Bulgarian Chemical Communications, Volume 49, Special Issue J (pp. 11 - 18), 2017

Multivariate optimization of the trace amount of chlorpromazine analysis based on solid phase micro-extraction using Al_2O_3 nanoparticles in environmental and biological samples by the spectrophotometry method

M. Saghravanian[1], M. Ebrahimi[*1], Z. Es'haghi[2], H.A. Zamani[1]

[1] *Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran*
[2] *Department of Chemistry, Payame Noor University [PNU], 19395-4697, I.R. of Iran*
Received: May 14, 2017; Revised: August 21, 2017

In this study, enrichment and determination of trace amount of chlorpromazine [CPZ] in environmental and biological samples is presented based on solid phase micro-extraction using the Nanoparticles of by Spectrophotometry of UV/Visible. This method is simple, fast, low cost, safe and available which compared with previous work easily can applied for determination sub-ppm amounts in everywhere. The effective Parameters on the extraction efficiency of the drug such as type of organic solvent ,ph donor phase optimized manually and the volume of aqueous phase ,nanoparticle amount ,extraction and desorption time ,salt effect optimized by experimental design. Under the optimal conditions, limit of detection [LOD] were obtained. The linearity method was in the range 0.005-2 µg.ml-1 with correlation coefficient [R2] equals to 99.17 and pre-concentration factor acquired 366.53. Finally, this method was used for analysis environmental and urine samples with satisfactory results.

Keywords: Nanoparticles, Al_2O_3, SPME, spectrophotometry, chlorpromazine, experimental design

1.INTRODUCTION

Chlorpromazine [CPZ] is one of the usable drugs for curing abnormal behaviors, decreasing the aggression and also has been used as anodyne.

CPZ [Fig. 1] is an antipsychotic phenothiazine which can be used in neurosis like schizoid, dementia, mania and is an auxiliary drug in curing high excitement and mental disorders, also it be used as anti nauseam and curing the hiccup [1] . Additionally, this drug has been used as an auxiliary drug in curing the addiction to heroin. In one study this drug showed an important role in decreasing the desire to use hallucinogens by altering the synapse of mesolimbic dopaminergic, therefore determination of this drug in the trace amounts is really significant. Also, study of interaction between this drug and proteins has been done too much [2-4].

Many analytical methods including electrochemical [5-8] and instrumental [9-12] methods have been used for quantification of CPZ in variety media such as biological medium[12] and pharmaceutical formulations, yet.

Spectrophotometry has been widely used in the determination of pharmaceutical compounds [13-18]. This method due to good sensitivity, much selectivity, economic and easy operation is appropriate.

Nowadays, we need to some new methods for the recognition and analyze the compounds in environmental. Due to environmental risks of organic solvents has been developed using of the types of micro-extraction methods that volume organic solvent reduced to drops or methods that organic solvent is removed.

Compared with the traditional unilabiate methods, multivariate methods are affordable and useful and widely used for optimization of analytical procedures [19].

Response surface methodology [20] has the most usage among other methods.

In this paper, we reported the new and easy method for determination of CPZ in trace amounts using SPME technique by nanoparticles by UV/visible spectrophotometry. We used synthetic Al_2O_3 Nano particles for concentration stage and then was performed desorption by low volume of organic solvent. The aim of this study was use of simple, available, trusty and sensitive method for determination of CPZ in environmental and urine samples.

Also, this nanoparticle can be used because of harmony in shape and distribution in nano scales to hallow fiber [HF] technique for pre-concentration and separation by gas chromatography [GC] and High performance liquid chromatography [HPLC].

2. MATERIALS AND METHODS

2.1 Instrumentation

The spectrophotometer UV/Visible device used in this study was a Varian [CARY Eclipse, Australia], containing a photomultiplier tube detector, which was set at the wave-length ranging from 190-800 nm and Xenon lamp. Quartz microcell with 1 cm path length and bandwidth set 5 nm were used. The

To whom all correspondence should be sent:
E-mail: m.ebrahimi@mshdiau.ac.ir

FT-IR instrument was applied for recording the IR spectra [East Norwalk, CT 06855, USA]. PH measurements were carried out with a Metrohm 780 pH-meter [Herisau, Switzerland]. Centrifuge device [Italy, A Heidolph MR 3001 magnetic stirrer [Schwabach, Germany] with an 8 mm × 1.5 mm magnetic stirring bar were used for stirring of the solutions. The ultrasonic processer apparatus model UP-100H [Hielscher-Germany] and the sonication bath model UP-40 H[sonica 2200 ETHS3 soltec, ultrasonic cleaner] were applied in this project. Digital balance Sartorius model GC1603P made by Germany with 0.0001 [gr] accuracy had been used for weighing solid materials.

