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ATOMIC ABSORPTION SPECTROMETRY OF ACIDIC PHARMACEUTICAL CONSTITUENTS THROUGH PRECIPITATION BY METAL IONS *: II. DETERMINATION OF MEFENAMIC ACID

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ABSTRACT

A simple and accurate method was described for the quantitative determination of mefenamic acid utilizing precipitation reactions with silver (I), copper (II) and iron (III). Mefenamic acid was precipitated from its neutral alcoholic solution by silver nitrate, copper acetate or ferric chloride standard solutions followed by direct determination of the above cited ions in the precipitate or its indirect determination in the filtrate applying atomic absorption spectroscopy. The optimum conditions for precipitation have been carefully studied. The molar ratio of the reactants were ascertained. Statistical analysis of the results obtained compared to the results of the official method revealed equal precision and accuracy. The suggested procedures were applied for determing mefenamic acid in pharmaceutial preparations as well and proved validity.

INTRODUCTION

Mefenamic acid is anti-inflammatory, antipyretic drug with analgesic properties. Its chemical structure is N- (2,3 xylyl) anthranilic acid [1].

Several techniques were used for the determination of this drug such as polarographic [2,3], fluorometric [4], chromatographic [5] and spectro photometric [6-9] ones.

Silver (I) was used in pharmaceutical analysis as a reagent for analysis of theophylline and theobromine [10]and some reducing sugar [11]. Copper (II)was recommended in pharmaceutica analysis as a reagent for analysis of certain sulfonamides (12), oxyphenbutazone [13], benzyl penicillin [14] and terbutaline sulphate [15]. Also, iron (III) was used for the determination of aminopyrine [16], methyl salicylate [17] and calcium pangamate [18].

The present work represents the utilization of silver (I), copper (II) and iron (III) as reagents for the mefenamic acid determinations through A.A.S. measurements applying direct and indirect techniques. The methods proved to be very sensitive and accurate for its determination in pharmaceutical preparations. The average recoveries of direct and indirect techniques were 99.36± 0.19 and 99.49±0.20 for the method utilizing silver (I); 99.50±0.30 and 99.44±0.24 for that utilizing copper (II) and 99.49±0.21 for that utilizing iron (III), respectively.

EXPERIMENTAL

Instruments:

1- Perkin-Elmer atomic absorption, Flame spectrophotometer

2- Shimadzu U.V. and visible recording spectrophotometer (U.V.-260).

Materials and Reagents:

1- Mefenamic acid (Park-Davis Co.).

2- Ponstan capsules and syrup, Nile Co., Egypt, labeled to contain 250 mg and 50 mg mefenamic acid per each capsule or 5 ml syrup, respectively.

3- 0.025 M silver nitrate (0.425% w/v solution)

4- 0.01 M copper acetate (0.2% w/v solution)

5- 0.01 M ferric chloride (0.18% w/v solution)

6- Stock mefenamic acid solution (dissolve 80 mg mefenamic acid in about 40ml alcohol. The solution was rendered neutral (pH 7.0-7.6) with 0.1N sodium hydroxide and then completed to 100 ml with redistilled deionized water.

7- 0.01 M mefenamic acid working solution for Job's method of continuous variation (19).

A- Procedures for authenic mefenamic acid:

1- Atomic absorption spectrophotometry utilizing silver (I):

To different aliquots of stock solution (equivalent to 3.5-70.6 mg mefenamic acid), 5 mls 0.025 M silver nitrate solution were added. Kept away from light, shaked well and then filtered (Whatman No. 44).The precipitate was washed with redistilled deionized water until silver (I) free.

a- Direct method:

The precipitate obtained above was dissolved in the least amount of dilute ammonia solution and completed to 25 ml with redistilled deionized water. One ml of the resulting solution was diluted to 25 ml with redistilled deionize water.

b- Indirect method:

The filtrate and washings were collected in 100 ml measuring flasks, completed to volume with redistilled deionized water. 5mls of the resulting solution were diluted to 100 ml with redistilled deionized water.

