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THE DETERMINATION OF NIFEDIPINE AND NICARDIPINE BY INDIRECT ATOMIC ABSORTION SPECTROSCOPY OVER CADMIUM

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SUMMARY

In this work, optimum conditions of the indirect atomic absorption spectroscopic (AAS) determination of nifedipine and nicardipine were investigated. The developed method is based on the reduction of the antihypertensive drug substances carrying an aromatic nitro group, by boiling them under reflux with cadmium metal in 0.05N hydrochloric acidic medium under a CO_2 atmosphere for half an hour. The amount of the drugs were calculated by measuring atomic absorbance of the released cadmium(II) ions, at 228.8nm.

Calibration graphs were plotted between absorbance and cadmium(II) concentrations in the ranges of 0.292-1.460 mg/mL for nifedipine and 0.196-0.980 mg/mL for nicardipine. The linear equations of the calibration graphs were calculated by regression analyses as A=0.214C + 0.012 (r=0.9999) for nifedipine, A=0.320C + 0.013 (r=0.9999) for nicardipine.

Atomic absorption spectroscopic method was applied to the quantitative determination of two compounds in commercially available drug formulations. The drugs were also analyzed with a visible spectrophotometric method based on diazotization-coupling of the amine group formed during the reduction of the aromatic nitro group.

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The results obtained from the two methods were compared statistically in terms of t and F tests. There were no significant differences between the means and precission of these two methods.

ÖZET

Çalışmada, nifedipin ve nikardipin'in indirekt atomik absorpsiyon spektrofotometrik tayin yönteminin optimum koşulları incelendi. Geliştirilen yöntem aromatik nitro grubu içeren antihipertansif ilaç etken maddesinin 0.05 N hidroklorik asit ortamda, CO_2 atmosferinde elementel kadmiyum ile geri soğutucu altında kaynatılarak indirgenmesine ve açığa çıkan kadmiyum(II) iyonunun 228.8 nm'deki atomik absorbansının ölçümüne dayanmaktadır.

Absorbans değerleri ile kadmiyum(II) konsantrasyonları arasında nifedipine için 0.292-1.460 mg/mL, nikardipin için 0.196-0.980 mg/mL aralığında ölçü eğrileri hazırlandı. Ölçü eğrilerinin doğru denklemi regresyon analizi ile nifedipin için A=0.214C + 0.012(r=0.9999), nikardipin için A=0.320C + 0.013(r=0.9999) olarak hesaplandı.

Atomik absorpsiyon spektroskopik yöntem, iki maddenin piyasada mevcut ilaç-formülasyonlarında miktar tayinine uygulandı. İlaçlar, aromatik nitro grubunun indirgenmesiyle elde edilen amin grubunun diazolama-kenetlenme reaksiyonlarına dayanan görünür bölge spektrofotometrik yöntemle de analiz edildi. İki yöntemden elde edilen sonuçlar birbiriyle t ve F testleri yönünden istatistik olarak kıyaslandı. İki yöntem arasında ortalamalar ve kesinlik yönünden anlamlı bir fark olmadığı saptandı.

Key words: Aromatic nitro compounds, Cadmium ion, Diazotization-coupling, Indirect determination, Atomic Absorption Spectroscopy.

INTRODUCTION

The indirect AAS method over cadmium can be applied to nitrite and nitrate ions and aromatic nitro and nitroso compounds(1). In a basic (pH 8-9) medium environment containing the nitrate ion, when the Cd^{2+}, that is created by reduction of nitrate, is measured using AAS, it is observed that the results are somewhat less than the expected one. This could be a result of the cadmium hydroxide that may form upon the surface of the metal. The experiments carried out determining the nitrite that originates with the same reactants, using the diazotization-coupling spectrophotometric method, gives the same low results which leads the writer to the same idea. Using different concentrations

of hydrochloric acid in a CO_2 atmosphere the nitrate ion was reduced with the cadmium metal and the solubility of the ion was measured, in the light of this the equation for the reaction was determined as;

$$2NO^-_3 + 4Cd + 10H^+ \rightarrow N_2O + 4Cd^{2+} + 5H_2O$$

The probability of the suggested reaction was backed up by putting the output of the reaction in gas form through an IR spectrum thus proving that N_2O was being produced.

After putting aromatic nitro and nitrozo compound through the same process the reaction equations were determined as(2,3);

$$Ar\text{-}NO_2 + 3Cd + 6HCl \rightarrow Ar\text{-}NH_2 + 3CdCl_2 + 2H_2O$$

$$Ar\text{-}NO + 2Cd + 4HCl \rightarrow Ar\text{-}NH_2 + 2CdCl_2 + H_2O$$

The structure of the reaction were investigated by reduction of p-nitro benzoic acid with Cd metal in a 0.05M HCl solution and obtaining uv absorbtion spectra of the reactants and the products.

In the presant investigation, an indirect AAS determination method over Cd metal was developed for the drug substances nifedipine and nicardipine containing aromatic nitro group.

RESULTS AND DISCUSSION

With the intention of determining the optimum conditions for the method; the solvent to dissolve the substances, the HCL concentration and the boiling time were investigated. Methanol, 0.05N HCL concentration and 60 minutes of boiling time were found suitable.

As stated in the method, standard solutions of cadmium (II) and the drug substances were measured under the same conditions, thus using the inclination of the graphs obtained from the regression analysis to calculate the remaining amount of each respective substance for each process. The ratio for nifedipine was calculated as 83.0% the same ratio for nicardipine was 87.8%. In the light of these results, it was decided to use own standards of the substances during the determination of them in pharmaceutical preparations. The amount of active material in each sample was obtained from each respective graph in mg. The results are stated on the tables.