2.2 Reagents

All the materials were prepared in high purity. The pure chlorpromazine powder was prepared from Dr Abidi pharmaceutical company [21]. Organic solvents such as Methanol [MeOH], Ethanol [EtOH], Acetonitrile [AN], Cyclohexane [CyHx], Dichloromethane [DCM] and also Hydrochloric acid [HCl] and Sodium Hydroxide [NaOH] were purchased from Merck Chemicals [Darmstadt, Germany] with analytical grade.

2.3. Hardware and software

All computations were performed on a computer with 8 GB memory and an Intel Pentium 7 3.07 GHz CPU .The optimized dimensional molecular structures were produced in Chem Office 2004. The Design Expert 7 software of were used for experimental designs, statistical evaluation, and model fitting in this work.

2.4 Synthesis of Al_2O_3 nanoparticles

In this study, we applied sol-gel method of Sharma et.al [22] for preparation of nano-Al_2O_3 powder. Firstly, appropriate amount of C_2H_5OH [27 ml, 0.4 mol] and H_2O [18 ml, 0.89 mol] were mixed, and then $AlCl_3$·6H2O [4.83g, 0.02 mol] was dissolved in the mixture, stirring for about 30 min for complete hydrolysis.

The reaction mixture was further stirred for 10 min, transferred to plastic molds, and the solutions were allowed to gel at room temperature within 3 h. The wet gels were aged at room temperature for 1 day and subsequently the gel parts were soaked in a bath of absolute ethanol for 5 days to exchange the water and reaction by products from the pores of the materials. After aging and solvent exchange, the wet gels were dried under C_2H_5OH to produce Al_2O_3 composite aerogel. In order to identify the thermal stabilities of the Al_2O_3 composite aerogels at elevated temperatures, they were all heat-treated with the same heating rate of 5°C/min to the peak temperatures [500 °C, 800 °C, 1000 °C, 1200 °C and 1300 °C] and maintained at that level for 4 h in muffle furnace to obtain nano-Al_2O_3.

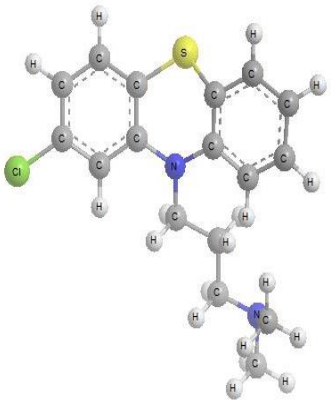

Fig. 1. Chemical structure of chloropromazine [CPZ].

2.5 Analytical procedure

Stock standard solution of CPZ [100 µg.mL^{-1}] was prepared by dissolving the 0.01gr of chlorpromazine powder in 100ml methanol. This solution was kept at 4 °C. The working solutions were prepared to diluting with deionized water a standard solution daily.

The first, 40 mg of Al_2O_3 was weighted and dispersed in 10 ml of working solution with appropriate concentration for 10 min to be done interaction between nanoparticle and drug. Then, adsorbent was deposited in the bottom of tube by centrifuge and be discarded supernatant. Subsequently, the isolated nanoparticles were sonicated in 500 µl of organic solvent for 5 min to desorbed analyte into the solvent and be done centrifuge again and were poured supernatant into microcell for measurement in UV/Visible device.

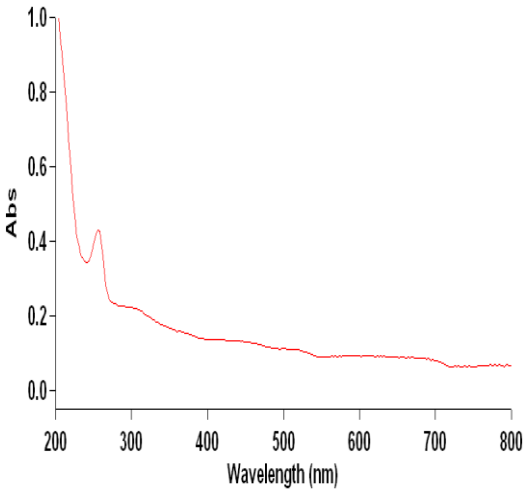

Fig. 2. UV-Vis spectra of aqueous solution of chloropromazine in maximum wavelength.[λ_{max} = 256 nm].

