Novel Method for Determination of Captopril in Pharmaceutical Formulations by Cloud – Point Extraction

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Abstract
A new, simple , fast and accurate spectrophotometric method for the determination of captopril in pure form and in pharmaceutical preparations is proposed by cloud point extraction . after complexation with bromo phenol blue used as complexing agent . using Triton X-114 as surfactant It is extracted and then separated into two phases, organic and aqueous by centrifugation and placed in an ice bath, then the aqueous layer is poured and the organic layer dissolves in the ethanol solvent, and the absorption is measured as it gives absorption at the wavelength 425 The optimum conditions for the reaction were studied, the triton x-114 volume, the acid volume, the reagent volume, the temperature and time affected on the cloud point extraction process, etc. To reach a high extraction of efficiency. It was found that the concentrations that obeyed Beer's law are in a linear range(1-12µg/ml), and the value of the correlation coefficient R^2=0.9959. The detection limit was calculated and was equal to (0.051µg/ml) and the method has been successfully applied to pharmaceutical preparations for captopril present in tablets containing known.
Keywords: captopril, Bromophenol blue, Cloud point extraction

1. Introduction

Captopril (CPL), is an orally active inhibitor its angiotensin I-converting enzyme inhibitor.(1)It is been widely widely utilized in treatment of hypertension and congestive heart failure.(2) And cardiovascular diseases.(3,4) CAP is metabolized in the liver and excreted mainly in the urine,(5) Captopril is a white to off-white crystalline powder with a slight mercaptan odor, The chemical name 1-(3-mercapto-2-D-methy1-1 -oxopropyl)-L-proline (S,S), has a molecular weight 217.29g/ mole, Molecular formula C9H15NOS3, and the chemical structure of the drug captopril is shown in (fig1).(6)It is considered an active agent in many pharmaceutical preparations as an ACE inhibitor.(7) Captopril is considered the drug is the preferred for the treatment of antihypertensive due to its efficacy and low toxicity.(8) For the quantity determination of captopril in pharmaceutical preparations and biological fluids, various instrumental methods have been reported, UV–Vis absorption spectrophotometry,(9) capillary zone electrophoresis,(10) electro-chemical detection (ECD)(11), mass spectrometry(12), fluorimetry gas chromatography(13), liquid chromatography with electrochemical methods,(14,15) fluorescence,(16) chemiluminescence,(17) potentiometry,(18) flow injection analysis,(19)high performance liquid chromatography,(20,21) amperometry,(22)and gas chromatography.(23)

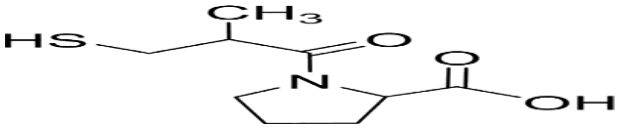

Figure 1: Chemical Structure of Captopril

Cloud point extraction is a separation and preconcentration.(24) This method has some advantages low cost, rapid, and has a very wide applications.(25) In this work , a spectroscopic - cloud point extraction procedure described using as surfactant of Triton X-114 for separation and preconcentration of the captopril. This method was applied to determine for captopril.in pharmaceutical preparations

2. 2. Experimental

Instrumentation

Spectrophotometer (SHIMADZU, Model UV-1800, made in Japan) .was used for all the measurements in this methods for the determine the concentration of the captopril .Water bath (S-HH) made in Korea maintained as the desired temperature was used for the cloud point extraction experiments .and phase separation was assisted using a centrifuge Type (EBA20) German-made, It has revolutions 6000 per min, sensitive scale with four decimal places(N-120 ABS kern balance).

Reagents

All chemicals used were of analytical purity grade and all solutions were prepared with distilled water. A standard solution of captopril (1000µg/ml) by dissolving 0.1 g of it in a small amount of distilled water, then complete the volume to the mark in a volumetric flask of 100 ml.
solution surfactant, Triton X-114 (10%) was prepared by draw 10 ml and diluting it to 100 mL in volumetric flask
Bromophenol blue dye (1×10^{-4}) M was prepared by dissolving (0.067) gm a accurately weighed dye and

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diluting it to 100 mL in volumetric flask.
A hydrochloric acid solution (0.1) M was prepared by drawing 0.83 ml from the concentrate and diluting it with distilled water to the mark in a volumetric flask of 100 ml.

