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Spectrophotometric Determination of Mefenamic Acid in Pharmaceutical Preparations Via Arsenazo III – Cerium (III) Reaction*

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ABSTRACT

A sensitive indirect spectrophotometric method is proposed for determining mefenamic acid in pure form and in its pharmaceutical preparations. The method is based on oxidation-reduction reaction between mefenamic acid and cerium (IV) ion, and subsequent Ce(III) reaction with arsenazo (III) reagent in acidic medium to produce a greenish-blue complex which is stable, water soluble and has a maximum absorption at 654 nm with a molar absorptivity of 1.731×10^5 $l.mol^{-1}.cm^{-1}$. Beer's law is obeyed in the concentration range from 1 to 10 μg mefenamic acid in a final volume of 25 ml. The proposed method has been applied successfully to determine mefenamic acid in pharmaceutical preparations.

التقدير الطيفي لحامض الميفينماميك في المستحضرات الصيدلانيه باستخدام تفاعل الارسين ازو الثلاثي مع السيريوم الثلاثي

الملخص

تم اقتراح طريقة طيفية غير مباشرة وحساسة لتقدير حـامض الميفينامیـك بـشكله النقـي وفـي مستحضراته الدوائيه. اعتمدت الطريقة على تفاعل الأكسدة والاختزال بين حامض الميفينامیـك وأيـون السيريوم الرباعي يتبعها مفاعلة ناتج التفاعل أيون السيريوم الثلاثي مع الكاشف آرسين آزو III في وسط حامضي ليعطي معقداً اخضراً مزرق اللون مستقر وذائب بالمحلول المائي تُقاس شدة امتـصاصه عنـد الطول الموجي 654 نانوميتر وكانت قيمة الامتصاصية المولارية 1.731×10^5 لتر.مول$^{-1}$.سم$^{-1}$ وانطبق قانون بير في مدى التركيز بين 1 و10 مايكروغرام من حامض الميفيناميك في حجم نهائي 25 مل. تـم تطبيق الطريقة المقترحة بنجاح في تقدير حامض الميفيناميك في مستحضراته الدوائية.

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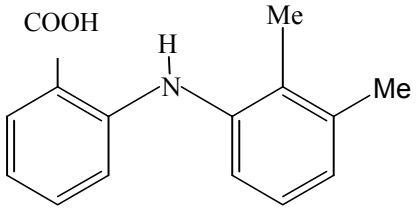
INTRODUCTION

Mefenamic acid [2-(2,3-dimethyl phenyl)amino]benzoic[I] acid is a non-steroidal anti-inflammatory drug which has analgesic, anti-inflammatory and antipyretic actions. It is used specially in the treatment of rheumatoid arthritis, osteoarthritis and other muscular-skeletal diseases (Martindale, 1982).



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The standard method for the assay of the pure drug is titrimetry, using sodium hydroxide as a titrant and phenol red as indicator (British pharmacopia, 2000).

Different techniques have been described for the determination of mefenamic acid: High performance liquid chromatography has been used for the determination of the drug in biological fluids such as human plasma (Niopas and Mamzoridi, 1994) or in human serum (Mohammed *et al.*, 2004), and in horse plasma (Ishidaka *et al.*, 1986).

Terbium sensitized fluorescence is used to develop a sensitive spectrofluorometric method for determination of mefenamic acid (Pinclopi *et al.*, 1998), another spectrofluorimetric method based on oxidation of mefenamic acid with cerium (IV) (Tabrizi, 2006).

Flow- injection technique was used in the determination of mefenamic acid, the methods based on formation of complex with Al(III) (Albero *et al.*, 1995), tris (2, ,$\bar{2}$ bipyridyl) ruthenium (III) (Fatma *et al.*, 2000).

Several spectrophotometric methods have been reported for the estimation of mefenamic acid using different reagents such as diazotised 4-amino-3,5-dinitrobenzoicacid (Idowut *et al.*, 2003), methyl-2-benzo-thiazolinone hydrazone hydrochloride after oxidation with Ce^{+4}or Fe^{+3} (Chilukuri *et al.*, 1989), sodium nitroprusside in the presence of hydroxyl ammonium chloride (Sastry and Rao, 1987), p-dimethylaminobenzaldehyde (Aman *et al.*, 2005), p-dimethylaminocinnamaldehyde (El-Sherif *et al.*, 1997), triton X-114 (Tabrizi, 2006), Fe^{+3} to form coloured complex (Zommer and Bojarowicz, 1986).

Many methods have been used in simultaneous determination of mefenamic acid in the presence of another drug such as paracetamol (Dinc *et al.*, 2002), ethamsylate (Garg and Saraf, 2007).

However some of these procedures suffer from one or another disadvantage such as: the product may be extracted to organic solvent (Idowut *et al.*, 2002), or require non-aqueous medium (El-Sherif *et al.*, 1997) and other required control of temperature (Aman *et al.*, 2005, Tabrizi, 2006).