3. RESULTS AND DISCUSSION

3.1 Characterization of nano-Al_2O_3

Typical FT-IR absorption spectra for Al_2O_3 using the KBr technique are displayed in Fig. 3 As shown, the large band between 1000 and 400 cm^{-1}[845.38 cm^{-1}] is a characteristic absorption band of transition aluminas [23] and it is explanatory of stretching vibration of Al-O-Al band . its broadening is due to the distribution of vacancies among the octahedral and tetrahedral sites [24] . Two large peaks could be observed at 3472.85 cm^{-1} and 1631.3 cm^{-1} which was applied to make a semi-quantitative determination of water contents of samples. The peak at 3472.85 cm^{-1} is specified to OH stretching of bonded groups. The band of 1631.3 cm^{-1} is because of bending of molecular water.

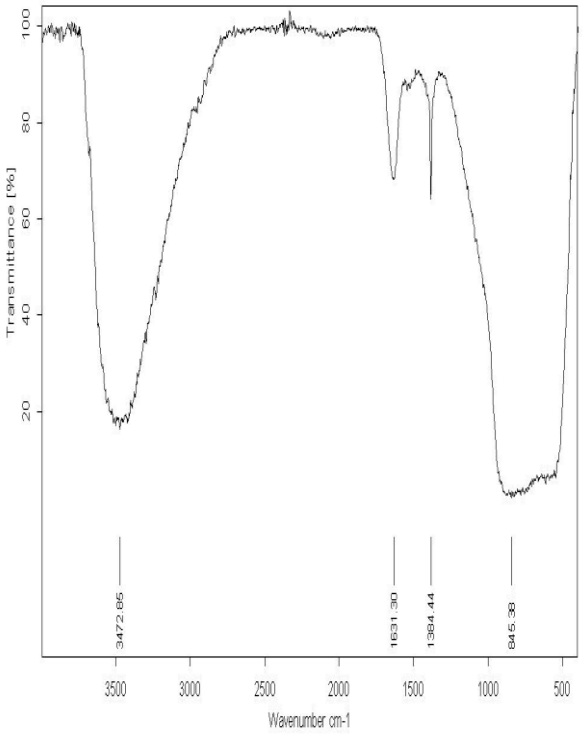

Fig. 3. FT-IR spectra for nano-Al_2O_3

An investigation of the SEM images of Al_2O_3 nano-particles [Fig. 4] showed that the porous surface formed with crystallin particles. This structure is mixture of small and large particles that provides the porous surface for adsorption and desorption processes.

3.2. Optimization of experimental conditions

According to primarily experiments, volume of organic solvent [500 µl] and stirring rate [1000 rpm] were not significant in responses and were considered constant in all experiments.

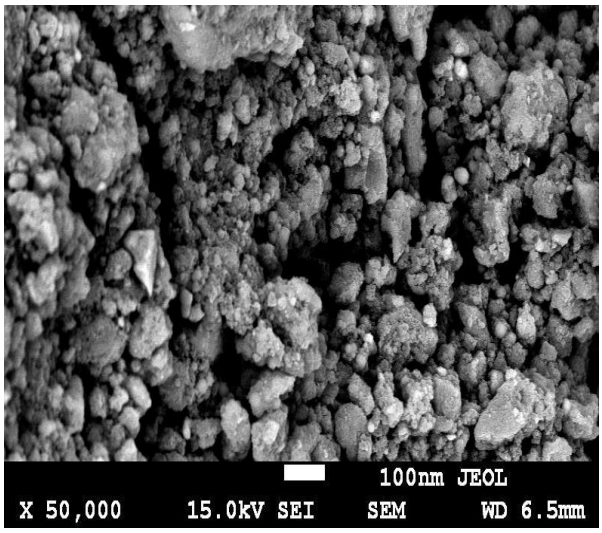

Fig. 4. Scanning electron microscope image of synthetic nano-Al_2O_3.