Using the stated method for every 1 mole of nitro compound, 3 moles of cadmium (II) ion is obtained. The drugs were also analysed by measuring the amines, obtained

as a results of reduction, with diazotization-coupling visible spectrophotometric method as a method of comparison(4). In this method, maximum absorption wavelenghs were 546 nm for nifedipine and 530 nm for nicardipine. The results obtained from the two methods were compared statistically in terms of t and F tests of confidence level at 95% level of probability. There was no significant difference between the two methods.

The selectivity of the reaction: Under the stated conditions the nitroso compounds also give the similar reaction; dinitro- and polynitro- compounds may react in 0.15M concentration and at a boiling time over 60 minutes(2). Organic nitrate group also reacts according to the following equation(1):

$$2R\text{-}ONO_2 + 4Cd + 8HCl \rightarrow N_2O + 4CdCl_2 + 2R\text{-}OH + 3H_2O$$

The other functional groups do not interfere.

An important advantage to this method is that four different methods of determination can be applied to the same solution. These are AAS, polarography, complexometric titration with EDTA and visible spectrophotometry over amine obtained. The other advantages are reagent stability and reaction selectivity. Producing 3 moles of Cd ion per 1 mole of nitro group cause the results tobe more precise and accurate.

Table 1: The values used to calculate the calibration graphs for nifedipine and nicardipine

Nifedipine Concentration (µg/mL)	Cd^{2+} Concentration in Nifedipine (µg/mL)	Absorbances	Nicardipine Concentration (µg/mL)	Cd2+ Concentration in Nicardipine (µg/mL)	Absorbances
0.3	0.292	0.075	0.3	0.196	0.077
0.6	0.584	0.138	0.6	0.392	0.137
0.9	0.876	0.204	0.9	0.588	0.202
1.2	0.168	0,270	1.2	0.784	0.263
1.5	1.460	0.332	1.5	0.980	0.328
A=0.214C + 0.012 r=0.9999			A=0.320C + 0.013 r=0.9999		

EXPERIMENTAL

Materials

Chemicals: Nitrendipine (Bayer), nicardipine (Sandoz),other materials (product of Merck): Hydrochloric acid, acetone, ethanol, methanol, cadmium granules, cadmium-

Table 2 : The determination of nifedipine(A,B,C,D) and nicardipine(E) in pharmaceutical preparates (n=6, p=0.05)

n	AAS Method					Visible Spectrophotometric Method				
	A	B	C	D	E	A	B	C	D	E
1	10.0	10.1	21.4	30.2	19.9	10.1	10.1	21.2	29.8	20.3
2	10.1	9.4	20.0	31.2	19.7	9.9	9.9	20.0	30.8	21.3
3	10.0	9.8	20.7	30.0	19.7	10.0	9.7	20.2	30.4	19.7
4	9.9	10.0	20.2	29.9	20.8	10.5	9.5	20.5	30.1	20.8
5	10.3	9.9	19.2	29.9	19.7	10.3	9.4	19.8	29.7	19.5
6	10.6	11.0	19.8	30.0	21.5	9.0	10.7	20.1	30.0	20.5
X	10.2	10.0	20.2	30.2	20.2	10.0	9.9	20.3	30.1	20.4
S	0.32	0.53	0.76	0.50	0.76	0.52	0.48	0.50	0.41	0.67
S/X.100	3.10	5.31	3.76	1.66	3.76	5.20	4.80	2.45	1.36	3.28
$\frac{X \pm (t.S)}{\sqrt{n}}$	10.3 -10.1	10.5 -9.5	20.3 -20.1	30.3 -30.1	20.4 -20.0	10.2 -9.8	10.3 -9.5	20.4 -20.2	30.2 -30.0	20.6 -20.2
t test	t_A=1.0	t_B=2.13	t_C=0.33	t_D=0.49	tE=1.31	t_{Table}=2.23				
F test	F_A=2.7	F_B=1.25	F_C=2.30	F_D=1.52	F_E=1.66	F_{Table}=5.05				

sulphate, a-naphtilamine, ammonium sulphamate, glacial acetic acid, sodium nitrate and double distilled water.

Instruments: Spectra AA-20 Varian AAS, Philips PU 8700 uv-visible spectrophotometers.

Methods

a) Conditions for the AAS Method: 5 mg nifedipine and 3 mg of nicardipine were weighed accurately and transferred into a double-necked glass flask. A solution was then prepared by adding 2mL of methanol. After adding 10mL of 0.05-0.2N hydrochloric acid and a Cd granule washed with conc. HCL and EtOH previously, the solution was boiled in CO_2 atmosphere for 60 minutes. After diluting the solution with H_2O to the desired concentration, the atomic absorbance of the cadmium (II) ion in the solution was measured against water at 228.8nm.

b) Conditions for the Spectrophotometric Comparison Method: The amine groups that were obtained during the reduction of the aromatic nitro group in an acid environment were spectrophotometrically defined using diazotization-coupling. With

this in view, after the reduction of the aromatic nitro compounds, samples taken from the standard solution at different concentrations were added to 2.5N solution of hydrochloric acid and a 1% sodium nitrate solution, after which the final solution was shaken and left for two minutes. After adding of 1% ammonium sulfamate, the solution was left for another minute, then a 0.2% α-naphtilamine solution was added. Ten minutes later the absorbances in the visible region were measured against empty trial solution.

c) Sample Preparation: The materials available on the market containing the drug substances were weighed one by one and the average weight calculated. The material was ground to a powder in a porcelain mortar. From the prepared powder the amounts containing 5mg of nifedipine and 3mg of nicardipine were weighed , after being dissolved and diluted with methanol and having been filtered, the method was carried out as stated.

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