Arsenazo (III) undergoes sensitive and selective reactions with several cations, such as reaction with cerium (III) ion in the presence of cerium (IV) ion. This reaction can be used in the determination of some organic compounds which have the ability to undergo

oxidation-reduction reaction with cerium (IV) ion (Al-Irhayim, 2004; Al-Abdaly, 2005; Jaime and William, 1991).

The objective of investigation reported in this paper is to develop a simple and accurate spectrophotometric method for the determination of mefenamic acid based on the oxidation of mefenamic acid with cerium (IV) ion, and the produced cerium (III) ion is subsequently reacted with arsenazo (III) reagent in acidic medium to form highly coloured complex.

EXPERIMENTAL

All spectrophotometric measurements are performed on Shimadzu UV-visible recording spectrophotometer UV-160 using 1-cm silica cells. pH meter type Philips PW 9420 is used for pH reading.

Reagents

All chemicals used are of analytical - reagent grade.

Standard mefenamic acid solution, 100μg.ml^{-1}. This solution is prepared by dissolving 0.01 g of pure mefenamic acid (SDI- Iraq) in a solution of sodium hydroxide (0.1N) containing 5 ml ethanol and the volume is diluted to 100 ml with sodium hydroxide (0.1N) in a volumetric flask. This solution was further diluted to 10μg. ml^{-1} with distilled water.

Ammonium ceric sulphate [cerium(IV) ion solution], 6.6×10^{-5}M. This solution is daily prepared by dissolving 0.0105 g of ammonium ceric sulphate dihydrate (BDH) in 250 ml of distilled water in a volumetric flask.

Arsenazo III reagent solution,2×10^{-4}M. This solution is prepared by dissolving 0.0411 g of arsenazo III (Fluka) in 250 ml distilled water in a volumetric flask.

Hydrochloric acid solution, 0.05 *N*.This solution is prepared by appropriate dilution of 4.2 ml of the concentrated hydrochloric acid (11.8 N) solution to 100 ml with distilled water in a volumetric flask.

Buffer solution, pH 3. This solution is prepared by mixing 50 ml of 0.1N glycine solution (0.3752g glycine dissolved in 50ml distilled water) with 5.7ml of 0.2N HCl, then the volume is completed to 100 ml with distilled water and adjusted to pH 3 by pH meter.

Procedure and calibration graph

To a series of 25-ml calibrated flasks, an increasing volume (0.1-1.8 ml) of 10 μg.ml^{-1} mefenamic acid solution are transferred to cover the range of calibration graph, followed by 9 ml of 6.6 ×10^{-5}M cerium (IV) ion solution and 0.9 ml of 0.05N HCl, the solutions are left for 25 minutes at room temperature, followed by addition of 2 ml of 2×10^{-4}M arsenazo (III) reagent solution then 3 ml of pH 3 was added and diluted to the mark with distilled water, the absorbances are measured at 654 nm against the reagent blank. Beer's law is obeyed over the range of concentration 1 to 10 μg mefenamic acid in 25 ml (Fig. 1). A negative deviation from Beer's law is occurred beyond the upper determination limit. The apparent molar absorptivity, referred to mefenamic acid, has been found to be 1.731 ×10^{5} l.mol^{-1}.cm^{-1}.

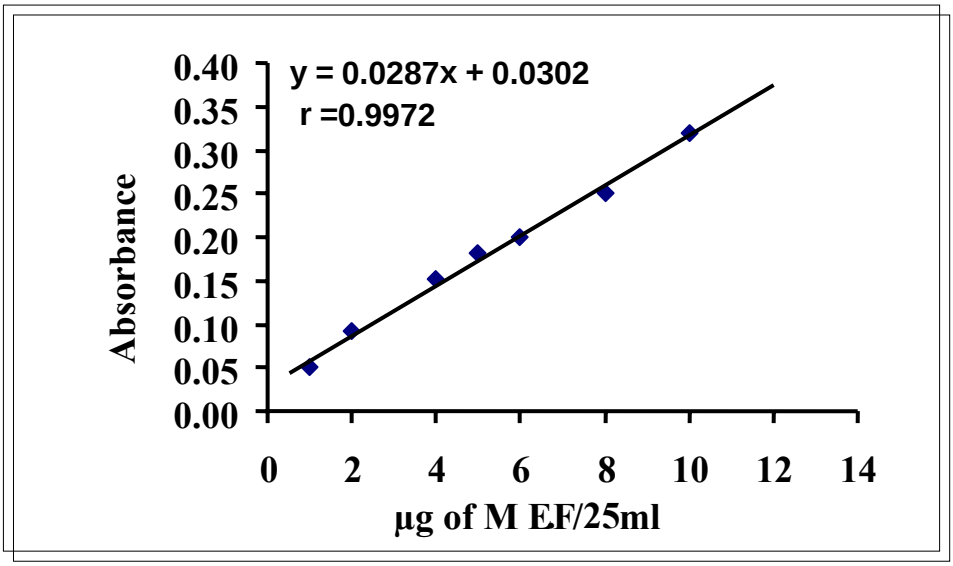


Fig. 1:Calibration graph for mefenamic acid determination using the reaction between arsenazo(III) and cerium(III).