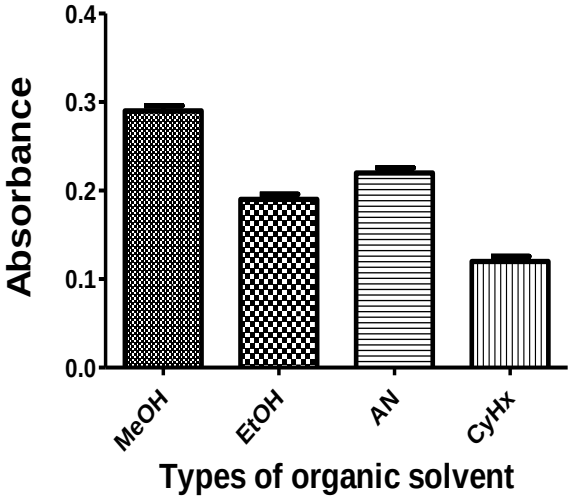

Fig. 5. Optimization of the type of organic solvent

3.2.1 Effect of type of organic solvent

The choice of organic solvent is one of the important factors in extraction process. In order to the selection of desorption solvent, we were investigated of 5 types of available solvents such as methanol, ethanol, acetonitrile, cyclohexane and dichloromethane. Based on the results, methanol was shown the best extraction efficiency than others. Due to its low vapor pressure under the extraction conditions and stability at the extraction period, methanol was selected [Fig. 5]. Dichloromethane was formed sticky mode and unable to do.

This parameter optimized manually because in experimental design causes to increase the number of runs very much.

3.2.2. The pH effect

The pH of the sample should be adjusted to ensure that the analyte is electrically neutral can efficiently be adsorbed, and desorption is unaffected by charges on the surface of the adsorbent. The pH of the samples were adjusted to between 4-12 using 0.1M HCl and NaOH [Fig. 6]. At the lower pH values was observed low extraction efficiency but at higher pH values, interaction of negatively charged adsorbent and positively charged drug was responsible for increasing drug extraction efficiency at pH values of up to 10. The highest drug extraction efficiency was achieved at this pH. CPZ is an alkaline drug with a pK_a value of 9.3 and exists in undissociated molecular form at higher pH values, which contributes to extraction. At higher alkaline pH values [pH=12], the negative charge of the drug surface was repulsed by the high negative charge of the nanoparticle and extraction efficiency decreased.

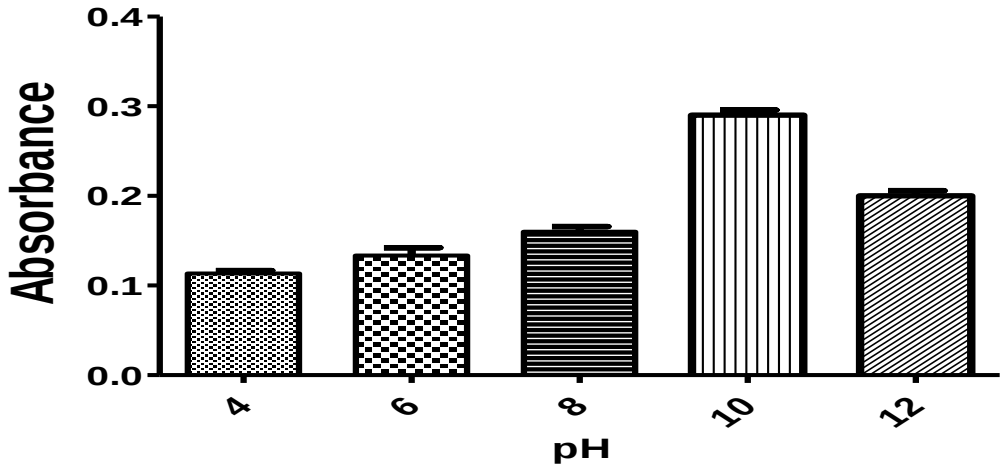

Fig. 6. The pH effect of aqueous solution on extraction, concentration 0.1 μg.ml $^{-1}$, methanol solvent.

3.2.3 Experimental design for optimization of other parameters

Other five parameters, such as volume of aqueous solution [Vaq], adsorption time [t ads], Desorption time [t des], nano-particle amount [NA], amount of salt [SE] expected to influence extraction process and absorbance. Due to low number of factors, we applied the 5 leveling central composite design [CCD], directly.

