Zag. J. Pharm. Sci., Vol. 3, No. 2, August 1994

USE OF CERTAIN METAL IONS FOR THE DETERMINATION OF INDOMETHACIN

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ABSTRACT

A simple and accurate method was described for the quantitative determination of indomethacin using Ag+ and Cu2+ ions. Indomethacin was precipitated from its neutral alcoholic solution by standard solutions of silver nitrate and copper acetate followed by determining the resulted slats using atomic absorption spectroscopy and colorimetric techniques. The optimum conditions for silver and copper indomethacin slat formations have been carefully studied. The molar ratio of the reactants in the case of copper was ascertained by atomic absorption spectroscopy and by formation of copper sodium diethyldithiocarbamate and was found to be 2 : 1 (indomethacin: cu^{+2}). Both of the developed methods were compared with the previous official methods to indicate high accuracy (t-test) and reproducibility (f-test).

INTRODUCTION

Indomethacin is anti-inflammatory, antipyretic with analgesic properties, having chemical structure 1- (4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl acetic acid.

Several methods were used for the determination of this drug such as direct titration in non aquous media using acetone or dimethyl formamide with NaoH[1] or sodium methoxide [2]. It was also determined by induced different spectrophotometry [3].

In these routes of determination different reagents such as p-dimethylaminobenzaldehyde and p-toulene sulphonic acid mixture [4] vanillin, cystein [5] or ferric chloride [6] for colorimetric determination of indomethacin were used. In the alkaline ethanol method indomethacin was hydrolysed to give the fluorescent compound 2-methyl-3-carboxymethyl-5-methyl indole whuch could be measured quantitatively [7,8]. Meanwhile, in biological fluids, the drug could be separated by thin layer chromatography followed by fluorimetric determination [9]. High performance liquid chromatography was also reported for indomethacin estimation [10].

Silver ion was recomended in pharmaceutical analysis as a reagent for analysis of captopril [11] and some reducing sugars [12]. Also, copper ion was used for the determination of certain antibiotics as neomycin [13], rifampicin [14], benzyl penicillin [15] and other pharamceutical compounds such as terbutalin sulphate [16] and ethambutol [17].

The persent work deals with the use of both Ag^{+} and Cu^{++} for the spectrophotometric and A.A.S. determinations of indomethacin . In its pharmaceutical formulations, the established methods proved to be very sensitive and

accurate. The average recoveries were 99.19±0.35, 99.11±0.37 using silver (by direct and indirect techniques). By using the copper method the recoveries were 98.98±0.37 and 98.96±0.31. They were 99.35±0.33 and 99.42±0.36 by A.A.S. and colorimetric procedures respectively.

EXPERIMENTAL

Instruments :

(1) Shimadzu Atomic Absorption flame spectrophotometer. Model AA-640-13.

(2) Beckman Du-7 spectrophotometer.

Materials and Reagents :

(a) Indomethacin (Pharco Co.). indomin capsules (25 mg indomethacin per capsule) Misr Co.

(b) 0.025 M AgNO3 (0.425% W/V solution).

(c) 0.01 M copper acetate (0.2% W/V solution)

(d) Sodium diethyldithiocarbamate 0.1% W/V. solution.

(e) 0.01 M indomethacin solution: (0.358 gm indomethacin was dissolved in about 25 ml alcohol. The solution was neutralised to fhenol red with 0.1 N sodium hydroxide and then completed to 100 ml with deionized water.

(f) Stock indomethacin solution (dissolve 100 mg indomethacin in about 25 ml alcohol) and complete as in part (e) above.

Atomic spectroscopy :

(1) Using silver :

To different aliquots of stock solution (equivalent to 2-30 mg of indomethacin), 5 ml 0.025 M silver nitrate solution was added away from light [wrapping the flasks with aluminium foil]. The mixture was shaked then filtered (Whatman No. 40-44), and the resulting precipitate was washed with deionized water until free from silver ions.

a. Direct mehtod :

The precipitate obtained above was dissolved in 5 ml dilute ammonia solution and completed to 25 ml with deionized water . Only 1 ml was diluted to 25 ml (solution I).

b. Indirect method :

The filtrate and washings were collected in 100 ml measuring flasks, completed to volume with deionized water. Only 10 ml was diluted to 100 ml (solution 2).

A blank (omitting addition of the drug) was performed by aspirating solution. 1 and 2 into an oxidizing air-acetylene flame and absorbance was mearsured at the flaming coditions :

Wave length 328.1 nm
Lamp current 7 mA
Slit width 3.8 A
Air pressure 10 1/min.
Acetylene pressure 2.6 1/min.