Preparation of captopril drugs

1- Rilcapton(Tablets 25mg) MEDOCHEMIE Pharmaceutical Industries- Cyprus

Ten tablets were weighed to calculate the average tablet weight. They were finely powdered and homogenized. A portion of the powder equivalent to about1.3422 g of captopril
was accurately weighed 0.5368 g and dissolving with 30 mL of water by sonicating for 10 min in an ultrasonic bath. The resulting mixture was filtered and Finally, this solution was diluted with water in a 100 mL flask (1000µg/ ml) and analysed under the same procedure described for captopril in pure form.

2- Rilcapton(Tablets 25mg) Pharmaceutical Industries- Samarra SDI

Ten tablets were weighed to calculate the average tablet weight. They were finely powdered and homogenized. A portion of the powder equivalent to about1. 488 g of captopril
was accurately weighed 0.5955 g and dissolving with 30 mL of water by sonicating for 10 min in an ultrasonic bath. The resulting mixture was filtered and Finally, this solution was diluted with water in a 100 mL flask (1000µg/ ml) and analysed under the same procedure described for captopril in pure form.

Cloud point extraction procedures (CPE)

For the CPE procedure , We take aqueous solutions with volumes of 10 ml containing a limited amount of the durg to be estimated and a suitable amount of organic reagent and other suitable additives are used to estimate the ion in question and take the optimal volume from The surface active substance is T-X114, then these solutions are heated in a water bath at the temperature The occasion and the appropriate time for when the point of the cloud is CP, and then we separate the layer of the point of the cloud by Centrifuge for a certain number of cycles and time, then put it in an ice bath for 5 minutes, then We separate the aqueous layer by pouring, and the cloud layer remains at the bottom of the tube by dissolving it in 5 ml of ethanol In order to decrease the viscosity and facilitate sample handing prior to the spectrophotometer instrument , then We measure the absorption of it at the greatest wavelength against a formal solution prepared in the same way except for the ion The person concerned with the study.

3. Results and discussion

Under the optimum experimental conditions which are represented in the coming results . reacts Captopril with reagent Bromophenol blue to form hydrophobic complexes , which is subsequently trapped in surfactant micelles.
The Spectroscopic study of the composition of the Captopril drug complex with the reagent
The Spectrum Vis-UV absorption spectrum of the captopril complex was drawn to make sure, that the interaction between the reagent and the extracted drug took place at the cloud point to determine the maximum absorption wavelength. Then the Vis-UV absorption spectrum was recorded against a mock solution prepared in the same way without drug. The UV-visible spectroscopic study revealed an absorption peak at the wavelength (λmax= 425nm), as shown in the following (fig.2)

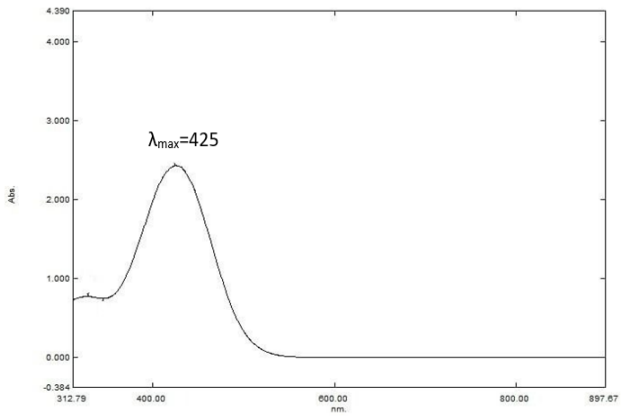

Fig.2 Absorption spectrum UV of the captopril complex with the reagent

(Bromophenol blue)