This design consists of a small factorial design [2^5 hypercube, 2×5 axial points, and 2 replicates of center points]. The 23 runs were randomized to provide protection against the effect of hidden variables. The values of factors is defined in Table 1. The absorbance values corresponding to the all factors and experiments are shown in Table 2

Table 1. The experimental range definition for CCD

Variables	Symbols	Low[-1]	High[+1]
Salt effect [% w/v]	A: SE	3	7
Nano-particle amount	B: NA	20	40
Volume of aqueous solution[mL]	C: V_{aq}	10	20
Time of extraction[min]	D: t_{ext}	10	20
Time of desorption[min]	E: t_{des}	7.5	12.5

The aim of this analysis is to maximize these responses estimated for the average value of three signals obtained under the same experimental conditions. By using regression analysis on experimental data, the results of CCD were fitted with a polynomial equation for each response. The following cubic models expressed an empirical relationship between response and input variables in uncoded values. Empirical models were generated in terms of coded factors and uncoded [actual] factors as following Equations 1, 2.

Final Equation in Terms of Coded Factors: Abs =+0.49+0.015* A+0.017* B-2.500E-003* C+2.500E-004* D-0.011* E+0.050 * A * B+0.040 * A * C+0.030* A * D+0.072* A * E+0.031* B * C+0.031* B * D+0.075 * B * E+0.036* C * D+0.052* C * E-0.22* D * E-7.500E-003* A^2-

3.875E-003* B^2+0.012* C^2-0.059 * D^2-7.125E-003* E^2+0.28* A * B * C (1)

Final Equation in Terms of Actual Factors: Abs = -5.03759+0.94453* SE+0.14982* NA+0.29711* Vaq+0.19529* t ext+0.062462* t des-0.038891* SE * NA-0.078756* SE * Vaq+3.00625E-003* SE * t ext+0.014312* SE * t des-0.013177* NA * Vaq+6.16250E-004* NA * t ext+3.01250E-003* NA * t des+1.43250E-003* Vaq * t ext+4.16500E-003* Vaq * t des-0.017885* t ext * t des-1.87500E-003* SE^2-3.87500E-005* NA^2+4.85000E-004* Vaq^2-2.38000E-003* t ext^2-1.14000E-003* t des^2+2.75875E-003* SE * NA *Vaq (2)

Table 2. The central composite design matrix and the experimental results.

Std	Run	A:SE	B:NA	C:Vaq	D:t ext	E:t des	Abs
5	1	7	40	10	10	12.5	0.445
12	2	1	30	15	15	10	0.432
16	3	5	30	5	15	10	0.545
7	4	3	20	20	20	12.5	0.293
2	5	7	20	20	20	7.5	0.326
17	6	5	30	25	15	10	0.535
13	7	9	30	15	15	10	0.491
18	8	5	30	15	5	10	0.253
11	9	3	20	10	10	7.5	0.324
10	10	3	40	20	20	7.5	0.305
23	11	5	30	15	15	10	0.495
4	12	7	40	20	10	7.5	0.342
3	13	3	40	20	10	12.5	0.322
20	14	5	30	15	15	5	0.484
6	15	7	20	10	20	12.5	0.317
22	16	5	30	15	15	10	0.488
14	17	5	10	15	15	10	0.443
21	18	5	30	15	15	15	0.442
1	19	7	40	10	20	7.5	0.327
8	20	3	40	10	20	12.5	0.348
15	21	5	50	15	15	10	0.509
9	22	7	20	20	10	12.5	0.331
19	23	5	30	15	25	10	0.254

The coefficients with one factor shows effect of the particular factor, while the coefficients with two and three factors and those with second order terms represent the interaction between two and three factors and the quadratic effects [25].

An ANOVA was executed due to verify whether the main effects are significant.[26] ANOVA was computed using Design expert 7.0.0 [Table 3] for to detecting the most important effect and interactions.

A p-value less than 0.05 in the ANOVA table shows the statistical significance of an effect at 95% confidence level. In this work, all of the main factors are significant.

However interaction between factors and square interaction factors were found to be significant. F-test was used to estimate the statistical significance of all terms in the polynomial equation within 95% confidence interval. Interaction curves for two parameters was indicated in Fig. 7.

The R^2 and R^2-[adj.] for the models were obtained 0.9999, 0.9972, respectively. The foresaid results indicated that the cubic model was significant.[19] In order to achieve the maximum response, the obtained equation was solved and the parameters of SE, NA, Vaq, t ext, t des and were calculated to be 5%, 40 mg, 10 ml, 16 min and 5 min ,respectively in maximum desirability.