Determination of mefenamic acid in capsule. Weight and mix the contents of five capsule (each one contains 250 mg mefenamic acid), an accurately weighed amount of powder equivalent to 0.01g mefenamic acid is dissolved in a mixture of 5 ml ethanol and 75 ml of 0.1N NaOH, after filtration the filtrate is completed to 100 ml with a 0.1N NaOH in a volumetric flask. A 10 ml of the above solution is diluted to 100 ml to prepare 10µg ml^{-1}. A suitable aliquot of solution was taken and the recommended procedure was followed for analysis of the drug.

Determination of mefenamic acid in suspension. The content of the container (100 ml, each 5ml contains 50 mg mefenamic acid) is dissolved in a mixture containing 25 ml of ethanol and 100 ml of 0.1N NaOH then the solution is warmed, then filtered and the volume is completed to 250 ml with 0.1N NaOH, 2.5ml which is equivalent to 0.01 g mefenamic acid is transferred into a 100. ml calibrated flask and the volume is completed with a distilled water. A 10 ml of the above solution is diluted to 100 ml to prepare 10µg ml^{-1}solution. A suitable aliquot of solution was taken and the recommended procedure was followed for analysis of the drug.

RESULTS AND DISCUSSION

Absorption spectra

Absorption spectrum of the coloured complex formed from the reaction between cerium (III) ion with arsenazo (III) in acidic medium against its corresponding reagent blank shows maximum absorption at 654 nm in contrast to the arsenazo reagent blank (Fig. 2).

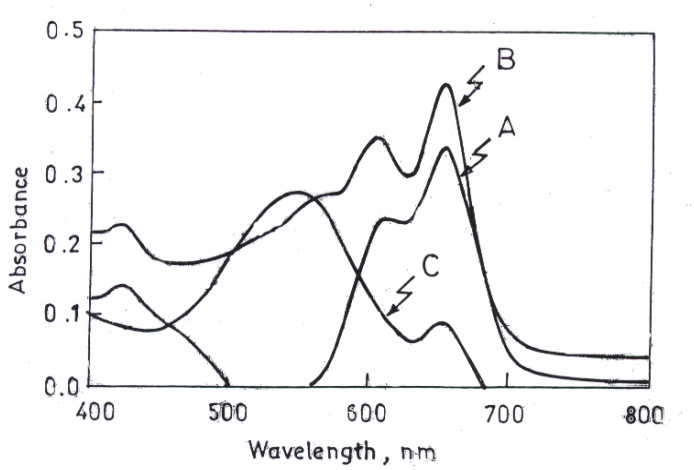


Fig.2:Absorption spectra of 10 μg mefenamic acid / 25 ml treated according to the recommended procedure and measured against (A) blank, (B) distilled water and (C) blank measured against distilled water.

Optimization of reaction conditions

The effect of various parameters on the absorption intensity of the coloured complex containing 10μg of mefenamic acid is studied and the reaction condition have been optimized.

Effect of pH

The effect of pH on the intensity of coloured complex is examined. Different volumes 0 - 3 ml of 0.05M hydrochloric acid solution is added to an aliquot of solution containing 10 μg of mefenamic acid. The intensities of absorption were measured against the reagent blank at 654 nm. The results are shown in Table 1.

Table 1: Effect of pH on absorbance

ml of 0.05N HCl	Absorbance	Final pH
0.00	0.031	9.43
0.1	0.077	6.11
0.3	0.207	4.13
0.5	0.213	3.50
0.7	0.217	3.39
0.8	0.220	3.30
0.9	0.223	3.09
1	0.221	2.98
3	0.218	2.71

The results shown in Table 1 indicate that the pH of 3.09 (0.9 ml of 0.05N HCl) is considered optimum. A pH 3 is selected for subsequent investigation because of good sensitivity. Five buffer solutions of pH 3 with different composition have been tested, tartaric acid-NaOH (B_1), citric acid-NaOH (B_2), KH phthalate-HCl (B_3), glycine-HCl (B_4) and formic acid-NaOH (B_5) (Table2).

