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Determination of Metoclopramide with Chromium(III) Thiocyanate Complexes

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The determination of metoclopramide (4-amino-5-chloro-N-[(2-diethylamino)ethyl]-2-methoxybenzamide) has been achieved by means of gravimetric, oxidimetric and spectrometric methods. The experimental data proves that the methods are accurate enough and not affected by systematic errors.

Keywords: Chromium(III) complexes, Metoclopramide, Drug analysis, Oxidimetric, Gravimetric and Spectrometric methods.

INTRODUCTION

Metoclopramide or 4-amino-5-chloro-N-[(2-diethylamino)-ethyl]-2-methoxybenzamide is tranquilizer drug. The commercial product is a white micro-crystalline powder sensible to the light, soluble in water and ethanol, insoluble in ether, having a bad taste.

Its preparation was performed by condensation of the 2-methoxy-4-nitro-5-chlorobenzoyl chloride and N,N'-diethyl-ethylendiamine, afterwards the reduction of nitro function and the transformation of resulted base to hydrochloride derivative [1].

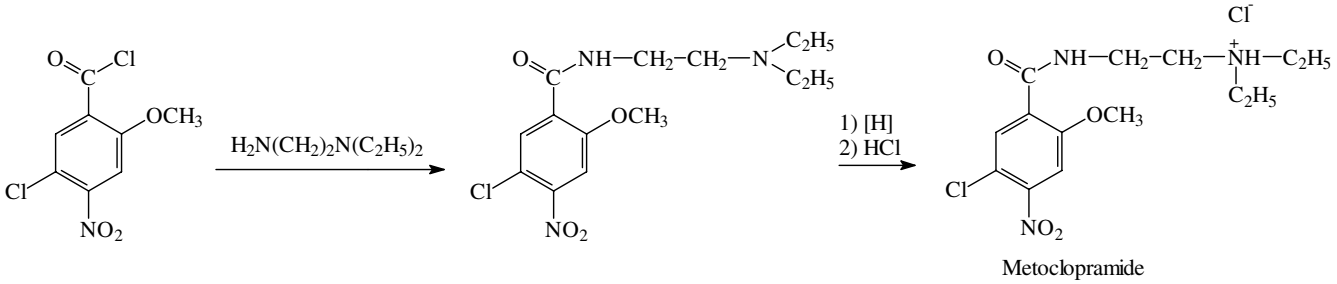
Several analytical methods are used to determine metoclopramide. The quantitative determination of this drug is accomplished by ultraviolet-visible spectrofotometric measurements [2-4]. Liquid chromatography-mass spectrometry (LC-MS) methods involving extraction of the drug with organic solvents, use of special expensive chromatographic columns and mobile phases consisting in mixtures of toxic solvents (methanol and acetonitrile), are usually employed for determination of metoclopramide [5-8]. Electrochemical methods concerning voltammetric and amperometric technique [9], capillary electrophoresis coupled with electrochemiluminescence detection [10,11], are also used to dose metoclopramide.

We propose a quantitative determination method of metoclopramide that uses the acid-base titration in non-aqueous medium: the drug is dissolved in acetic anhydride, the chloroform and mercuric acetate are added, afterwards the titration is made with 0.1 N $HClO_4$ solution until the colour of the Metanil Yellow indicator (in dioxane) becomes red-violaceous.

Because of structural resemblance with procainamide, the metoclopramide hydrochloride is employed as anti-emetic, anti-convulsion and antiarrhythmic drug [12]. Therapeutic range of this drug is from 1 mg for pediatric use to 40 mg for adults [13].

EXPERIMENTAL

Synthesis of the reactive used in the experimental determinations $NH_4[Cr(SCN)_4(amine)_2]$ (where amine is: aniline, toluidine, benzylamine, imidazole, uroptropine, *etc*.) was made using Ganescu's method [14] and $K_3[Cr(SCN)_6]$ anhydrous was prepared [15], using chromium alum $KCr(SO_4)_2{\cdot}12H_2O$ and potassium thiocyanate KSCN. To obtain the chromium-drug complexes previous reported protocol was performed [16-18].



Novel complex salt of metoclopramide: A sample of 20 mmol of metoclopramide was treated with 4-5 mL of 20 % HCl, then completed with 50-80 mL of H_2O. Afterwards, the reagents $NH_4[Cr(SCN)_4(amine)_2]$ dissolved in 3 % aqueous ethanol solution were added until the solution of precipitate became red-violet. The obtained precipitates was left in solution for 15-20 min and filtered off under vacuum, washed up with 10 mL of distilled water and finally dried with air.