A blank (omitting addition of the drug) was performed and absorbance was measured at the

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following conditions; wavelength 32.1 cm, lamp currnt 7 mA, slit width 3. A, ar pressur 10 L/min, and cetylene pressure 2.6 L/min.

Silver (I) concntraton wre calcuated from a clbraton curve.

2- Atomic absorpton spctrometry utlizing copper (II):

To diffrent aliquots of mefnamc acid solution (equivalent to 1.7-34.0 mg of mfenamc acd), 5 mls of coppr ctate soluton were added, shaked well and filterd (Whatman No. 44). The precpitte was washed with redistlled deionzed water tll copper (II) free.

a- Direct method:

The obtained precipitate was dissolved in the least amopunt of diluteammonia solution and completed to volume with redistilled deionized water.

b- Indirect method:

The fitrate and washings were collectedion 100 ml volumetric flask and completed to volume with redistilled deionized wter. 5 mls of the resulting solution were diluted to 100 ml with redistilled deionized water.

A blank (omitting addition of mefenamic acid) was carried out and measuring the absorbance at the flaming conditions; wavelength 327.7 nm, lamp current 7 mA, lit with 3.8 A, air pressure 10 l/min, and acetylene pressure 2.3 l/min.

Copper (II) concentrations were calculated from a calibration curve.

3- Atomic absorption spectrometry utilizing iron (III):

To different aliquots of stock solution (equivalent to 2.4-48.0 mg of mefenamic acid), 5 mls of ferric chloride solution were added, shaked well and then filtered (Whatman No. 44). The precipitate was washed with redistilled deionized water until iron (III) free.

a- Direct method:

The precipitate obtained above was dissolved in the least amount of dilute ammonia solution and completed to 25 ml with redisitilled deionized water. 5mls of the resulting solution were diluted to 50 ml with redistilled deionized water.

b- Indirect method:

The filtrate and washings were collected in 100 ml volumetric flask, completed to volume with redistilled deionized water. 5 mls of the resulting solution were diluted to 100ml with redistilled deionized water.

A blank (Omitting addition of the drug) was performed and absorbance was measured at the flaming conditions; wavelength 240.7 nm, lamp current 7 mA, slit width 3.8 air pressure 10 l/min, and acetylene pressure 2.5 l/min.

Iron (III) concentrations were calculated from a calibration curve.

B- procedures for mefenamic acid in pharmaceutical preparations:

1- For Ponstan Capsules:

The content of twenty capsules were weighed and finely powdered. An accurately weighed portion of the powders equivalent to 80 mg of mefenamic acid was added to 40 ml of alcohol and shaked constantly for 15 minutes in a 100 ml volumetric flask -filtered if necessary-, the solution was rendered neutral (pH 7.0-7.6) with 0.1 N NaOH and completed to volume with redistilled deionized water. To 5 mls aliquots of the resulting solution, was added the specified amount of metal solution and then completed as under A-1, A-2 and A-3.

2- For Ponstan Syrup:

An aliquot equivalent to 80 mg mefenamic acid was pipetted into a 100 ml volumetric flask. 40 ml ethanol was added and shaked for 5 min. The solution was rendered neutral (pH 7.0 - 7.6) with 0.1 N sodium hydroxide, then filtered in a 100 ml volumetric flask and completed to volume with redistilled deionized water. The specified amount of the metal solution was added to 5 mls. aliquots of the resulting solution and then completed as under A-1, A-2 and A-3.

RESULTS AND DISUCSSION

Neutral (pH 7.0 - 7.6) alcoholic solution of mefenamic acid give white coagulated precipitate with silver nitrate, green precipitate with copper acetate and violet precipitate with ferric chloride. These precipitates form the basic of micro - quantitive determination of mefenamic acid. The metal ions content can be determined either directly in the precipitate or indirectly in the filtrate by atomic absorption spectrometry (tables 1,2 and 3).Addition of the recommended amount of alcohol must be avoided otherwise it will solubilize the formed precipitate itself.

