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TITRIMETRIC AND SPECTROPHOTOMETRIC DETERMINATION OF MEBENDAZOLE AND FLUBENDAZOLE USING N-BROMOSUCCINIMIDE

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ABSTRACT

Titrimetric and spectrophotometric determination methods are described for mebendazole and flubendazole in dosage forms.

The first method depends upon addition of an excess of standard N-bromosuccinimide (NBS) and after the specified time, the residual reagent is determined iodometrically. This procedure permits semi-micro determination (3-30 mg) of the drug.

An alternative procedure involves measurement of the colour produced after reaction with N-bromosuccinimide (λ_{max} 465 nm). The stoichiometry of the reaction was studied and found 1:1 for mebendazole-NBS and 1:2 for flubendazole-NBS. The methods were applied successfully for the analysis of either of the two drugs in some formulations. Average recoveries ranging from 98.70±1.64 to 101.94±0.82 for titrimetric and from 97.5±0.65 to 101.30±0.55 for spectrophotometric methods were obtained. The methods were compared with U.S.P. XX method in case of mebendazole and were found in good agreement.

INTRODUCTION

Mebendazole (5-benzoyl-1H-benzimidazol-2yl)carbamic acid methyl ester and its monofluorinated derivative, flubendazole {5(4-fluorobenzoyl)-1H-benzimidazol-2yl)carbamic acid methyl ester, are frequently used as anthelmintic drugs. Among the methods used for the determination of these compounds are non-aqueous titration[1,2], direct UV spectrophotometry[2], colorimetry[3], HPLC[4], fluorimetry and phosphorimetry[5-7].

In this investigation new simple titrimetric and colorimetric methods are presented for their assay depending on the reaction of either of the two drugs with N-bromosuccinimide (NBS) after hydrolysis with sodium hydroxide solution.

EXPERIMENTAL

Apparatus :

1- A Zeiss Spectrophotometer PM2. (Zeiss, Oberkochen, West Germany).

2- Unicam-SP 1750 UV-VIS Spectrophotometer-(Pye-Unicam Cambridge,England).

Meterials:

Mebendazole and flubendazole were generously donated by Janssen Pharmaceutica (Belgium). N-bromosuccinimide (BDH, England). All other chemicals were analytical grade.

Mebendazole tablets (Vermox, Janssen), were purchased from the local market and claimed to contain 100 mg of mebendazole. Flubendazole synthetic mixture, prepared by mixing flubendazole with some of the commonly used diluents such as acacia, lactose, starch, carboxymethylcellulose followed by direct compression. Each tablet contains 100 mg of active ingredient.

Titrimetric and Spectrophotometric Determination of Mebendazole and Flubendazole Using N-Bromosuccinimide.

Reagents:

1- N-Bromosuccinimide solution: 0.01 M solution freshly prepared by dissolving 1.78 g of NBS in about 200 ml of warm water (about 60°C) and diluting to 1 liter with water . The solution was standardized iodometrically[8] and used in the titrimetric method. A similarly aqueous solution of NBS containing 0.2 mg/ml was used in the spectrophotometric method.

2- Sodium Thiosulphate: 0.02 M aqueous solution.

3- Potassium Iodide: 10% aqueous solution.

Standard or Sample Preparation:

1- Titrimetric method: a 0.01 M solution of either of the two drugs (295 mg/100 ml for mebendazole and 313.3 mg/100 ml for flubendazole) in 1 N sodium hydroxide was heated for 30 minutes in a boiling water bath, cooled and readjusted to volume by water.

2- Spectrophotometric method: a similarly prepared solution of either the two drugs containing about 0.1 mg/ml in 1 N NaOH.

General Procedure:

1- Titrimetric method: measure 1 to 5 ml of the sample solution and mix with known excess (e.g.10 ml) of 0.01 M NBS solution. The reaction was instantaneous in case of mebendazole and required 15 minutes for flubendazole. Add 10 ml of potassium iodide solution (10%) and 10 ml sulphuric acid solution (10%) and determine the residual NBS by titration against standard sodium thiosulphate solution (0.02 M) using starch for end point detection.