Table 2: Effect of buffer solution without and with hydrochloric acid on absorbance

ml of Buffer solution	Variable	Absorbance/ml of Buffer added				
		B1	B2	B3	B4	B5
2	Without HCl	-0.049	-0.002	0.022	0.024	-0.049
	With HCl	0.143	0.125	0.203	0.213	0.194
3	Without HCl	-0.046	0.020	0.024	0.025	-0.098
	With HCl	0.128	0.111	0.208	0.218	0.206
4	Without HCl	-0.044	0.001	0.014	0.019	-0.066
	With HCl	0.130	0.102	0.154	0.202	0.188
Final pH of reaction mixture	HCl+ buffer	3.02-3.10	2.87-3.0	3.13-3.15	2.95-3.20	3.22-3.34

The results shown in Table 2 indicate that all types of buffer solutions decrease the intensity of the coloured complex, but the results improved when buffer solution added after adding 0.9 ml 0.05 N HCl. 3ml of glycine-HCl buffer solution (B4) is recommended in the subsequent experiments according to the highest intensity of the complex and it produces more stable complex (Table 3).

Table 3: The stability of complex without and with buffer solution

Time (minute)	0	5	10	15	20	25	35
Absorbance(A*)	0.217	0.212	0.207	0.198	0.190	0.183	0.176
Absorbance(B**)	0.223	0.220	0.220	0.217	0.217	0.216	0.216

*Using hydrochloric acid only.
** Using HCl + 3 ml of glycine-HCl

Effect of oxidizing agent [cerium(IV) ion] amount

The effect of cerium (IV) ion concentration on the absorbance of the complex was studied. It was found that 9 ml of 6.6×10^{-5}M of Ce(IV) gave maximum absorption which is recommended in subsequent experiments (Table 4).

Table 4: The effect of ceric ion amount on absorbance

ml of 6.6×10^{-5}M Ce(IV) Solution	Absorbance/µg of mefenamic acid present					Absor-bance of blank	Correlation coefficient(r)
	2	4	6	8	10		
4	0.084	0.123	0.147	0.164	0.182	0.042	0.9829 .
5	0.099	0.136	0.171	0.187	0.209	0.048	0.9864
6	0.093	0.139	0.170	0.191	0.213	0.064	0.9847
7	0.099	0.141	0.175	0.203	0.221	0.087	0.9890
8	0.119	0.170	0.222	0.239	0.291	0.085	0.9897
9	0.116	0.191	0.237	0.285	0.323	0.099	0.9917
10	0.121	0.189	0.246	0.260	0.316	0.117	0.9817

Effect of time on reduction of cerium (IV) ion

The effect of time needed to complete the reduction of cerium (IV) ions to cerium (III) ions was studied by standing of the solutions after adding cerium (IV) ion solution for different times at room temperature, then the other reagents were added and the absorbances were measured against the reagent blank (Table 5).

Table 5: Effect of time on reduction process

Time (min.)	0	10	20	25	30	35	40
Absorbance	0.073	0.256	0.291	0.319	0.320	0.323	0.324

The results indicate that complete reduction of cerium (IV) ions needed 25 minutes and the increase in intensity at 30 minutes and above is considered tolerable from that at 25 minutes. Therefore, the standing time 25 minutes was recommended for the subsequent experiments.

Effect of arsenazo III reagent amount

The effect of the amount of arsenazo III (AzIII) reagent on maximum formation of the coloured complex is investigated. The results are shown in Table 6.

Table 6: Effect of arsenazo III reagent amount on absorbance

ml of AzIII Solution 2×10^{-4}M	**Absorbance /µg mefenamic acid**					**r**
	2	4	6	8	10	
1	0.103	0.199	0.236	0.273	0.291	0.9543
2	0.120	0.183	0.240	0.283	0.325	0.9955
3	0.109	0.179	0.234	0.274	0.312	0.9908
4	0.110	0.175	0.241	0.263	0.301	0.9809

The results shown in Table 6 indicate that 2 ml of arsenazo (III) reagent solution give higher sensitivity and higher value of correlation coefficient (r), therefore it has been selected for subsequent experiments.

Effect of order of addition of reagents

The effect of order of addition of reagents on the absorbance of coloured complex is investigated (Table 7).

Table 7: The order of addition of reagents

Reaction component	**Order number**	**Absorbance**
MEF + O + A + B + R	I*	0.322
MEF + O + B + A + R	II	0.099
MEF + O + R +A + B	III	0.174
MEF + O + R + B + A	IV	0.057

***** Mefenamic acid (MEF) + Ce^{+4} (O) +HCl (A) + Buffer solution (B) + Arsenazo (III) (R)

The results indicate that the order of addition of reagents should be followed as given under procedure (order I).

Effect of Time

The effect of time on the development and stability of the coloured complex for different amounts of mefenamic acid was investigated under the optimum experimental conditions established. The colour formation occurs immediately after the addition of all reaction mixtures and the absorbance of the complex remains constant for at least 1 hour (Table 8).