Concerning the effect of pH on precipitation, buffer, solutions covering the acid to the alkaline range have been tried. Acid media have a solubilizing effect on the precipitate leading to lower results for the direct technique and higher ones for the indirect technique while akali media precipitate the metal as its oxide or hydroxide leading to higher results for the direct technique. The optimum pH was found to be neutral (pH 7.0 - 7.6).

Considering metal ion concentration effect on precipitation, 5 ml of the precipitating solutions were found to be sufficient for complete precipitation.

Regarding the temparture effect on precipitation, room temperature was found to be the most efficient. Higher temperatures lead to solubilizing effect on the precipitate producing lower results for the direct technique and higher ones for the indirect technique.

Concerning the stoichiometric relationships, the Job's method of continuous variation (19) indicated a molar ratio of 1:1, 2:1 and 3:1 mefenamic acid to silver (I), copper (II) and iron (III) respectively (Figures 1,2 & 3).

Statistical analysis of the results obtained by the proposed methods compared with those of the official method are given in tables 1,2 & 3 at 95% confidence level, the calculated t and F values do not exceed the tabulated ones, revealing equal precision and accuracy

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Table (1): Determination of mefenamic acid by the proposed A.A. S (Ag^{+} method) compared to the official method (1).

	Silver method		Official method
	Direct	Indirect	
Mean ± S.D	99.36 ± 0.19	99.49 ± 0.20	99.48 ± 0.25
N	8	8	8
V	0.03	0.04	0.06
t	0.57	0.45	(2.14)*
F	2.0	1.5	(3.79)*

*** P = 0.05**

Table (2): Determination of mefenamic acid by the proposed A.A.S (Cu^{2+} method) compared to the official method (1).

	Copper method		Official method
	Direct	Indirect	
Mean ± S.D	99.50±30	99.44 ± 0.24	99.49 ± 0.25
N	8	8	8
V	0.09	0.06	0.06
t	0.37	0.08	(2.14)*
F	1.5	1.00	(3.79)*

*** P = 0.05**

Table (3): Determination of mefenamic acid by the proposed A.A. S (Fe^{3+} method) compared to the official method (1).

	Iron method		Official method
	Direct	Indirect	
Mean ± S.D	99.49 ± 0.29	99.42 ± 0.21	99.49 ± 0.25
N*P= 0.05	8	8	8
V	0.08	0.04	0.06
t	0.31	0.47	(2.14)*
F	1.30	1.50	(3.79)*

*** P = 0.05**

Table (4): Determination of mefenamic acid in Ponstan capsules by the A.A.S methods compared to the official method.(1)

	A.A.S method						Official method
	Silver method		Copper method		Iron method		
	Direct	Indirect	Direct	Indirect	Direct	Indirect	
Mean ± S.D	99.3 ± 0.21	99.4± 0.19	99.2± 0.29	99.5± 0.20	99.3± 0.17	99.5± 0.30	99.48 ± 0.2
N	8	8	8	8	8	8	8
V	0.04	0.04	0.08	0.04	0.03	0.09	0.06
t	0.2	0.4	0.6	0.3	0.4	0.2	(2.14)*
F	1.5	1.5	1.3	1.5	2.0	1.5	(3.79)*

* P = 0.05

Table (5): Determination of mefenamic acid in Ponstan capsules by the A.A.S methods compared to the official method. (1)