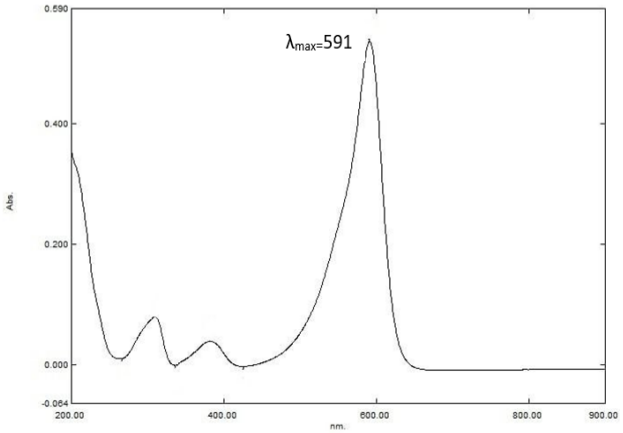

Fig.3 Absorption spectrum UV of the reagent Bromophenol-blue

Study the effect of temperature

Temperature is one of the important factors in the extraction process to form the cloud point, and this was The study showed that temperature has a direct effect on the formation of the complex between the drug and the reagent, and by increasing the temperature With time, the volume of the surfactant-rich phase decreases due to the decrease in the amount of water at this temperature in this The phase and leads to an increase in the efficiency of the extraction,(26) This is because high temperature increases the

hydrophobic property of micelles.(27) High temperatures may cause thermal disintegration of the material to be analytical.(28) It is preferable to use the lowest temperature for equilibrium and the least possible time(29) was studied The temperature range of (40-80°C°), the separation of the two phases was not completed at a temperature less than 70C° and the temperature was given 70 C° The best absorption of the cloud point extraction process is as shown in the following (fig4)

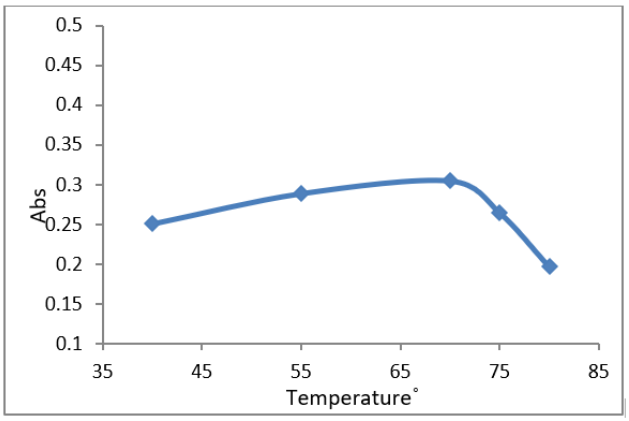

Fig.4. The effect of temperature

Study the effect of heating time

The heating time at the optimum temperature has a significant effect on the formation of the cloud point and obtaining efficiency High extraction time ranges (10-30) mint were taken, and after the completion of the extraction process for the cloud point. Absorption was measured, and the best time for the extraction efficiency with the highest absorption value was 20 mint, as shown in the following (fig.5)

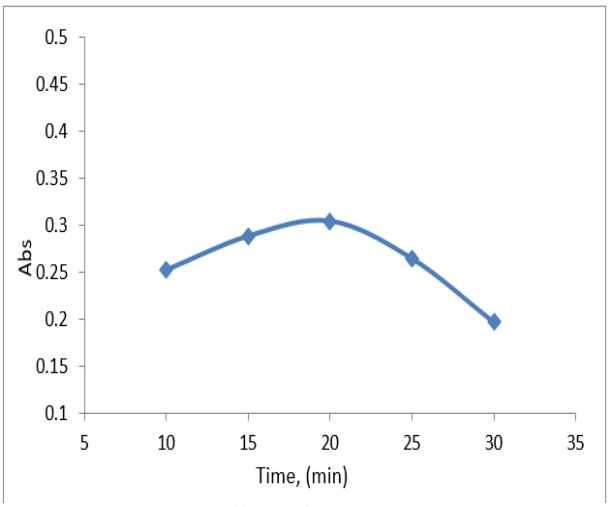

Fig.5.Effect of heating time

Effect the volume of HCl

The results in the figure below showed that the best volume of hydrochloric acid (0.6 ml) at a concentration of 0.1 M was sufficient. For the process of complex formation, which gave the highest absorption, so the volume was fixed in subsequent experiments. (Fig.6)