Calculate the amount of the drug from the following equation:

$$\text{Amount of drug (mg)} = \frac{(V_1 - V_2)\ MR}{N}$$

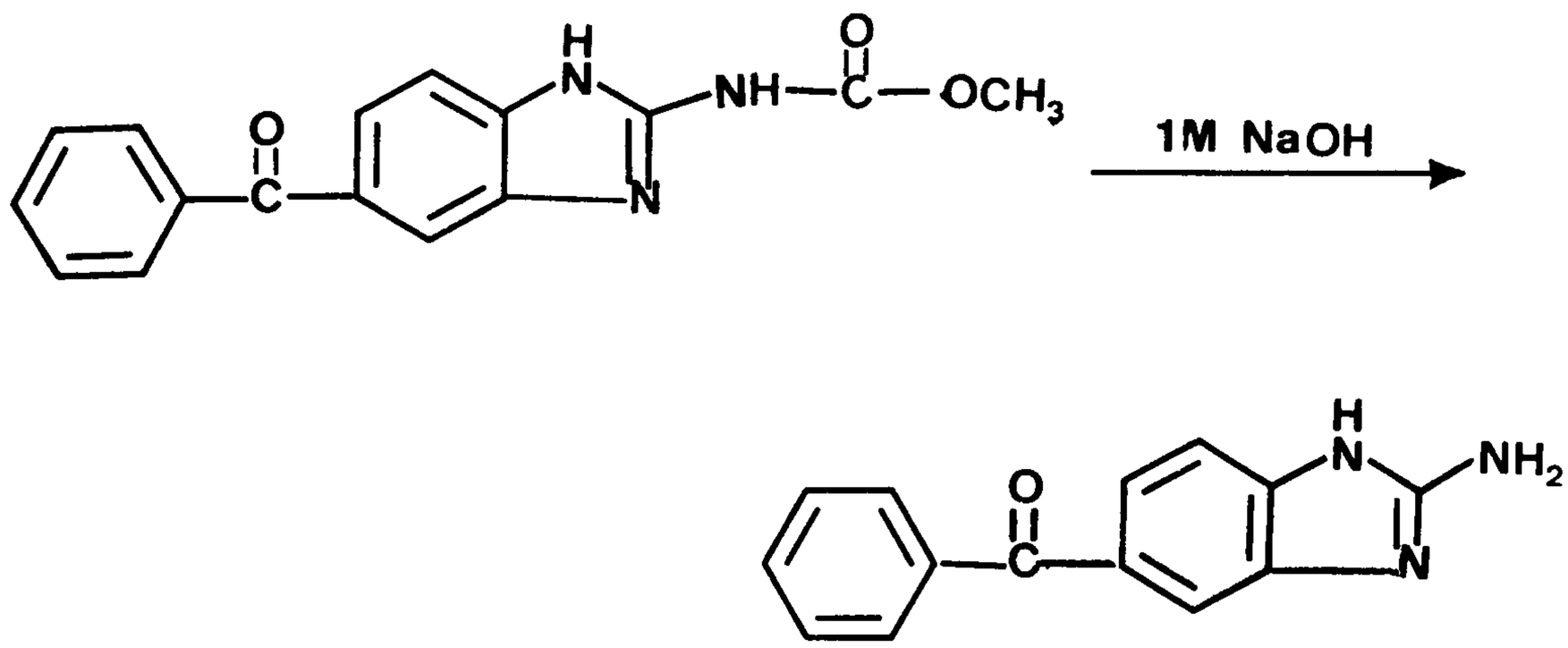
Where V_1 = Volume of thiosulphate solution consumed in the blank titration (ml), V_2 = Volume of thiosulphate solution consumed in the experiment, M = relative molecular mass of the drug, R= Molarity of the NBS solution and N = number of moles of NBS per mole of the sample.

2- Spectrophotometric method: measure accurately 1 ml of standard or sample solution into a 10-ml volumetric flask. Add 1 ml or 0.5 $\pm$ 0.1 ml of NBS solution (0.2 mg/ml) in case of mebendazole or flubendazole, respectively. Allow to stand for 5 minutes and complete to volume with ethanol. Meassure the absorbances for the two drugs at 465 nm against a blank prepared similarly using 1 ml of 1 N sodium hydroxide instead of the sample. Calculate the quantity, in mg/ml of the drug by the formula: 10 C (Au/As), in which C is the concentration, in mg per ml, of standard solution, and Au/As are absorbances of solutions from sample and standard preparations, respectively.

3- Analysis of Tablets: weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 20 mg of active ingredient to a 50 ml volumetric flask and dissolve in about 30 ml 1 N sodium hydroxide solution. Heat in a boiling water-bath for 30 minutes, cool and complete to volume with 1 N sodium hydroxide. Filter, reject the first portion of the filtrate. Analyze an aliquot of this solution according to the above mentioned methods 1 and 2.

