig. 5: The effect of extraction time.

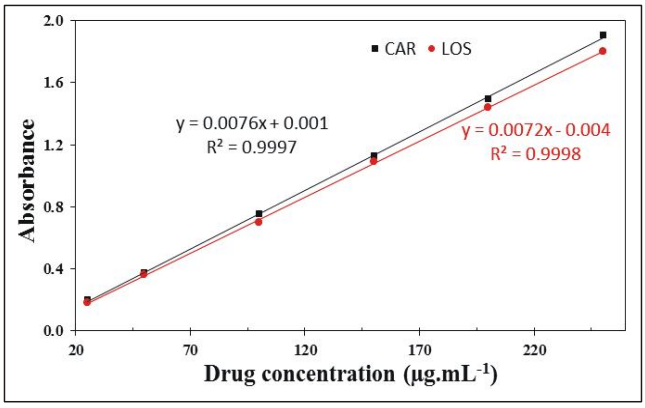

Fig. 6: Calibration curves for final spectrophotometric measurements at 520 nm of carvedilol and Losartan.

studied univariately. The effects of the type and pH various buffers [NaOAc–HCl (pH 1.99-4.92), NaOAc–AcOH (pH 3.6-5.6) and KCl–HCl (pH 1.0-2.2)], the amount of the Eriochrome black-T reagent (using 0.25-3.0 ml of 1%) were investigated. Fig. 3 and 4 show that using 1mL of the chromogenic reagent at pH 2 (using KCl–HCl buffer) results in obtaining maximum color intensity for both drugs.

On the other hand, the type and volume of many organic solvents (acetone, carbon tetrachloride, dichloromethane and chloroform) are tested for carrying out extraction. 2mL of chloroform proved to give the highest extraction efficiency. Moreover, optimum shaking time for a period of 0.5-5 min for only one extraction was investigated to attain equilibration. The results show that only one extraction for 2.0 min period (Fig. 5) was the shortest time to achieve equilibrium between the phases since it provided a constant absorption signal of the organic phase. Therefore, it was selected as an optimum extraction time. Table 1, summarize the optimum experimental conditions.

Validation of the Method

• Calibration curve: Under the optimized experimental conditions, the measured absorbance value at 520 nm was in proportion with the concentrations of carvedilol and losartan. Accordingly, the linear plots of the concentration of the cited drugs in range (25-250) µg. mL^{-1}, against the value of absorption signal at the mentioned wavelength indicates the obeyance of Beer's law, fig. 6. The slopes of two plots confirm the values of the respective carvedilol and losartan molar absorptivities to be $3.0894 \times 10^{+3}$ L. $mol^{-1}.cm^{-1}$ and $3.0449 \times 10^{+3}$ L. $mol^{-1}.cm^{-1}$.

Other optical and statistical parameters of the suggested method for the spectrophotometric determinations regarding losartan and carvedilol through ion pair complexes formation are tabulated in table 2.

• Accuracy and Precession: The accuracy and precisions of the suggested approach have been studied under optimum experimental conditions by analyzing six replicates of three different standard concentrations of carvedilol and losartan. The measurements were accomplished within the same day. Table 3 shows the results with regard to relative standard deviation ratio (% RSD) as well as relative error percent indicating that the approach is accurate and precise.

• Stability: No changes were observed in the tested standard samples after 24 hours, which indicates the

Table 2: Quantitative parameters for the reaction of spectrophotometric determination of carvedilol and losartan with EBT.

Parameter	Carvedilol	Losartan
λmax (nm)	520	
Color	purple	
Linear range (μg.mL^{-1})	25 - 250	
Regression equation	y= 0.0076x + 0.001	y= 0.0072x - 0.004
Correlation coefficient	0.9997	09998
Molar absorptivity (L.mol^{-1}.cm^{-1})	$3.0894 \times 10^{+3}$	$3.0449 \times 10^{+3}$
Detection Limit (μg.mL^{-1})	0.182	0.159
Sandell's sensitivity (μg.cm^{-2})	0.1316	0.1389

Table 3: Accuracy and precision for the estimation of carvedilol and losartan by the recommended method.

Drug	Conc. of the drug (μg.mL^{-1})		*RE	*RSD
	Taken	Found	%	%
Carvedilol	10	9.98	-0.20	0.09
	20	20.10	0.50	0.16
	30	29.97	-0.10	0.31
Losartan	10	10.02	0.20	0.10
	20	19.88	-0.60	0.04
	30	29.98	-0.07	0.21

stability regarding such drugs in solvent, as well as stability and color acquired. However, a decrease in absorbance was observed after that.

• Analysis of Pharmaceutical Dosage Forms: Ten tablets of each drug were carefully weighed and crushed. After that, each drug of (100 mg) has been transferred to volumetric flask of (100 ml) dissolved in methanol of (10 ml) and completed with distilled water up to the mark. In addition, the sample solution with regard to each of the drugs has been filtered via filter paper and after that the aliquots regarding each of the drug solutions are subjected to analysis following the recommended procedure. The unknown concentration was calculated from the regression equation. Table 4 presents the results of recovery analysis.