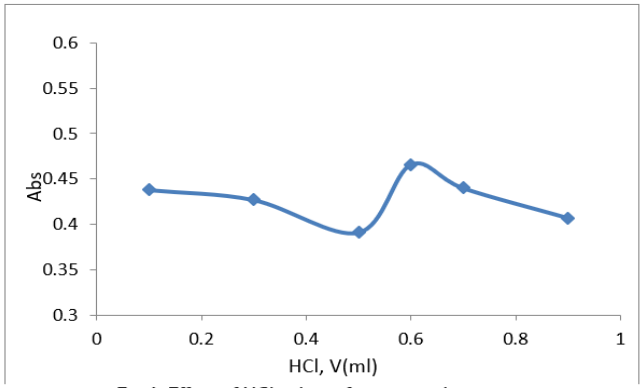

Fig.6. Effect of HCl volume for captopril extraction

Fig.6. Effect of HCl volume for captopril extraction

Effect of volume(%10 Triton X-114)

The effect of the volume of the surfactant active(10%Triton-X114) within the range (0.1-0.7) ml was studied. and the absorption results for each volume were shown in (Fig7) and the best absorption was at the volume(0.6)ml Note that at low amount of TX-114 the absorption is low due to insufficient The micelles attract the analyzed material, and the increase in the amount of TX-114 leads to a decrease The absorption and extraction efficiency is likely due to the increase in the volume of the surfactant-rich phase, as the hydrolysis becomes more diluted, leading to poor sensitivity and thus lower extraction efficiency.(30)

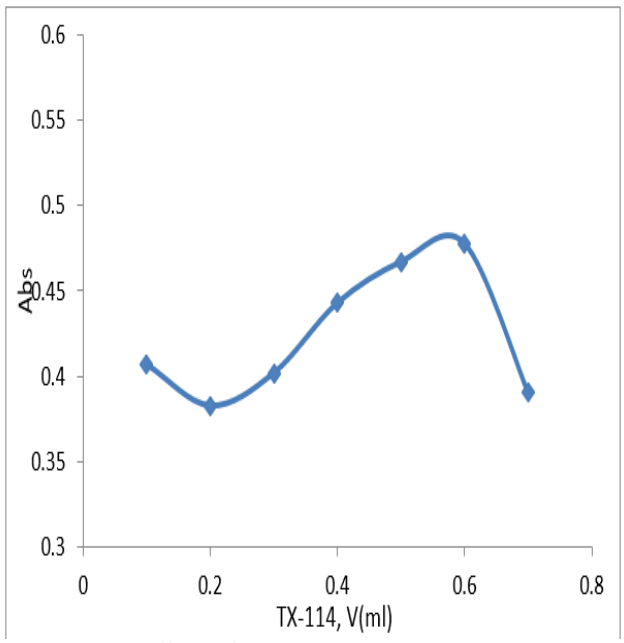

Fig.7. Effect of volume(%10 Triton X-114)

Effect of reagent volume on the cloud point extraction

The effect of reagent volume on captopril determination was studied by changing the volume (1×10-4)M of reagent in the range (0.1-1.2) ml. The absorption was measured for it at the greatest wavelength, where it was found that the volume of 0.9 ml gives the highest absorption. Which represents the optimum volume as it was fixed in the subsequent experiments as shown in the (fig8).