The concentration of silver was calculated from the calibration curve.

(2) Using copper :

[A] A.A.S method :

To different aliquots of 0.01 M indomethacin solution (equivalent to 1.79-35.8 mg of indomethacin). 5 ml 0.01 M copper acetate solution was added and shaked well. The precipitate was filtered through filter paper (Whatman No. 44) and washed with deionized water till free from Cu^{++}.

a. Direct method :

The obtained precipitate was dissolved in the least amount of dilute ammonia solution and completed to 100 ml with deionized water. Only 5 ml of the solution was transferred into 50 ml measuring flask and completed to volume (solution 3).

b. Indirect method :

The filtrate And washings were collected in 100 ml measuring flask and completed to volume. 5 ml of the filtrat was diluted to 100 ml (solution 4).

A blank (omitting addition of indomethacin) was carried out by aspirating solution (3) and (4) into an oxidizing air acetylene flame and measuring the absorbance at the flaming conditions :

Wavelength 327.7 nm
Lamp current 7 mA
Slit width 3.8 A
air pressure 10 1/min.
acetylene pressure 2.3 1/min.

The concentration of copper was calculated from the calibration curve.

[B] Colorimetric method :

a. Direct method :

The precipitate obtained from Cu++ method was dissolved in the least amount of dilute ammonia and completed to 50 ml with distilled water. To 2 ml in 10 ml measuring flask, 4 ml sodium diethyl dithiocarbamate solution was added and diluted to volume with distilled water. The absorbance was measured at 446 nm and the concentration of copper was calculated from the calibration curve. (NB : 1mg Cu^{++} 11.3 mg indomethacin).

b. Indirect method :

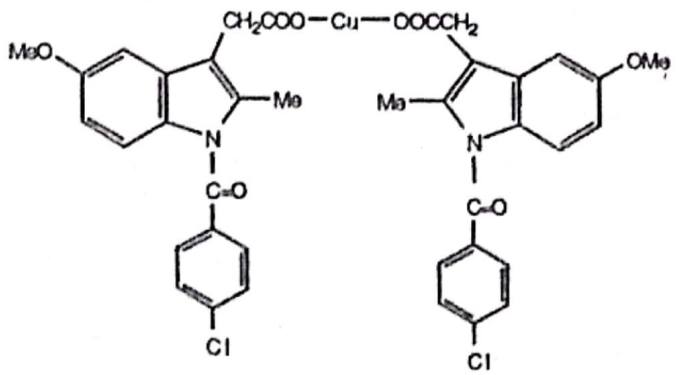
The filtrate and washing from Cu^{++} method was completed to 100 ml with distilled water. To 2 ml of the filtrate, in 10 ml measuring flask was added 4 ml sodium diethyldithiocarbamate. Completed to volume with distilled water and was measured the absorbance at 446 nm. The concentration of copper was calculated from the calibration curve.

Procedure for indomethacin capsules :

The contents of 20 capsules were thoroughly mixed. An amount equivalent to about 100 mg indomethacin in a 100 ml measuring flask was added to 10 ml of water and shaked constantly for 10 minutes. Exactly 25 ml of alcolhol was added and the solution was rendered neutral to phenol red with 0.1 NaOH and completed to volume with deionized water. To 5 ml of this solution was added specified amount of metal solution. The concentration of indomethacin was calculated by the A.A.S. and colorimetric methods described above.

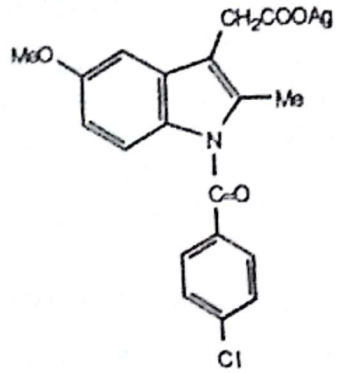
RESULTS AND DISCUSSION

A neutral alcoholic solution of indomethacin was found to give a white coagulated precipitate when treated with silver nitrate and a green bluish precipitate when treated with copper acetate solution. This precipitation forms the basis for the quantitative determination of



Suggested structure of indomethacin - copper salt

microquantities of indomethacin (tables 1&2). Both metal ions could be determined directly and indirectly by A.A.S.



Suggested structure of indomethacin - silver salt

Moreover, copper ion could be measured colorimetrically using sodium diethyldithiocarbamate at λ 446 nm. Different factors affecting the reaction have been carefully studied.