Table 3. ANOVA for response surface reduced cubic model.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	0.19	21	9.18E-03	374.52	0.0407	Significant
A-SE	1.74E-03	1	1.74E-03	71.04	0.0752	
B-NA	2.18E-03	1	2.18E-03	88.9	0.0673	
C-Vaq	5.00E-05	1	5.00E-05	2.04	0.3888	
D-t ext	5.00E-07	1	5.00E-07	0.02	0.9097	
E-t des	8.82E-04	1	8.82E-04	36	0.1051	
AB	6.90E-03	1	6.90E-03	281.81	0.0379	
AC	4.47E-03	1	4.47E-03	182.29	0.0471	
AD	2.52E-03	1	2.52E-03	102.64	0.0626	
AE	0.014	1	0.014	581.64	0.0264	
BC	2.64E-03	1	2.64E-03	107.83	0.0611	
BD	2.64E-03	1	2.64E-03	107.83	0.0611	
BE	0.016	1	0.016	644.2	0.0251	
CD	3.57E-03	1	3.57E-03	145.67	0.0526	
CE	7.54E-03	1	7.54E-03	307.85	0.0362	
DE	0.024	1	0.024	967.11	0.0205	
A^2	9.00E-04	1	9.00E-04	36.73	0.1041	
B^2	2.40E-04	1	2.40E-04	9.81	0.1968	
C^2	2.35E-03	1	2.35E-03	96.01	0.0647	
D^2	0.057	1	0.057	2312	0.0132	
E^2	8.12E-04	1	8.12E-04	33.15	0.1095	
ABC	0.03	1	0.03	1212.26	0.0183	
Pure Error	2.45E-05	1	2.45E-05			
Cor Total	0.19	22				

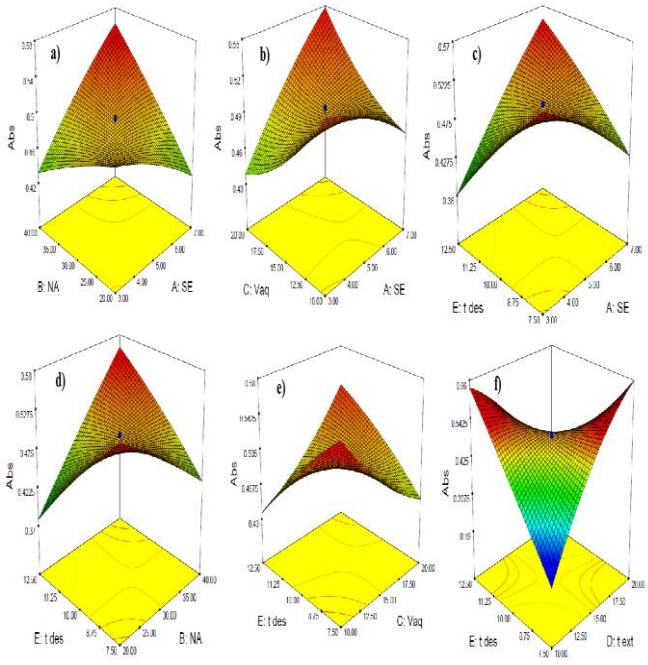

Fig. 7. Interaction curve for two parameters. a]AB interaction b]AC interaction c] AE interaction d]BE interaction e] CE interaction f] DE interaction.