The high recovery percentage indicates that the approach is considered as free from interference due to the presence of excipients, which might be found in formulation dosage; hence could be used for routine analysis and in quality control to monitor the quality of these drugs. Moreover, the results acquired via using the suggested approach for analysis of commercial tablets have been statistically compared with reference approach (Tulja *et al*., 2012). These decisions were used in batches of the same samples. The t- and F- values are not exceeding the theoretical values in any of the tests, specifying that there weren't considerable differences between the comparative approaches.

Table 4: Assay and Recovery studies of the proposed method.

Name of the dosage form	Labeled amount (mg)	Content of the drug found mg a ± S.D		% Recovery by the proposed method
		Proposed method	Reference method	
Carvedilol	150	150.02±0.0715 F=0.2990 t=0.4561	149.95±0.043	100.01
Losartan	20	19.99.±0.059 F = 0.7828 t=0.6540	20.025=0.051	99.95

Conclusion

The suggested approach is sensitive, simple and rapid and might be effectively utilized for determining such drugs in the pharmaceutical samples. Also, the suggested detector is cheap and available and the approach doesn't require to be heated to develop color.

References

Abbas, M.A. and A.S. Rasheed (2017a). Famotidine determination in pure and pharmaceutical formu-lations by zwitterionic chromatography-hydrophilic interaction liquid chromatography. *International Journal of Chem. Tech. Research,* **10:** 785-791.

Abbas, M.A. and A.S. Rasheed (2017b). Study on the retention behavior of famotidine in hydrophilic interaction liquid chromatography. *International Journal of Chem. Tech. Research,* **10:** 674-680.

Abbas, M.A. and A.S. Rasheed (2018). Retention characteristic of ranitidine hydrochloride on new polymer-based in zwitter ion chromatography-hydrophilic interaction chromatography stationary phases. *Journal of the Chemical Society of Pakistan,* **40:** 89-94.

Abdelmegied, A.M., A.A. Abdelgaber, O.H. Abdelmageed and M.A.J.S.J.O.O.U. Omar (2014). Determination of Losartan in tablet dosage form and some biological body fluids via copmlexation with Cu (II) using Cathodic Adsorptive Stripping Voltammetry. **2:** 40-49.

Abdulla, F.H. and A.S. Rasheed (2020). Hydrophilic Interaction Chromatography Analysis of Esculin in Oint-ments with UV Detection. *Current Pharmaceutical Analysis,* **16:** 935-941.

Al-Phalahy, B.A., Y.H. Muhamad and A.S. Rasheed (2016). Zwitterionic Ion Chromatography of Dansyl Amino Acids with 4-Vinylbenzyl Dimethyl Ammonio Pentanesulfonate as Stationary Phase. *Asian J. Chem.,* **28:** 2411-2414.

Al-Phalahy, B.A. and A.S. Rasheed (2016). ICP Spectrometric-Vis Separation of

Cerium (IV)–Desferal Complex Using 4-Vinylbenzyl-Dimethylammonio Pentanesulfonate Zwitterionic Stationary Phase. *Al-Nahrain Journal of Science,* **19:** 25-32.

Ali, A.S. and A.S. Rasheed (2020a). Application of Hydrophilic Interaction Chromatography Methods For Prednisolone Acetate Determination in their Pure and Tablet, Syrup Dosage Forms. *Plant Archives,* **20:** 2807-2812.

Ali, A.S. and A.S. Rasheed (2020b). Separation And Quantitative Analysis of Chlorpheniramine Maleate by The Application of The Zic-hilic Technique in Bulk and Medicine Formulations. *Plant Archives,* **20:** 2865-2870.

Bebawy, L.I., S.S. Abbas, L.A. Fattah and H.H.J.I.F. Refaat (2005). Application of first-derivative, ratio derivative spectrophotometry, TLC-densitometry and spectrofluorimetry for the simultaneous determination of telmisartan and hydrochlorothiazide in pharmaceutical dosage forms and plasma. **60:** 859-867.

Darwish, I.A.J.A.C.A. (2005). Analytical study for the charge-transfer complexes of losartan potassium. **549:** 212-220.

Furtek, C.I., M.W.J.J.O.C.B.B.S. Lo and Applications (1992). Simultaneous determination of a novel angiotensin II receptor blocking agent, losartan and its metabolite in human plasma and urine by high-performance liquid chromatography. **573:** 295-301.

Galanopoulou, O., S. Rozou, E.J.J.O.P. Antoniadou-vyza and B. Analysis (2008). HPLC analysis, isolation and identification of a new degradation product in carvedilol tablets. **48:** 70-77.