Tthe role of the added alcohol was to solubilize the drug and to help the coagulation of the precipitate. Larger volumes of alcohol solubilize the formed precipitate [18].

Concerning the effect of pH buffer solutions of different pH values have been tried in the precipitation process. Incomplete precipitation was obtained in acid media. On the other hand, excess alkali woud precipitate the metal as oxide

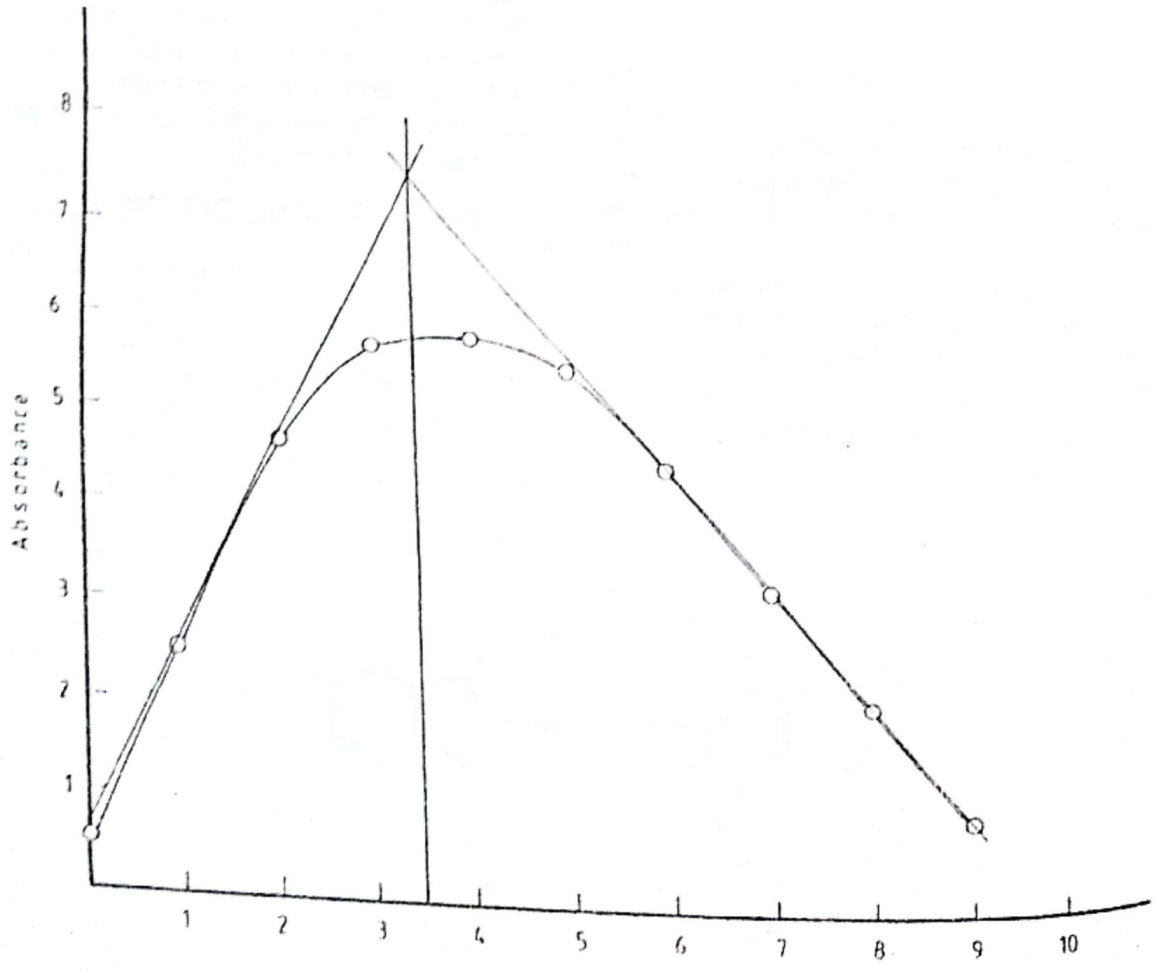


Fig. (1) : Continuous variation plot of indomethacin-copper salt.

Table (1) : Determination of indomethacin by the proposed A.A.S (Ag^{+} method) and the official mehtod (1).

	Silver method		Official method (acid-base titration)
	Direct	Indirect	
Conc. range	3.20-48.00 ug ml^{-1}	14.83-42.83 ug ml^{-1}	
Mean ± SD	99.19±0.35	99.11±0.37	99.07±0.31
N	8	8	8
V	0.120	0.139	0.098
t	0.729	0.233	(2.14)*
f	1.226	1.415	(3.79)*

* Theoretical value.