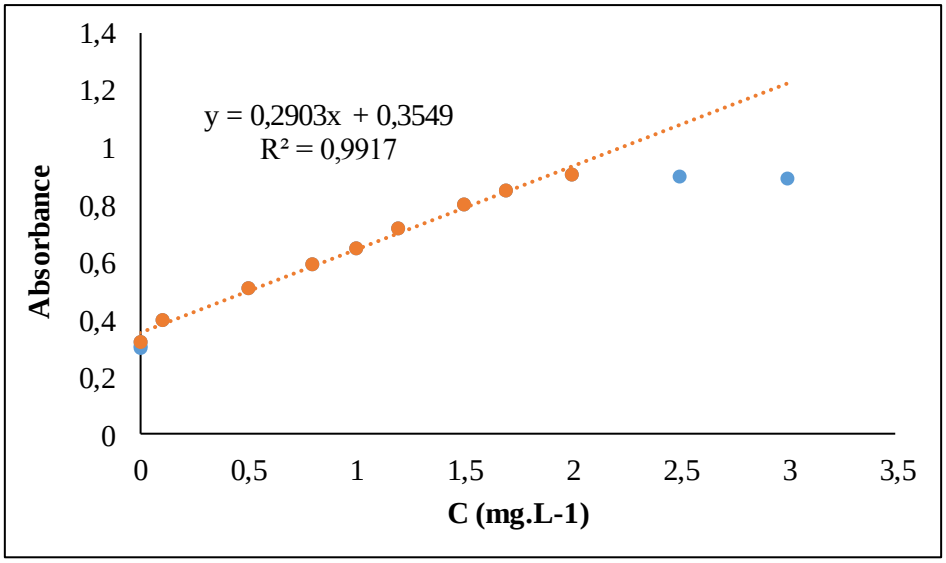

Fig. 8. The calibration curve for 10 ml CPZ aqueous solution with concentration of the 0.005 to 2 µg.ml^{-1} range pH=10, organic solvent: methanol, extraction time: 16 minutes, the Nanoparticle amount: 40mgr , desorption time:5 minutes and salt: 5% W/V .

3.3. Calibration curve

The calibration curve was plotted by drawing absorbance vs. concentration of CPZ in optimum conditions in range 0.0001-3 µg/ml. Linearity viewed in range from 0.005 to 2 µg/ml. All the experiments were repeated 3 times [Fig. 8].At lower and higher concentrations, linear mode diverted. Outside of the linear range, absorption do not follow the Beer-Lambert law. The equation of Beer' law defined as:

$$A=\varepsilon bC \qquad (3).$$

That A is indicative of absorbance, ε; molar extinction coefficient and C; concentration of analyte.

3.4. Practical validation of analytical performance

In the present work, standard solutions were obtained by spiking calculated amounts of stock solution into the aqueous and urine sample samples, which were prepared and described previously. At each level, three replicate extractions were performed. Under optimal conditions, calibration curves were plotted in aqueous media and the figures of merit of this method including pre-concentration factor [P.F], correlation coefficient [R], LOD and LOQ and linear dynamic rang [27] were investigated. The pre-concentration factor is a ratio of concentration between acceptor phase and initial donor phase aqueous solution. For the determination of this factor, the absorbance after extraction of 0.1 µg/mL analyte be divided to absorbance peak before extraction at same conditions was multiplied dilution factor. Dilution factor was calculated volume of aqueous solution/ volume of organic solvent. The pre-concentration factor [P.F] was calculated based on equation 3. The RSD% for analyte was obtained lower than 4 % and was satisfactory.

Results were tabulated in Table 5.

$$PF=\frac{A\,final}{A\,initial} \times \text{dilution factor [Vaq/Vorg] [4] .}$$

PF is calculated as 366.53 for the proposed method.

Table 5. Figures of merit of the proposed method in the determination of CPZ in aqueous sample.

Matrix	LDR [µg/mL]	R	LOD [µg/mL]	LOQ [µg/mL]	RSD % [n=5]	Equation
Water	5×10^{-3}- 2	0.9917	4.4×10^{-3}	1.46×10^{-2}	3.54	y=0.2903x+0.3549

3.5. Real sample analysis

3.5.1. Preparing urine Samples

Urine samples were collected in a polyethylene tube from a male and female healthy volunteers. The pH of urine samples were adjusted to 10 and then centrifuged at 1500 for 15 min until a white lipidic solid sedimented in the bottom of the tube. Then the supernatant was transferred into a clean tube and spiked with CPZ. All samples were stored at 4°C and directly used for analyze.

3.5.2. Preparing waste water samples

Waste water samples after filtering with 0.5µm filter membrane for separating additional compounds are being used.

3.5.3. Extraction procedure

Applicability of the extraction method to extract the CPZ from aqueous and urine sample samples were investigated by spiking certain concentration of CPZ to sample. Absorbance of urine sample and waste water before and after extraction were presented in Table 6.

Table 6. The results of CPZ determination in real samples [n=3].