	A.A.S method						Official method
	Silver method		Copper method		Iron method		
	Direct	Indirect	Direct	Indirect	Direct	Indirect	
Mean ± S.D	99.2 ± 0.30	99.4± 0.29	99.5± 0.27	99.5± 0.15	99.5± 0.24	99.4± 0.29	99.48 ± 0.2
N	8	8	8	8	8	8	8
V	0.09	0.09	0.07	0.02	0.06	0.08	0.06
t	0.4	0.3	0.3	0.5	0.4	0.3	(2.14)*
F	1.5	1.5	1.2	3.0	1.0	1.5	(3.79)*

* P = 0.05

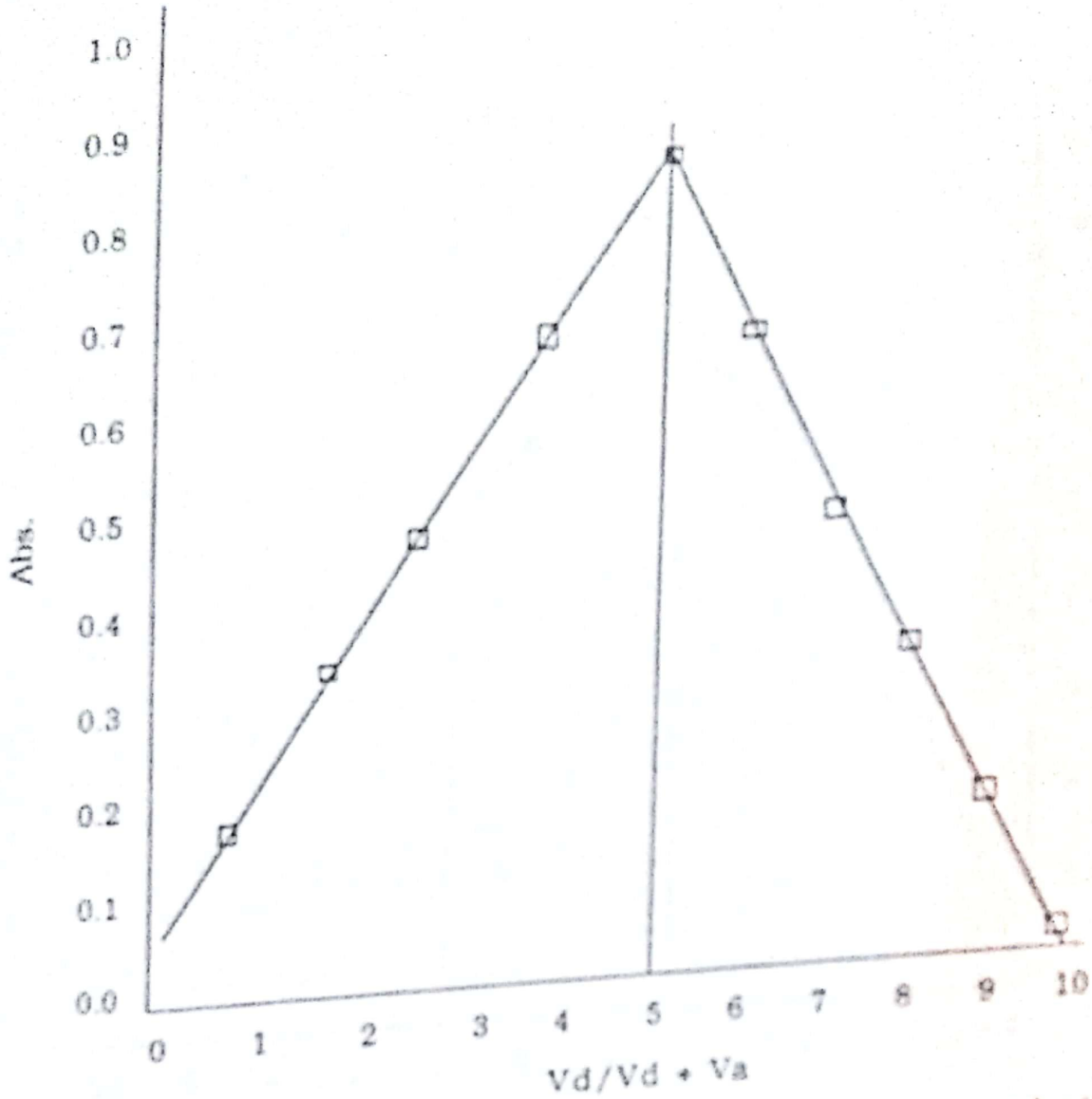