Table 8: Effect of time on the absorbance of complex

Time/ Minute	Absorbance / µg of Mefenamic acid in 25 ml*		
	4	8	10
0	0.199	0.270	0.327
5	0.199	0.270	0.327
10	0.199	0.270	0.326
15	0.199	0.270	0.325
20	0.201	0.269	0.325
25	0.201	0.269	0.325
30	0.201	0.269	0.324
35	0.201	0.269	0.322
40	0.201	0.269	0.322
45	0.201	0.269	0.322
50	0.201	0.269	0.322
55	0.201	0.269	0.320
60	0.201	0.269	0.320

*After 25 minutes reaction time of mefenamic acid with Ce (IV) ion.

The above stability period is sufficient to allow several measurements to be performed sequentially.

Effect of interferences

The effect of some foreign compounds which often accompanied pharmaceutical preparations are studied by adding three different amounts (100, 500 and 1000µg) to 10 µg of mefenamic acid in a final volume 25 ml (Table 9).

Table 9: Effect of foreign compounds for assay of mefenamic acid

Foreign compound	Recovery(%) of mefenamic acid per µg foreign added		
	100	500	1000
Glucose	98.9	102.7	100
Lactose	103.1	104.1	100
Starch	104.1	104.8	103.7
Arabic gum	97.5	92.9	91.7

The results in Table 9 indicated that the studied foreign compounds did not interfere in the determination of mefenamic acid by using the proposed method except Arabic gum at high concentration.

Accuracy and precision

To check the accuracy and precision of the calibration graph, mefenamic acid was determined at three different concentrations. The results shown in Table 10 indicate that the calibration graph is satisfactory.

Table 10: Accuracy and precision

Amount of MEF taken , µg	Relative error, %*	Relative Standard deviation, %*
2	1.65	1.90
5	0.93	1.26
10	-0.92	1.56

*Average of five determinations

Nature of the reaction between mefenamic acid and cerium(IV) ion

Job's method was used in the determination of the reaction ratio of mefenamic acid with cerium (IV) ion. The results obtained (Fig. 3) showed that a 1:1 mefenamic acid to cerium (IV) ion ratio is obtained.

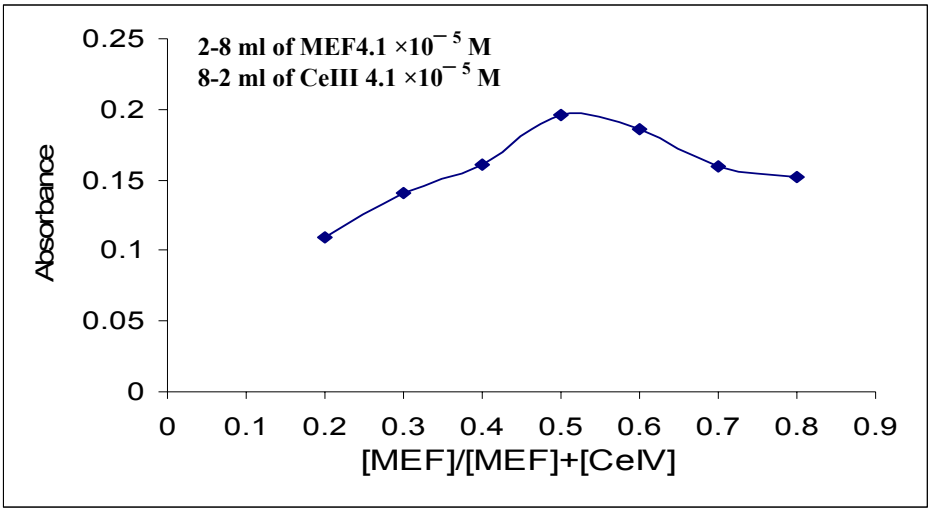
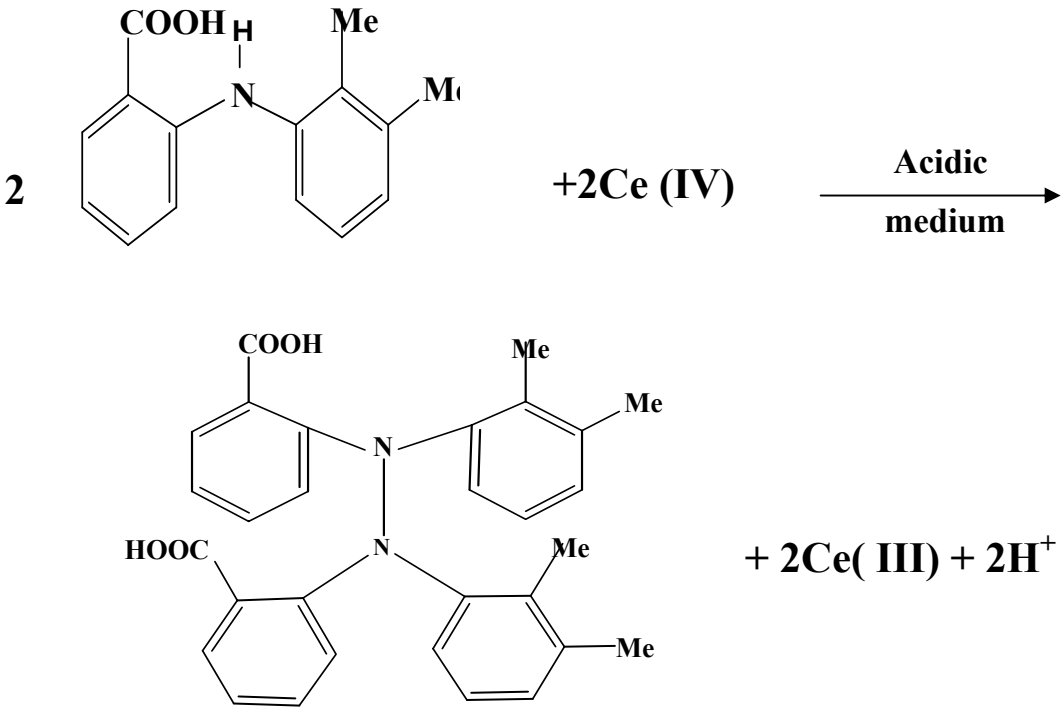