The amount of chromium was determined as Cr_2O_3, by calcinations of 100-200 mg sample at 800 °C. The sulfur was determined gravimetric in the form of $BaSO_4$ and nitrogen was determined by volumetric method. The physico-chemical characteristic data of the synthesized compounds are summarized in Table-1.

RESULTS AND DISCUSSION

Thermal analysis of the synthesized compounds reveals absence of crystallized water and their stability in the temperature range of 150-200 °C. Over these temperatures the decomposition process became rather complicate and we didn't achieve to isolate the intermediary products, the residue of crucible being constituted from Cr_2O_3 only (at 750° C) [19].

Gravimetric determination of metoclopramide as metoclopramide·H[Cr(SCN)$_4$(pilocarpine)$_2$] (A) and metoclopramide·H[Cr(SCN)$_4$(scopolamine)$_2$] (B), respectively: 2.49-24.96 mg of metoclopramide was precipitated with the above mentioned reagents in the 3 % aqueous alcoholic solution. The red-violet precipitate formed was filtered off after 15-20 min through a G_4 fritted-glass funnel, then washed with 3-4 time with 10 mL of distilled water, until the filtrate flowed colourless. The crucible with the precipitate was dried into drying stove at 80-100 °C for 1 h until the weight was constant, then the precipitate was weighed on an analytical scale [20]. The experimental data are recorded in the Table-2.

Oxidimetric determination of metoclopramide after precipitation in the form of Metoclopramide·H[Cr(SCN)$_4$(amine)$_2$]: 2.49-24.96 mg of Metoclopramide was treated with 3-5 mg of 20 % HCl solution, then was precipitated with the above mentioned reagents dissolved in 3 % aqueous alcoholic solutions. The precipitates were filtered on filter paper using a 5 cm diameter Büchner funnel. The precipitates were washed with 10 mL distilled water till the filtrate flowed colourless. The paper with the precipitate was transferred in a high-shaped Berzelius glass of 500 mL to which 10 mL solution of 5 % NaOH and 10 mL water are added, washing the filtration funnel concomitantly. The glass containing the precipitate is boiled on a gas burner sieve when green-coloured $Cr(OH)_3$ appears. $Cr(OH)_3$ is decomposed with concentrated hydrochloric acid so that its normal concentration in each sample should be 1.7-2 N. The quantity of concentrated hydrochloric acid added in each sample is calculated with the equation:

$$V_{HCl} = \frac{1.7(V_{initial} + V_{oxidizer})}{10.4}$$

The normality of concentrated HCl with a density of 1.19 g/cm^3 was 12.1N. After the addition of the calculated quantity of HCl, 5 mL of CCl_4 and 10 drops of ICl [21] indicator were added to the solution. Further, NCS^- was titrated with 0.1N $KMnO_4$ under continuous stirring until the non aqueous violet layer became colourless. The reaction that took place was the following:

$$5SCN^- + 6MnO_4^- + 13H^+ \rightarrow 6Mn^{2+} + 5SO_4^{2-} + 5HCN + 4H_2O$$

TABLE-1
NOVEL COMPLEX SALTS OF METOCLOPRAMIDE WITH COMPLEX ANIONS OF Cr(III):Metoclopramide·H[Cr(SCN)$_4$(amine)$_2$]

Formula	m.w. calc.	Solubility (mg/mL)	Yield (%)	Colour	Elemental analysis (%): Calcd. (Found)		
					Cr	S	N
A·H[Cr(SCN)$_4$(NH$_3$)$_2$]	599.22	1.20×10^{-2}	96	Red-violet	8.67 (8.61)	21.40 (21.00)	21.02 (19.86)
A·H[Cr(SCN)$_4$(aniline)$_2$]	770.35	0.86×10^{-2}	97	Red-violet	6.67 (6.60)	16.64 (16.58)	16.35 (16.28)
A·H[Cr(SCN)$_4$(benzylamine)$_2$]	799.35	1.35×10^{-2}	95	Red-violet	6.50 (6.47)	16.04 (15.94)	15.76 (15.70)
A·H[Cr(SCN)$_4$(imidazole)$_2$]	721.51	1.41×10^{-2}	91	Red-violet	7.20 (7.18)	17.77 (17.71)	21.34 (21.30)
A·H[Cr(SCN)$_4$(benztriazole)$_2$]	824.39	1.71×10^{-2}	92	Red-violet	6.30 (6.28)	15.55 (15.48)	22.07 (21.90)
A·H[Cr(SCN)$_4$(urotropine)$_2$]	865.49	0.93×10^{-2}	93	Red-violet	6.00 (5.92)	14.81 (14.75)	19.41 (19.37)