Fig. (1-a): Continuous variation plot of mefenamic acid-silver salt

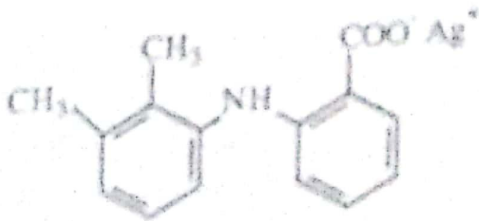

Fig. (1-b): Suggested structure of mefenamic acid-silver salt

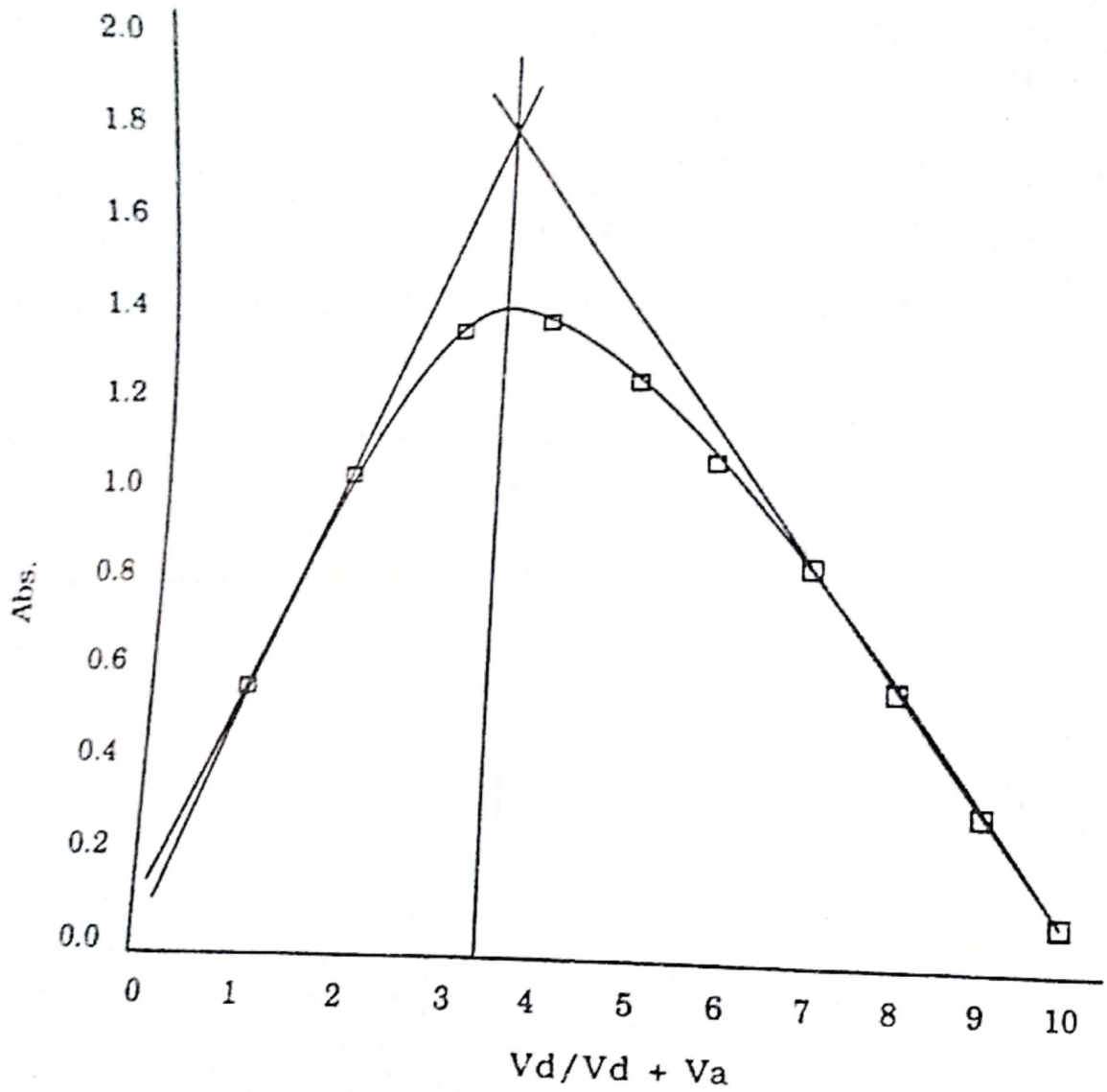

Fig. (2-a): Continuous variation plot of mefenamic acid-copper salt

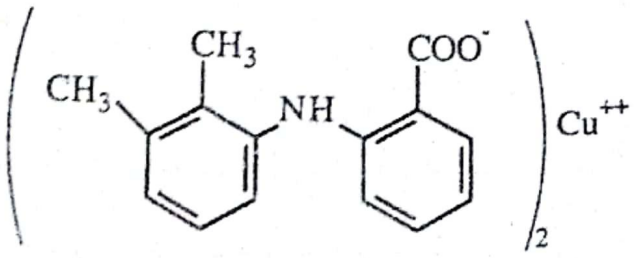

Fig. (2-b): Suggested structure of mefenamic acid-copper salt.