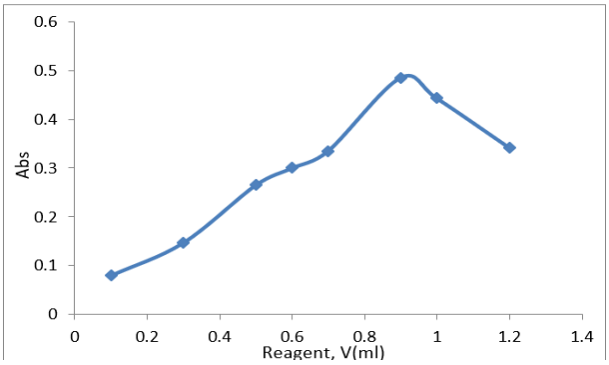

Fig.8. Effect of Bromophenol blue volume for captopril extraction

Effect of centrifugation time

The effect of centrifugation time was studied to separate the effective phase by centrifugation at a speed of 3000 rpm on different time intervals ranging from 5 to 25 minutes, (10) minutes were determined as the optimal centrifugation time to obtain the highest absorption, as shown in the following .(fig.9)

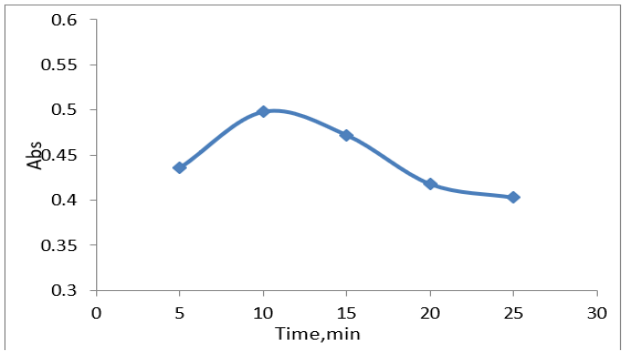

Fig.9. Effect of centrifugal time for captopril extraction

Order of Additions

The effect of the sequence of additions on absorption was studied. It was found that the sequence of additions had an important effect on the absorption of the products formed, as the absorption was measured for it at the greatest wavelength, and it was found that sequence (Drug+Reagent+HCl+TX-114) was the best of the sequences that gave the highest absorption as shown in the following Fig.(10)

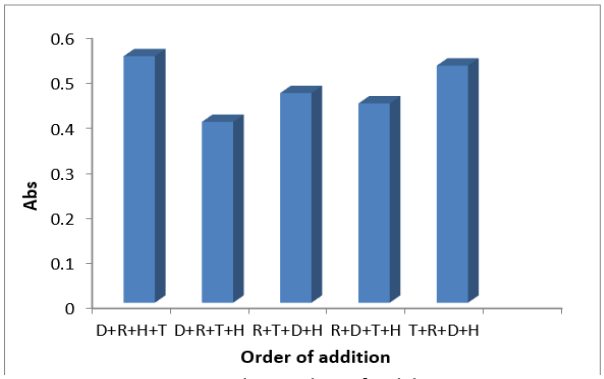

Fig.10. The order of addition

Calibration curve

The calibration curve was prepared in the range of a number of concentrations of the captopril drug solution. In order to estimate the captopril using the (bromo phenol blue) reagent, with taking into amount all the ideal conditions that has been studied previously. find from the figure that Beer's law (1-12µg/ml) and the value of the correlation coefficient,R2=0.9959 and the value of the molar absorption coefficient was ε=3867.94 mol. L The sensitivity of the sandle was calculated, and it was equal to S= 0.056 µg.cm, and the limit of detection(0.051µg/ml) which indicates an excellent linear relationship between the analytic signal,(absorption) and concentration as shown in the following(fig.11).