Fig.3: Job's plot for mefenamic acid -cerium (IV) ion

The probable mechanism of the reaction might be the following:



Nature of arsenazo (III)-cerium (III) ion complex

The stoichiometry of arsenazo III and cerium ion, the reaction is investigated using the Job's method under the optimized conditions. The results obtained (Fig. 4) showed that a 1:1 arsenazo (III) to cerium (III) ion ratio is obtained.

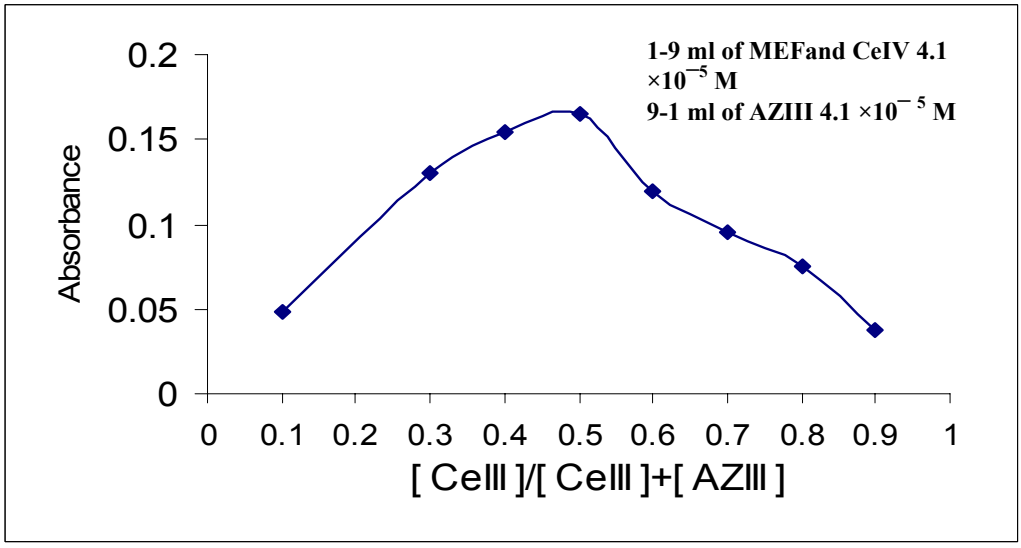


Fig. 4: Job's plot for arsenazo III-cerium (III) ion complex

Analytical applications

The proposed method was applied to determine mefenamic acid in different pharmaceutical preparations. On applying proposed procedure, good recoveries were obtained as shown in Table 11.

Table 11: Analytical applications

Pharmaceutical preparation	µg mefenamic acid present/25ml	µg mefenamic acid measured/25ml	Recovery(%)
Ponstidin capsule(250 mg) N.D.I-Iraq	5	4.98	99.6
	10	9.87	98.7
Ponstidin capsule(250 mg) GMBH,Germany	5	4.82	96.4
	10	9.87	98.7
Mefastan (50 mg/5 ml) Al-Anaam pharma-Ind. (Baghdad-Iraq)	5	5.14	102.8
	10	10.12	101.2

Evaluation of the proposed method

The performance of the proposed method is assessed by calculating the student's t–test compared with the standard method (British Pharmacopoeia, 2000). At the 95% confidence limit for four degree of freedom, the calculated t - values do not exceed the theoretical value (2.776). The results in Table 12 indicate that there is no significant difference between the proposed method and the standard method.

Table 12: Analysis of mefenamic acid in pharmaceuticals by proposed and official method

Drug	Recovery, (%)*		t-exp.
	Present method	Official method	
Ponstidin capsule(250 mg) N.D.I-Iraq	99.10	100	1.072
Ponstidin capsule(250 mg) GMBH,Germany	97.66	99.45	1.904

*Average of five determinations

Standard addition method has been used in determination two of drugs under investigation in order to prove that the proposed method is applied to the determination of mefenamic acid without interferences (Table 13 and Fig. 5).