GŁOdowski, S., R. Bilewicz and Z.J.A.C.A. Kublik (1986). Determination of traces of purine by cathodic stripping voltammetry at the hanging copper amalgam drop electrode. **186:** 39-47.

Habib, I., S. Weshahy, S. Toubar and M.J.D.P.A. I.J.O.P.S. El-alamin (2008a). Stripping voltammetric determination of valsartan in bulk and pharmaceutical products. **63:** 337-341.

Habib, I., S. Weshahy, S. Toubar and M.J.P.E.A. El-alamin (2008b). Cathodic stripping voltammetric determination of losartan in bulk and pharmaceutical products. **26:** 315-324.

Howland, R.D., M.J. Mycek, R.A. Harvey and P.C. Champe (2006). *Lippincott's illustrated reviews: Pharmacology*, Lippincott Williams & Wilkins Philadelphia.

Kardani, K., N. Gurav, B. Solanki, P. Patel and B.J.J.O.A.P.S. Patel (2013). RP-HPLC method development and validation of gallic acid in polyherbal tablet formulation. **3:** 37.

Lande, N., B. Shetkar, S. Kadam and S.J.I.D.B. Dhaneshwar (2000). Simultaneous spectrophotometric estimation of Losartan potassium and Hydrochlorothiazide in tablet dosage form. **37:** 577-581.

Lifshitz, I., I. Kor and S. Shabat (2004). Process for preparing losartan potassium with improved flow ability. Google Patents.

Manohar, S.D., D.A. Sridhar and S.C.J.A.J.O.R.I.C. Mallikarjuna (2013). Development of UV spectrophotometric method for estimation of carvedilol in bulk and pharmaceutical formulations. **6:** 956-959.

Mccarthy, K.E., Q. Wang, E.W. Tsai, R.E. Gilbert, IP, D.P., M.A.J.J.O.P. Brooks and B. Analysis (1998). Determination of losartan and its degradates in COZAAR® tablets by reversed-phase high-performance thin-layer chromatography. **17:** 671-677.

Mctavish, D., D. Campoli-Richards and E.M.J.D. Sorkin (1993). *Carvedilol*., **45:** 232-258.

Obando, M.A., J.M. Estela, V.J.A. Cerdà and B. Chemistry (2008). Simultaneous determination of hydrochlorothiazide and losartan potassium in tablets by high-performance low-pressure chromatography using a multi-syringe burette coupled to a monolithic column. **391:** 2349-2356.

Seubert, A. and A. Saad Rasheed (2017). Separation of Metal-Trifluoperazine Hydrochloride Complexes Using Zwitterionic Ion Chromatography (ZIC) Coupled Online with ICP-AES. *Current Pharmaceutical Analysis,* **13:** 328-333.

Shah, S.A., I.S. Rathod, B.N. Suhagia, S.S. Savale and J.B.J.J.O.A.I. Patel (2001). Simultaneous determination of losartan and hydrochlorothiazide in combined dosage forms by first-derivative spectroscopy and high-performance thin-layer chromatography. **84:** 1715-1723.

Sripalakit, P., S. Kaewnok, S.J.M.I.J.O.S. Tubtonglang and Technology (2010). Development of carvedilol assay in tablet dosage form using HPLC with fluorescence detection. **4:** 8-19.

Stafylas, P.C., P.A.J.V.H. Sarafidis and R. Management (2008). Carvedilol in hypertension treatment. **4:** 23.

Theivarasu, C., S. Ghosh, T.J.A.J.O.P. Indumathi and C. Research (2010). UV spectrophotometric determination of carvedilol in pharmaceutical formulations. **3:** 64-68.

Toda, N.J.P. and Therapeutics (2003). Vasodilating β-adrenoceptor blockers as cardiovascular therapeutics. **100:** 215-234.

Tulja, R., G. Sankar and B. Satyanarayana (2012). Extractive visible Spectrophotometric method for determination of Telmisatan and Irbesartan in bulk and pharmaceutical formulations. *Asian J. Pharm. Clin. Res.,* **5:** 41-4.

Verma, J. and H.J.I.J.O.P.S. Syed (2007). Extractive spectrophotometric method for determination of carvedilol in tablets. **69:** 303.

Williams, R., M. Alasandro, V. Fasone, R. Boucher, J.J.J.O.P. Edwards and B. Analysis (1996). Comparison of liquid chromatography, capillary electrophoresis and super-critical fluid chromatography in the determination of Losartan Potassium drug substance in Cozaar® tablets. **14:** 1539-1546.

Zarghi, A., S. Foroutan, A. Shafaati, A.J.J.O.P. Khoddam and B. Analysis (2007). Quantification of carvedilol in human plasma by liquid chromatography using fluorescence detection: *application in pharmacokinetic studies*, **44:** 250-253.

Zhang, M., F. Wei, Y.F. Zhang, J. Nie and Y.Q.J.J.O.C.A. Feng (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. **1102:** 294-301.