Sample	Added [µg/mL]	Found [µg/mL]	Recovery [%]	RSD %
Urine sample	0	-	-	-
	0.05	4.68×10^{-2}	93.6	4.2
	0.5	4.74×10^{-1}	94.8	3.95
Waste water	0	-	-	-
	0.05	4.51×10^{-2}	90.2	5.3
	0.5	4.81×10^{-1}	96.2	4.1

4. CONCLUSION

In this work, we were used SPME method for extraction and determination of CPZ. The advantages of this method is fast, high sensitivity, relatively good accuracy and precision, use of low volume of organic solvent and low cost. Moreover, using the Al_2O_3 Nanoparticles in this project is one of the advantages of this method which is easy in preparation. The first stage for optimization, by manual methods were optimized some of parameters like type of organic solvent and pH of aqueous solution and the next other parameters were optimized by CCD and successfully were applied for determination of CPZ in urine and waste water samples.

Acknowledgements. *The authors acknowledge Islamic Azad University of Mashhad [IAUM] Research Council for financial support of this work.*

REFERENCES

1. P. Chue, G .Baker, *Drugs Annual*, **37,** 63 (2015).
2. M .Bhattacharyya, U .Chaudhuri, R. Poddar, *Biochem. Biophys. Res. Commun.* **167,** 1146 (1990).
3. D. Silva, C.M.S.R. Cortez, Louro, *Spectrochim. Acta*, Part A, **60**, 1215 (2004).
4. Ni Y, Lin D, S. Kokot, *Talanta*, **65,** 1295 (2005).
5. G..J Patriarche, J.J. Lingane, *Anal. Chim. Acta*, **49,** 25 (1970).
6. F.H. Merkle, C.A. Discher, *J. Pharm. Sci*., **53,** 620 (1964).
7. D. Bouchta, N. Izaoumen, H. Zejli, M. El Kaoutit, K.R. Temsamani, *Biosens. Bioelectron*., **20,** 2228 (2005).
8. C.N. .Svendsen, E.D. Bird, *Psychopharmacology* **90,** 316 (1986).
9. F.A. Mohamed, *Polymer—Plastics Technol. Eng.*, **28,** 2491 (1995).
10. C. Davis, C. Meyer, D. Fenimore, *Clin. Chim. Acta*, **78,** 71 (1977).
11. R. Grabic, J. Fick, R.H. Lindberg, G. Fedorova,M. Tysklind, *Talanta*, **100,**. 183 (2012).
12. L. Gruenke, J.C. Craig, F. Klein, Nguyen T.L., Б.А. Hitzemann, J.W. Holaday, H.H. Loh, L. Braff, A. Fisher, I.D. Glick, F. Hartmann, D.M. Bissell, *Biomed. Mass Spectrom.*, **12,** 707 (1985).
13. N. Erk, M. Kartal, *Il Farmaco*, **53,** 617 (1998).
14. I. Al-Momani, *J. Pharm. Biomed. Anal*., **25,** 751 (2001).
15. M. Sorouraddin, J. Manzoori, E. Kargarzadeh, A.H. Shabani, *J. Pharm. Biomed. Anal.*, **18,** 877 (1998).
16. G. Mohamed, *J. Pharm. Biomed. Anal.*, **24,** 561 (2001).
17. A.-A.Wahbi, O. Abdel-Razak, A.A. Gazy, H. Mahgoub, M.S. Moneeb, *J. Pharm. Biomed. Anal*., **30,** 1133 (2002).
18. N. Rahman, M.N. Hoda, *J. Pharm. Biomed. Anal.*, **31,** 381 (2003).
19. A. Nezhadali, M. Mojarrab, *Sens. Actuators*, B. **190,** 829 (2014).
20. M.A. Bezerra, R.E. Santelli, E.P. Oliveira, L.S. Villar, L.A. Escaleira, *Talanta*, **76,** 965 (2008).
21. M.S. Tehrani, M.T. Vardini, P.A. Azar, S.W. Husain, *J. Iran. Chem. Soc.*, **7**, 759 (2010).
22. Y. Sharma, V. Srivastava, A. Mukherjee, *J. Chem. Eng. Data*, **55,** 2390 (2010).
23. T.M. Costa, M.R. Gallas, E.V. Benvenutti, J.A. da Jornada, *The Journal of Physical Chemistry* B, **103,** 4278 (1999).
24. M. Baraton, P. Ouintard, *J. Mol. Struct*., **79,** 337 (1982).
25. T.K. Trinh, L.-S. Kang, *Environ. Eng.* Res., **15,** 63 (2010).
26. D.C. Montgomery, Design and Analysis of Experiments. 1997.
27. R. Saito, G. Dresselhaus, M.S. Dresselhaus, Nanoscience and Nanotechnology in Engineering, in: World Scientific.1998, p.32.