TABLE-2
GRAVIMETRIC DETERMINATION OF METOCLOPRAMIDE IN THE FORM OF
Metoclopramide·H[Cr(SCN)$_4$(pilocarpine)$_2$] (A) AND Metoclopramide·H[Cr(SCN)$_4$(scopolamine)$_2$] (B)

Metoclopramide taken (mg)	Form of determination (A)				Form of determination (B)			
	Weighed $G_{complex}$	Metoclopramide found (mg)	Error		Weighed $G_{complex}$	Metoclopramide found (mg)	Error	
			mg	%			mg	%
2.49	9.31	2.48	-0.01	0.40	9.40	2.48	-0.01	0.40
4.99	18.70	4.98	-0.01	0.20	18.96	5.00	+0.01	0.20
7.50	28.24	7.52	+0.02	0.27	28.51	7.52	+0.02	0.27
12.48	46.79	12.46	-0.02	0.16	47.17	12.45	-0.03	0.24
14.97	56.27	14.98	+0.01	0.07	56.59	14.93	-0.04	0.27
17.47	65.76	17.51	+0.04	0.23	66.36	17.51	+0.04	0.23
19.97	74.81	19.92	-0.05	0.25	75.52	19.93	-0.04	0.20
24.96	93.59	24.92	-0.04	0.16	94.39	24.91	-0.05	0.20
	$M_A = 1125.70$; $f_A = 0.2663$; $\bar{X} = 14.98$; $S^2 = 7.66 \times 10^{-4}$; $S = 2.77 \times 10^{-2}$; $t = 0.36$; $t_{n-1,\alpha} = 2.37$; $\alpha = 95$ %; $\bar{X} - ts < A < \bar{X} + ts$; $14.96 < 14.97 < 14.98$				$M_B = 1135.84$; $f_B = 0.2639$; $\bar{X} = 19.98$; $S^2 = 7.11 \times 10^{-4}$; $S = 2.66 \times 10^{-2}$; $t = 0.38$; $t_{n-1,\alpha} = 2.37$; $\alpha = 95$ %; $\bar{X}$-ts < A < $\bar{X}$ + ts $19.96 < 19.97 < 19.98$			

$$2SCN^- + 3IO_3^- + 4H^+ \rightarrow 2SO_4^{2-} + 3I^+ + 2HCN + H_2O$$

$$2SCN^- + 3BrO_3^- + 4H^+ \rightarrow 2SO_4^{2-} + 3Br^+ + 2HCN + H_2O$$

This method is very sensitive. The titration is made without excess consumption of reactive reagents. The experimental data are recorded in Table-3.

Spectrophotometric determination of metoclopramide after precipitation in the form of metoclopramide·H[Cr(SCN)$_4$(aniline)$_2$]: A sample of 2.37-18.72 mg of metoclopramide was acidulated with some drops of 20 % HCl, next was precipitated with poor excess of above mentioned reagents as Metoclopramide·H[Cr(SCN)$_4$(aniline)$_2$]. The precipitate was filtered off using a G_4 fritted-glass funnel, then washed 3-4 time with 10 mL of distilled water, then it was dissolved in acetone up to mark. The absorbance was measured at 540 nm and the Lambert-Beer's law followed in the titer concentration range of 0.0936-0.7488 mg/mL metoclopramide. The molar extinction coefficient is $\varepsilon = 274.69$ L cm^{-1} mol^{-1}. The statistic interpretation of the experimental data was accomplished by means of linear regression method [22] and the obtained results are presented in Table-4.

From the data of the Table-4 statistically processed, we verified the calculation as follows:

$$\Sigma x^2 + \Sigma y^2 + 2\Sigma xy = 1149.122028$$

$$\Sigma(x + y)^2 = 1149.130028$$

The two values being very close to each other, leads us the idea that the proposed spectrophotometric method to dose metoclopramide is reproducible and precise. The standard deviations and the regression coefficient were calculated with the help of the following relations:

$$\sigma_x = \sqrt{\frac{\sum x^2}{n} - \bar{x}^2} = 5.36;\ \bar{x} = 10.53$$

$$\sigma_y = \sqrt{\frac{\sum y^2}{n} - \bar{y}^2} = 0.077;\ \bar{y} = 0.15$$

$$r = \frac{\frac{\sum xy}{n} - \overline{xy}}{\sigma_x \sigma_y} = 0.99949 \approx 1$$

The equation, which give in the best way the dependence between absorbance and the concentration of the drug expressed by titre (mg/mL) measured, deduced out of a linear regression analysis are as follows:

$$y - \bar{y} = r\frac{\sigma_x}{\sigma_y}(x - \bar{x});\ y = 0.0143583x - 0.0011933$$

$$x - \bar{x} = r\frac{\sigma_x}{\sigma_y}(y - \bar{y});\ x = 69.5748883y + 0.0937667$$