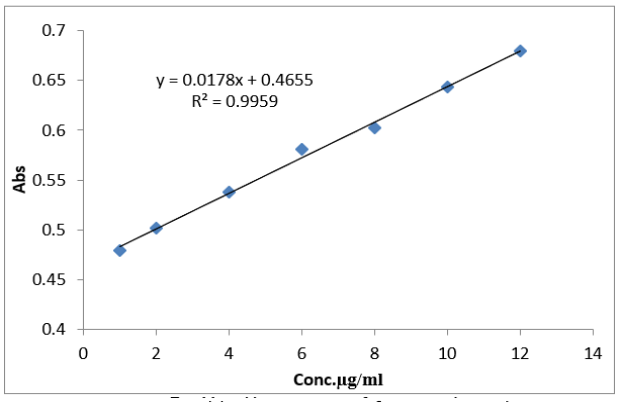

Fig.11. calibration curve for captopril

Conjugation ratio between drug with Reagent

Job's method of continuous changes was depend upeon the purpose of finding the structural formula of the extracted complex by mixing equal concentrations and different volumes of the drug and the reagent so that the final volume is equal (1ml) and followed the extraction method mentioned previously, and the absorption was measured for it at the greatest wavelength the relationship between absorption and the ratio of the volume of the drug solution to the ratio of the total volume of the drug solution and It was found that the correlation ratio between the drug and the reagent is 2:1, as shown in the following(fig12).

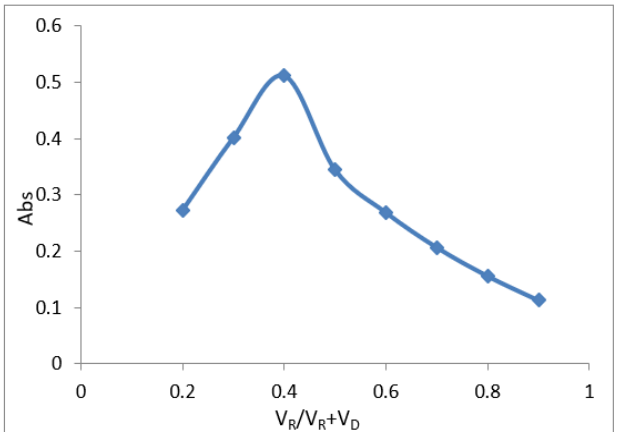

Fig.12. Conjugation ratio by Job method (variable ratios) to extract captopril

The proposed equation for complex formation

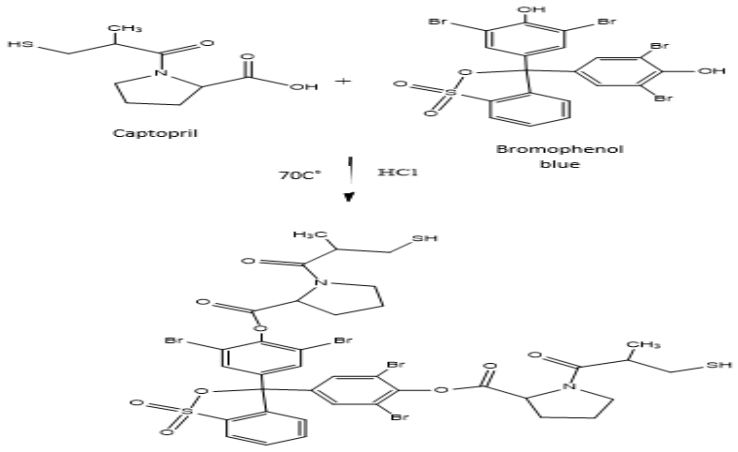

Fig.13.Conjugation and complex formation method (drug + reagent) to extract CAP in a ratio of (2:1)

Effect of interactions the (CPE)

The effect of pharmaceutical additives on the formation of the studied complex under optimal conditions was by taking two concentrations of the studied drug in a series of volumetric flask with a capacity of 10 ml. The absorption of the organic layer after extraction is measured at the maximum wavelength 430nm. Retrieval was calculated and was within the permissible range, as shown in the following table (1)

Table (1)The effect of interactions		
Foreign compound Captopril 70C°	Rec% of 2µg/ml of CAP	
Amounts in (µg/ml)	Bromophenol blue 2µg/ml	4µg/ml
Aerosil	102.5	98.00
Maize starch	99.50	101.0
Talc powder	99.00	100.10
Magnesium stearate	98.20	99.56

Accuracy and Precision

To evaluate the accuracy and precision of the method a pure drug solution was analyzed Three different concentration, each determination being repeated Six times. the relation error(%) and relative standard deviation (RSD) values were summarized in table (2).