Table 13: The results of standard addition method

Pharmaceutical preparation	µg mefenamic acid present/25ml	µg mefenamic acid measured/25ml	Recovery * (%)
Ponstidin capsule(250 mg) N.D.I-Iraq	2	2.02	101.0
	4	4.00	100.0
Mefastan (50 mg/5 ml) Al-Anaam pharma-Ind. (Baghdad-Iraq)	2	2.05	102.5
	4	4.00	100.0

*Average of three determinations

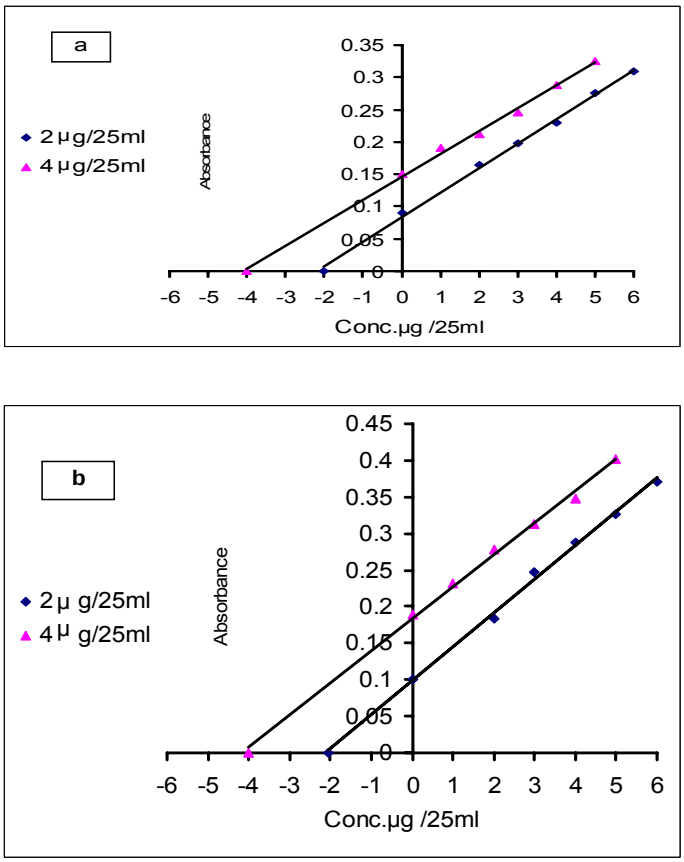


Fig.5. Graphs of standard addition method for the determination of mefenamic acid in Ponstidin capsule (250 mg) N.D.I-Iraq (a) and on Mefastan (50 mg/5 ml) Al-Anaam pharma.-Ind. (Baghdad-Iraq) (b)

The results in Table 13 and Fig. 5 indicated that the proposed method can be applied successfully to the determination of mefenamic acid in pharmaceutical formulations .

COMPARISON OF THE METHODS

Table 14 shows the comparison between some of analytical parameters of the present method with another recent spectrophotometric method.

Table 14: The comparison of the methods

Analytical parameters	Present method	Literature method*
pH	3	Alkaline medium
Temperature (°C)	Room temperature	30° C
λ_{max} (nm)	654	490
Medium of reaction	Aqueous	Non-aqueous
Reagent	Arsenazo(III)	4-amino-3,5-dinitrobenzoic acid
Beer's law range (ppm)	0.04-0.4	1-6
Molar absorptivity ($l.mol^{-1}.cm^{-1}$)	1.634×10^5	1.558×10^4
RSD (%)	≤ 1.93	1.37
Stability of the colour (minute)	60	-----
Colour of the product	Bluish green	Orange-red
Application of the method	Has been applied to the assay of mefenamic acid in capsule and in suspension solution	Has been applied to the assay of mefenamic acid in capsule

* Idowut,S.,Adegoke,A. and Olaniyi,A.,2003.

The results in Table 14 show that the suggested method for the determination of mefenamic acid was sensitive and needs neither temperature control nor extraction step.

CONCLUSION

The proposed method for the determination of mefenamic acid in pharmaceutical preparations was sensitive. The complex formed was fairly soluble in aqueous solution. The statistical analysis of the results indicates that the method has good accuracy (average relative error between -0.92 to +1.65 %) and good precision (average relative standard deviation not more than 1.93 %). The t-value indicates that there was no significant difference between the proposed method and the standard method. Moreover, the proposed method needs neither temperature control nor extraction step.

REFERENCES

Al-Abdaly, Z.Z., 2005. Spectrophotometeric Determination of *p*-Aminobenzoic Acid-Application to Pharmaceutical Preparations, M.Sc., Hesis, Mosul University, 61p.