Table (2) : Determination of indomethacin by the proposed A.A.S (Cu^{+2} method) colorimetric method and the official one [1].

	Copper method				Official method (acid-base titration)
	A.A.S		Colorimetric method		
	Direct mehod	Indirect method	Direct mehod	Indirect method	
Conc. range	3.58-35.80 ug ml^{-1}	3.58-32.22 ug ml^{-1}	7.16-143.10 ug ml^{-1}	7.16-114.48 ug ml^{-1}	
Mean ± SD	98.99±0.31	98.96±0.31	99.35±0.33	99.42±0.36	99.07±0.31
N	8	8	8	8	8
V	0.095	0.094	0.107	0.131	0.098
t	0.515	0.706	1.745	2.069	(2.14)*
f	1.031	1.017	1.089	1.337	(3.79)*

* Theoretical values at p = 0.05

Table (3) : Determination of indomethacin in indomin capsule by the A.A.S method, colorimetric method and the official one.

	A.A.S method				Colorimetric method		Official method (Spectrophotometric method)
	Silver method		Cooper method				
	Direct mehod	Indirect method	Direct mehod	Indirect method	Direct mehod	Indirect method	
Taken ug ml^{-1}	7.00 - 20.00		7.16 - 32.22		14.31 - 100.17		25-150
Mean ± SD	99.58±0.80	101.4±0.48	99.63±0.71	101.54±0.42	99.72±0.54	101.14±0.78	100.81±0.91
N	5		5		5		5
V	0.65	0.23	0.50	0.18	0.29	0.61	0.83
t	2.27	1.28	2.23	1.63	2.29	0.62	(2.31)*
f	1.28	3.61	1.65	4.67	2.85	1.37	(6.39)*

* Theoretical value at p = 0.05

or hydroxide. Thus, the optimum pH was found to be alcoholic neutral solution to phenol red (6.8-8.4).

Regarding the effect of metal ion concentration, 5 ml of 0.025N silver nitrate and 5 ml of 0.01 M copper acetate solutions were found to be the most suitable for complete precipitation.

Considering the effect of temperature, room temperature was found to be the most suitable for both silver and copper method. Trying higher temperature leads to lower results.

Concerning the stoichiometric relationship, the Job's method of continuous variation [19] indicated a molar ratio of 1:1 and 2:1 indomethacin-metal salts using silver [18] and copper methods respectively, Fig. (1).

Regarding the linearity of Beer's law, the absorbance of the reaction products obeyed Beer's law at the concentration ranges mentioned in tables (1) and (2).

Table (3) shows the results obtained by application of the three proposed methods and the official method (1) for the determination of indomethacin in pharmaceutical preparations as well.

The statistical data for the proposed methods are given in Table (3). At the 95% confidence level, the calculated t and f values did not exceed the theoretical values in all the methods. Obviously the results obtained did not significantly differ from official ones.

The proposed methods are more sensitive, selective and specific for assay of indomethacin both as a raw material and in dosage forms. These results encourage the successful use of these methods in routine analysis of the drug in quality control laboratories.

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استخدام بعض أيونات المعادن للتقدير الكمى للاندوميثاسين

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فى هذا البحث تم استحداث طريقة بسيطة ودقيقة للتقدير الكمى لعقار الأندوميثاسين، وذلك باستخدام أيونات الفضة وأيونات النحاس، حيث يرسب الاندوميثاسين من محلوله المتعادل الكحولى بحاليل عيارية من خلات النحاس ونترات الفضة. ثم قياس الناتج بطريقتين وهما طريقة التحليل اللونى وطريقة الامتصاص الطيفى الذرى.

وقد تم دراسة الظروف الملائمة لتكوين أملاح الأندوميثاسين مع الفضة ومع النحاس، كما تم تعيين النسب المولارية بين المواد المتفاعلة (الاندوميثاسين وأيونات المعادن) باستخدام طريقة الامتصاص الطيفى الذرى مع أملاح ثنائى الأيثيل ثنائى الثيوكاربامات.

وقد تم مقارنة نتائج الطريقتين المقترحتين (طريقة التحليل اللونى وطريقة الامتصاص الطيفى الذرى) للتقدير الكمى للاندوسيثاسين مع الطرق الدستورية الإنجليزية (طريقة المعايرة). ووجد أنهما متماثلان فى الدقة. ولكن الطرق المقترحة تفوقها فى الحساسية وفى الاختيارية. مما يشجع استعمالها فى تقييم المادة الفعالة فى المستحضرات الصيدلانية.