Table .2. Accuracy and precision of the proposed method.				
Taken conc. µg/ml	Found conc. µg/ml	RE%	Rec%	RSD%
4	4.07	1.97	101.75	0.1828
10	9.97	-0.3	99.70	0.1302
12	11.99	-0.083	99.16	0.1202

Analytical Applications

The proposed method was successfully applied for captopril determination in tablet formulations. The results presented in Table (3) the percentage recall Rec% and the relative standard deviation RSD% were calculated as in the table (3).

Table. (3). Determination of captopril in pharmaceuticals using the proposed method				
Pharamaceutical drug µg/ml	Taken conc. µg/ml	Found conc. µg/ml	RSD%	Rec%
MEDOCHEMIE	2	1.99	0.1030	99.5
	4	3.9	0.0762	97.5
SID	2	1.94	0.1634	97.0
	4	4.01	0.1560	100.25

Conclusions

The proposed method developed was simple, selective inexpensive and environmentally friendly The study also demonstrated that the concentration and type of surfactant- reach play an important role in controlling the captopril process Extraction. Determining optimal conditions is the main method to reach the highest extraction efficiency. and successfully applied to the determination of Captopril in Pharmaceutical preparation

Refrence

1/Mariangela de Burgos, M. D., Tasic, L., Fattori, J., Rodrigues, F. H., Cantos, F. C., Ribeiro, L. P., ... & Santos, R. A. (2011). New formulation of an old drug in hypertension treatment: the sustained release of captopril from cyclodextrin nanoparticles.