Albero, M., Sanchez, C., and Farcia, M., 1995. Flow-injection Spectrofluorimetric Determination of Flufenamic and Mefenamic, J.Pharm. Biomed .Anal., 13, pp. 1113-1117.

Al-Irhayim, A.N., 2004. Spectrophotomtric Assay of Isoniazide in Tablet, M.Sc., Thesis, Mosul University, 33p.

Aman, T., Asrar, A., and Mateen, B., 2005. Colorimetric Determination of Two Nonsteroidal Anti-inflammatory Drugs Using p-dimethylaminocinnamaldehyde Anal. let., 38, pp. 1899-1912.

British Pharmacopeia on CD-ROM, 3rd Edn., System Simulation Ltd, the Stationary Office, London, 2000.

Chilukuri, S., and Ambati, R., 1986. Spectrophotometric Determination of some Analgesic and Anti-inflammatory Agents with Methyl-2-Denzothiazolinone Hydrazone Hydrochloride, Mikrochimi.a Acta, 97, pp. 237-244.

Dinc, E., Yucesoy, C., and Onur, F, 2002. Simultaneous Spectrophotometric Determination of Mefenamic Acid and Paracetamol in a Pharmaceutical Preparation Using Ratio Spectra Derivative Spectrophotometry and Chemometric Methods, J. Pharma. Biomed. Anal., 28, pp. 1091-1100.

EL-Sherif, Z., Walash, M., EL-Tarras, M., and Osman, A., 1997. Colorimetric Determination of Two Nonsteroidal Anti-inflammatory Drugs Using p-dimethylaminocinnamaldehyde, Anal.lett., 30, pp. 1881-1896.

Fatma, A., Aly; Salma, A., AL-Tamimi, and Abdulrahman A., ALwarthan, 2000. Determination of Flufenamic Acid and Mefenamic Acid in Pharmaceutical Preparations and Biological Fluids Using Flow Injection Analysis with Tris (2,2′-bipyridyl) Ruthenium (II) Chemiluminescence Detection, Anal. Chim. Acta, 416, pp. 87-96.

Garg, G., and Sarsf, S., 2007. Simultaneous Estimation of Mefenamic Acid and Ethamsylate in Tablets. Indian J. Pharm. Sci., 69, pp. 2-7.

Idowut, S., Adegoke, A., and Olaniyi, A., 2003. Novel Colorimetric Assay of Mefenamic Acid Using 4-Amino-3,5-Dinitrobenzoic Acid (ADBA), Tropical J. Pharm. Research, 1, pp. 15-22.

Ishidaka, O., Shinohara; T., Tanaka, T., and Momose, A., 1986. Determination of Mefenamic acid in Horse Plasma by High Performance Liquid Chromatography, Japan analyst, 35, pp. 332-334.

Jaime, N.D., and William, A.R., Wilson and Gisvold's, 1991. Text Book of Organic Medicinal and Pharmaceutical Chemistry, 9th Edn., J.B. Lippincott Company, London, 201p.

Martindale, 1982. The Extra Pharmacopoeia, 28th Edn., The Pharmaceutical Press, London. pp. 262-263.

Mohammed, R., Ali; A, Yalda, H., and Fakhredin, A., 2004. Liquid Chromatography Method for Determination of Mefenamic Acid in Human Serum. J. Chrom. B, 800, pp. 189-192.

Niopas, I., and Mamzoridi, k., 1994. Determination of Indomethacin and Mefenamic Acid in Plasma by High-performance Liquid Chromatography, J. Chromatogr. B, Biomed. Appl. 656, pp.447-450.

Pinelopi, C., Natalie, V., Dimitra, A., Kiriaki, G., and Georgia, M., 1998. Spectrof-Luorimetric Determination of Anthranilic Acid Derivatives Based on Terbium Sensitized Fluorescence, Analyst, 123, pp.2839-2843.

Sastry, C., and Rao, A., 1987. Spectrophotometric Method for Determination of Pentazocine and Mefenamic acid, Indian J. Pharm. Sci., 49, pp. 95-96.

Tabrizi, A.B., 2006. Determination of Mefenamic Acid in Human Urine by Means of two Spectroscopic Methods by Using Cloud Point Extraction Methodology as a Tool for Treatment of Samples, Bull. Korean Chem. Soc., 27, pp. 1780-1784.

Tabrizi, A.B., 2006. A Simple Spectrofluorimetric Method for Determination of Mefenamic Acid in Pharmaceutical Preparation and Urine, Bull. Korean Chem. Soc., 27, pp.1199-1202.

Zommer, S., and Bojarowicz, H., 1986. Spectrofluorimetric Investigations on Protolytic Equilibria of Mefenamic Acid and Determination by Means Fe (III) in Methanol-Aqueous Media, J. Pharm. Biomed. Anal., 4, pp.475-481.