These two equations represent two straight lines which are practical confounded; the angle between them is given by following relation:

$$tg\alpha = \frac{m_2 - m_1}{1 + m_1 m_2}$$

where m_1 and m_2 are angular coefficients (slope) of the straight lines, which can be calculated to the following formulae:

TABLE-3
OXIDIMETRIC DETERMINATION OF METOCLOPRAMIDE AS
Metoclopramide·H[Cr(SCN)$_4$(pilocarpine)$_2$] (A) AND Metoclopramide·H[Cr(SCN)$_4$(scopolamine)$_2$] (B)

Metcl. taken (mg)	Determination No.	$\bar{X}$ (mg)	S	t_a	t_b	$t_{n-1,\alpha}$; α = 95 %
Permanganatometric determination						
2.49	10	2.500	1.73×10^{-2}	2.385×10^{-4}	3.061×10^{-2}	2.57
14.97	10	14.983	2.77×10^{-2}	4.579×10^{-4}	6.216×10^{-2}	2.57
Bromometric determination						
7.50	10	7.509	1.89×10^{-2}	18.121×10^{-4}	4.584×10^{-2}	2.57
19.97	10	19.982	2.66×10^{-2}	8.814×10^{-4}	6.067×10^{-2}	2.57
Iodometric determination						
4.99	10	5.00	2.41×10^{-2}	1.800×10^{-4}	6.283×10^{-2}	2.57
17.47	10	17.478	2.63×10^{-2}	7.711×10^{-4}	5.308×10^{-2}	2.57

1 mL solution of 0.1 N ($KMnO_4$, $KBrO_3$, KIO_3) is equivalent to 1.2492 mg of metoclopramide.

TABLE-4
SPECTROPHOTOMETRIC DETERMINATION OF METOCLOPRAMIDE AFTER
ITS PRECIPITATION AS Metoclopramide·H[Cr(SCN)$_4$(aniline)$_2$]

Serial No.	x (mg)	x^2	y	y^2	x+y	xy	$(x + y)^2$
1	2.34	5.4756	0.033	0.001084	2.373	0.07722	5.631129
2	4.68	21.9024	0.067	0.004489	4.747	0.31356	22.534009
3	7.02	49.2804	0.100	0.010000	7.120	0.70200	50.694400
4	9.36	87.6096	0.134	0.017956	9.494	1.25424	90.136036
5	11.70	136.8900	0.167	0.027889	11.867	1.95390	140.825689
6	14.04	197.1216	0.200	0.040000	14.240	2.80400	202.777600
7	16.38	268.3044	0.234	0.054756	16.614	3.83292	276.024996
8	18.72	350.4384	0.267	0.071289	18.987	4.99824	360.506169
Total	84.24	1117.0224	1.202	0.227468	85.442	15.93608	1149.130028

$$m_1 = r\frac{\sigma_x}{\sigma_y}$$

$$m_2 = \frac{1}{r}\frac{\sigma_y}{\sigma_x}$$

From the Fig. 1 one can remark that the angle between the two straight lines of regression (the plot of y *versus* x and the plot of x *versus* y) is nearly nought, so that r = 1.

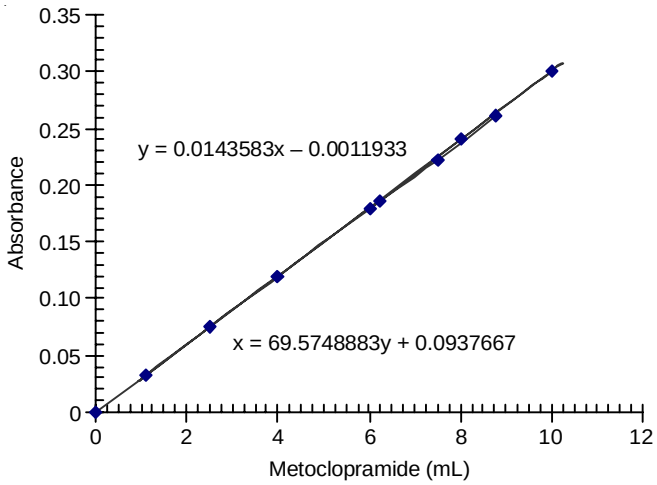


Fig. 1. Linear dependence between absorbance and titer concentration of metoclopramide

Conclusion

We have proposed a new estimation methods of metoclopramide using chromium thiocyanate complexes. The method of determination is very easy and the sensibility of the reactions requires a few quantities of compound. The statistic calculation proves that this method is highly accurate comparative to other literature methods.

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