International journal of nanomedicine, 6, 1005
2. Taketomo CK, Hodding JH, Kraus DM. Pediatric & neonatal dosage handbook with international trade names index. 18 th ed. Ohio, USA: Lexi-Comp, Inc., 2011
3.Pfeffer M. A.; Braunwald E.; Moyé L. A.; Basta L.; Brown E. J.; Cuddy T. E.; Davis B. R.; Geltman E. M.; Goldman S.; Flaker G. C.; Klein M.; Lamas G. A.; Packer M.; Rouleau J.; Rouleau J. L.; Rutherford J.; Wertheimer J. H.; Hawkins C. M. Effect of Captopril on Mortality and Morbidity in Patients with Left Ventricular Dysfunction after Myocardial Infarction. N. Engl. J. Med. 1992, 327, 669–677. 10.1056/NEJM199209033271001.
4.Plosker G. L.; McTavish D. Captopril. Drugs Aging 1995, 7, 226–253. 10.2165/00002512-199507030-00007.
5. J.E. Rush, D.D. Merrill, J. Cardiovasc. Pharmacol. 9 (1987) S99–107.
6. Kadin, H. (1982). Captopril. In Analytical profiles of drug substances (Vol. 11, pp. 79-137). Academic Press.
7. 12http:\drugs.com. Accessed in, 2021.
8. Abubkar O Nur, Zhang JS. Recent progress in sustained/controlled oral delivery of captopril: An overview. Int J Pharm 2000; 194: 139-146.
9 .T. Pérez-Ruiz, C. Martínez-Lozano, R. Galera Electrophoresis, 27 (2006), pp. 2310-2316 View PDFCrossRefView Record in Scopus.
10.N. Rahman, M. Singh, M.N. Hoda Il Farmaco., 60 (2005), pp. 569-574 ArticleDownload PDFView Record in Scopus.
11. Khamanga SM, Walker RB. The use of experimental design in the development of an HPLC-ECD method for the analysis of captopril. Talanta 2011;83:1037-49.
12/A. Jankowski, A. Skorek, K. Krzyśko, P.K. Zarzycki, R.J. Ochocka, H. Lamparczyk J. Pharm. Biomed. Anal., 13 (1995), pp. 655-660 ArticleDownload PDFView Record in Scopus.
13/. Franklin ME, Addison RS, Baker PV, Hooper WD. Improved analytical procedure for the measurement of captopril in human plasma by gas chromatography--mass spectrometry
and its application to pharmacokinetic studies. J Chromatogr B Biomed Sci Appl 1998;705:47-54.].
14.G. Favaro, M. Fiorani Anal. Chim. Acta, 332 (1996), pp. 249-255 ArticleDownload PDFView Record in Scopus].
15.K. Kuśmierek, E. Bald Chromatographia, 66 (2007), pp. 71-74 View PDFCrossRefView Record in Scopus].
16.R.J. Kok, J. Visser, F. Moolenaar, D. de Zeeuw, D.K. Meijer J. Chromatogr. B Biomed. Sci. Appl., 693 (1997), pp. 181-189 ArticleDownload PDFView Record in Scopus
17.S. Hillaert, W. Van den Bossche J. Pharm. Biomed. Anal., 21 (1999), pp. 65-73 ArticleDownload PDFView Record in Scopus.
18. Khalilzadeh MA, Karimi-Maleh H, Amiri A, Gholami F and Mazhabi RM, Determination of captopril in patient human urine using ferrocenemonocarboxylic acid modified carbon nanotubes paste electrode, Chin. Chem. Lett., 21 (12), 2010, 1467-1470.
19.Palomeque ME, Band BS, Flow injection biamperometric determination of captopril, J. Pharm. Biomed. Anal., 30 (3), 2002, 547-552.
20.Mirza T and Tan HS, Determination of captopril in pharmaceutical tablets by anionexchange HPLC using indirect photometric detection; a study in systematic method development, J. Pharm. Biomed. Anal., 25 (1), 2001, 39-52
21. Huang T, He Z, Yang B, Shao L and Zheng X, Simultaneous determination of captopril and hydrochlorothiazide in human plasma by reversephase HPLC from linear gradient elution, J. Pharm. Biomed. Anal., 41 (2), 2006, 644- 648.
22.Stefan RI, Van Staden JF and Aboul-Enein HY, An amperometric biosensors/SIA system for the simultaneous determination of Sand R-captopril, Biosensors and Bioelectronics, 15 (1-2), 2000, 1-5.
23. Ito T, Matsuki Y, Kurihara H and Nambara T, Sensitive method for determination of captopril in biological fluids by gas chromatography-mass spectrometry, J. Chrom., 417 (1), 1987, 79-87.
24. Stalikas C.D.,(2002)"Micell-medicated extraction as a tool for separation and preconcentration in metal analysis",Trend Anal.Chem.21,343.
25. Peng W., Zhang Y. b, Lvb Y., Hou X.,(2006)" Cloud point extraction–thermospray flame quartz furnace atomic absorption", Spectrochimica Acta Part B, 61 ,1310.
26- Pourreza, N., Sharifi, H., and Golmohammadi, H. (2016). Curcumin nanoparticles combined with cloud point extraction for citrate determination in food and drug samples. Microchemical Journal, 129, 213-218.
27- Armstrong, J. K., Chowdhry, B. Z., Snowden, M. J., and Leharne, S. A. (1998). Effect of sodium chloride upon micellization and phase separation transitions in aqueous solutions of triblock copolymers: a high-sensitivity differential scanning calorimetry study. Langmuir, 14(8), 2004-2010.
28- Gao, N., Wu, H., Chang, Y., Guo, X., Zhang, L., Du, L., and Fu, Y. (2015). Mixed micelle cloud point-magnetic dispersive μ-solid phase extraction of doxazosin and alfuzosin. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 134, 10-16.
29- Hassanien, M. M., Hassan, A. M., Mortada, W. I., and El-Asmy, A. A. (2011). A new thioamide derivative for separation and preconcentration of multi elements in aquatic environment by cloud point extraction. American Journal of Analytical Chemistry, 2(06), 697.
30-Khammas, Z. A., Jawad, S. K., and Ali, I. R. (2014). A new approach for extraction and determination of manganese in environmental samples using cloud-point extraction coupled with spectrophotometry. Chem. Sci. Trans, 3(1),255-267.