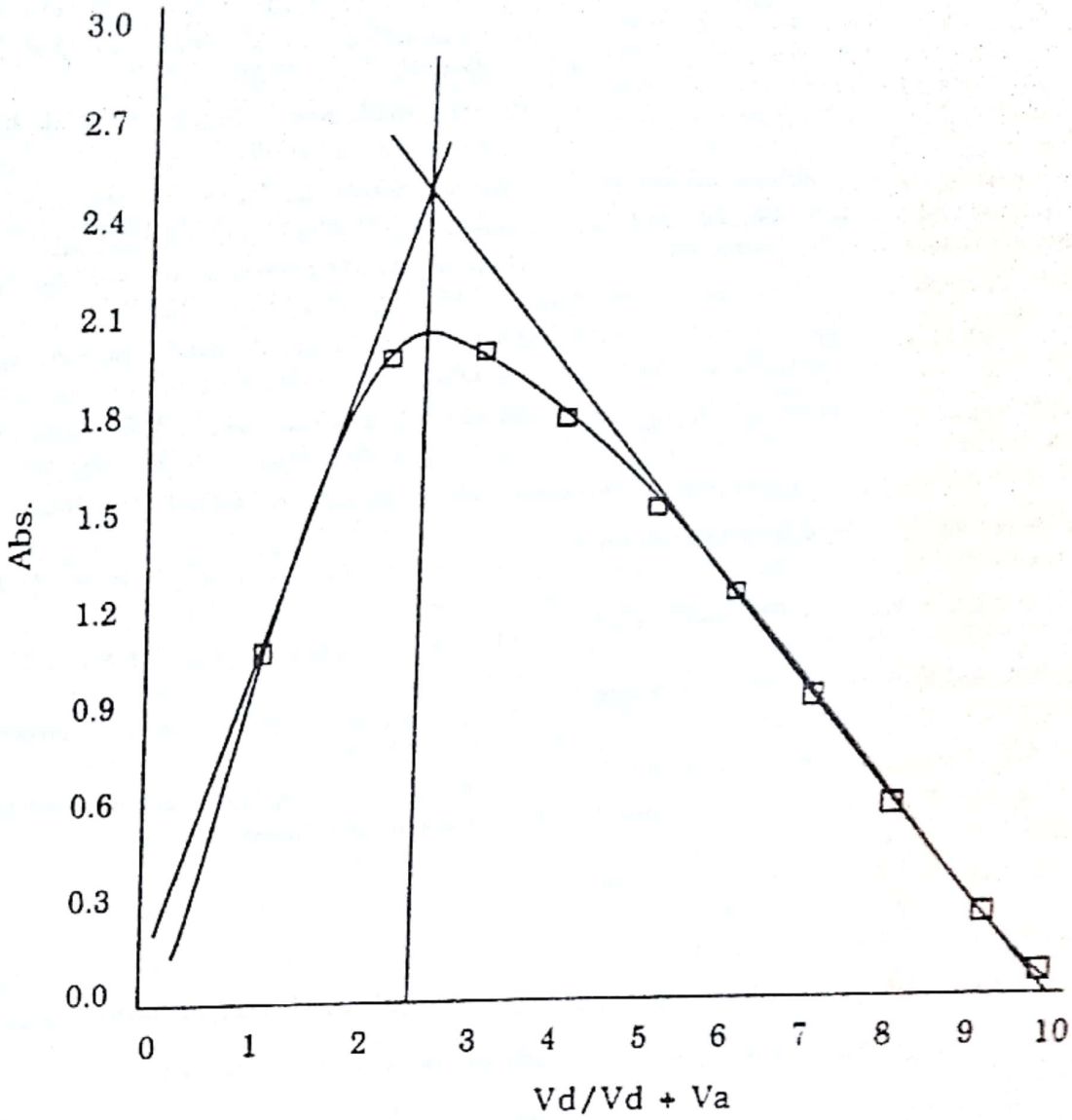

Fig. (3-a): Continuous variation plot of mefenamic acid-iron salt.

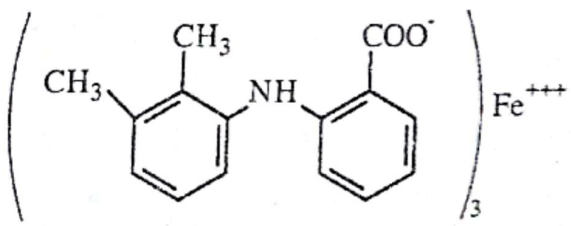

Fig. (3-b): Suggested structure of mefenamic acid-iron salt.

In order to prove the validity and applicability of the proposed methods, Ponstan capsules and syrup are analyzed for their mefenamic acid content applying the proposed method. The results obtained compared with the official method (1) showed high degree of accuracy and reproducibility.

As a conclusion, the proposed methods can be considered sensitive and selective ones for routine analysis of mefenamic acid either in raw material or in dosage forms.

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إستخدام طريقة الإمتصاص الطيفى الذرى لتعيين بعض المكونات الصيدلية الحامضية وذلك بترسيبها بإستخدام بعض أيونات المعادن .

٣ - تعيين حمض الميفينامك

هشام سالم - عفاف ابو الخير×

صيدلية مصر - مينا القمح - الشرقية×

قسم الكيمياء -كلية البنات - الرياض - السعودية

فى هذا البحث تم تقدير مركب حمض الميفينامك وذلك بإستخدام أيونات الفضة وايونات النحاس وايونات الحديد حيث يرسب حمض الميفينامك من محلول المتعادل الكحولى بمحاليل عيارية من نترات الفضة وخلات النحاس وكلوريد الحديد ثم قياس الناتج بطريقة الإمتصاص الطيفى الذرى.

ولقد تم تطبيق الطريقة المقترحة علي المستحضرات الصيدلية (**كبسولات وشراب البونستان**) وبمقارنة الطرق المقترحة بالطريقة الدستورية أعطت نتائج متناهين فى الدقة ومتماثلة في الدقة والتكرار.