RESULTS AND DISCUSSION

NBS was observed to give no reaction with intact mebendazole or flubendazole in acid or neutral medium as indicated from the colour of the solution and the volume of consumed standard NBS. Therefore pre-hydrolysis of either of the two drugs was achieved using 1 N NaOH in order to obtain the corresponding amino derivatives[5]:



The direct titration of both hydrolyzed compounds with standard NBS solution was tried in neutral, acid and alkaline media and was found to be unsuccessful in all cases. This may be attributed to the unsuitability of the indicator (methyl red) being more easily attacked by NBS than either of the two drugs. Moreover, the products of the reaction had orange-red colour, which interfered with the indicator colours. Therefore, indirect titration was tried. An excess standard NBS solution was added to the alkaline solution of the hydrolyzed drugs. The unreacted NBS was determined iodometrically, after acidification with 10% sulphuric

acid, by titration of the liberated iodine with standard sodium thiosulphate solution using starch as indicator. Substitutes of sulphuric acid such as hydrochloric acid and acetic acid 10% solution resulted in less reproducible results.

The reaction of NBS with mebendazole was found to take place instantaneously, while with flubendazole ten minutes are required for completion (Table 1). This was checked by thin-layer chromatography on silica gel-G plates, where the spots corresponding to the starting materials disappeared completely and new two spots appeared. The solvent system used was ethyl acetate-methanol -ammonia solution, (78:20:2).

Regarding, the spectrophotometric measurements, a characteristic reddish colour, with absorption maximum at 465 nm for both drugs was developed when the hydrolyzed drugs in sodium hydroxide were reacted with NBS. Figure 1 shows the spectra of the reaction products in alkaline ethanolic medium. Optimum concentration of NBS for maximum colour intensity was 1 ml of 0.2 mg/ml solution in case of mebendazole and 0.5 ml of the same solution for flubendazole. The maximum colour intensity was obtained within 5 minutes for both drugs at room temperature and the colour was stable for further 20 minutes.

In addition, the reaction of the two compounds with NBS takes place at room temperature and no significant increase in intensity of absorption occurs upon heating.

The solvent used for dilution of the reaction mixture does not affect the wavelength of maximum absorption, but affects the colour intensity for the same concentration of the drug. The apparent absorptivities of mebendazole-NBS chromogen in ethanol, methanol, isopropanol, DMF, DMS and dioxane were found to be 3.34×10^3, 2.25×10^3, 2.07×10^3, 2.83×10^3, 2.04×10^3 and 2.56×10^3,

respectively. Consequently, ethanol was considered to be the solvent of choice for dilution.

Beer's law was obeyed for mebendazole and flubendazole at λ_{max} 465 nm. Data listed in Table II show a typical linear regression correlation for the two drugs. Very small intercepts values were obtained for both drugs. The stoichiometry of the reaction was studied utilizing the titration method and was found to be 1:1 for flubendazole-NBS (Table III). In addition, the continuous variation method[9] performed on the investigated drugs and NBS (Fig 2) showed parallel results with the titration method. Table (IV) shows the results of application of the proposed two methods for the analysis of both compounds in some of their dosage forms. In contrast to other methods that require preliminary extraction procedures[4], the present methods allow direct and rapid estimation of both anthelmintics. No interference was observed from any of the commonly used adjuvants in formulations such as acacia, starch lactose, tragacanth, talc. In addition, the methods were compared with U.S.P. XX in case of mebdendazole and were found in good agreement.

Table I : Effect of time on mebendazole and flubendazole N-bromosuccinimide reaction.

Time (minutes)	Volume of NBS (0.01 M) Consumed* Mebendazole	Flubendazole
Direct	0.95	1.45
5	1.05	1.7
10	1.05	1.95
15	1.05	1.95
20	1.00	1.95
30	0.95	2.00

* Each Figure is an average of three determinations.

Table II : Summary of statistical data at λ_{max} 465 nm.

Drug	linearity range µg/ml	Slope	Intercept	Correlation Coefficent
Mebendazole	0.2-5	0.416	0.005	0.9963
Flubendazole	0.8-5	0.059	0.029	0.9953

Table III : The Stoichiometry of the reaction of N-bromosuccinimide with mebendazole and flubendazole

Volume of 0.01M mebendazole or flubendazole	Volume Consumed of 0.01M NBS with Mebendazole*	Flubendazole*
1	0.95	2.12
2	2.00	4.05
3	3.10	5.90
4	4.00	8.05
5	5.05	9.95
10	10.10	20.00

* Each Figure is an average of three determinations.

Table IV : Determination of mebendazole and flubendazole in some pharmaceutical preparations.

Compound	Preparation	Average% recovery ± S.D. (%) * Titrimetric method	Spectrophotometric method	U.S.P. XX
Mebendazole	Vermox Tablets	98.70 ± 1.64 t = 1.79 ** F = 0.56	97.50 ± 0.65 t = 1.33 F = 0.088	97.00 ± 2.19
Flubendazole	Flubendazole Prepared Tablets	101.94 ± 0.82	101.30 ± 0.55	

* Each Figure is an average of Three determinations.

** Theoretical values at 95% confidence levels; t=4.3, F=19.00

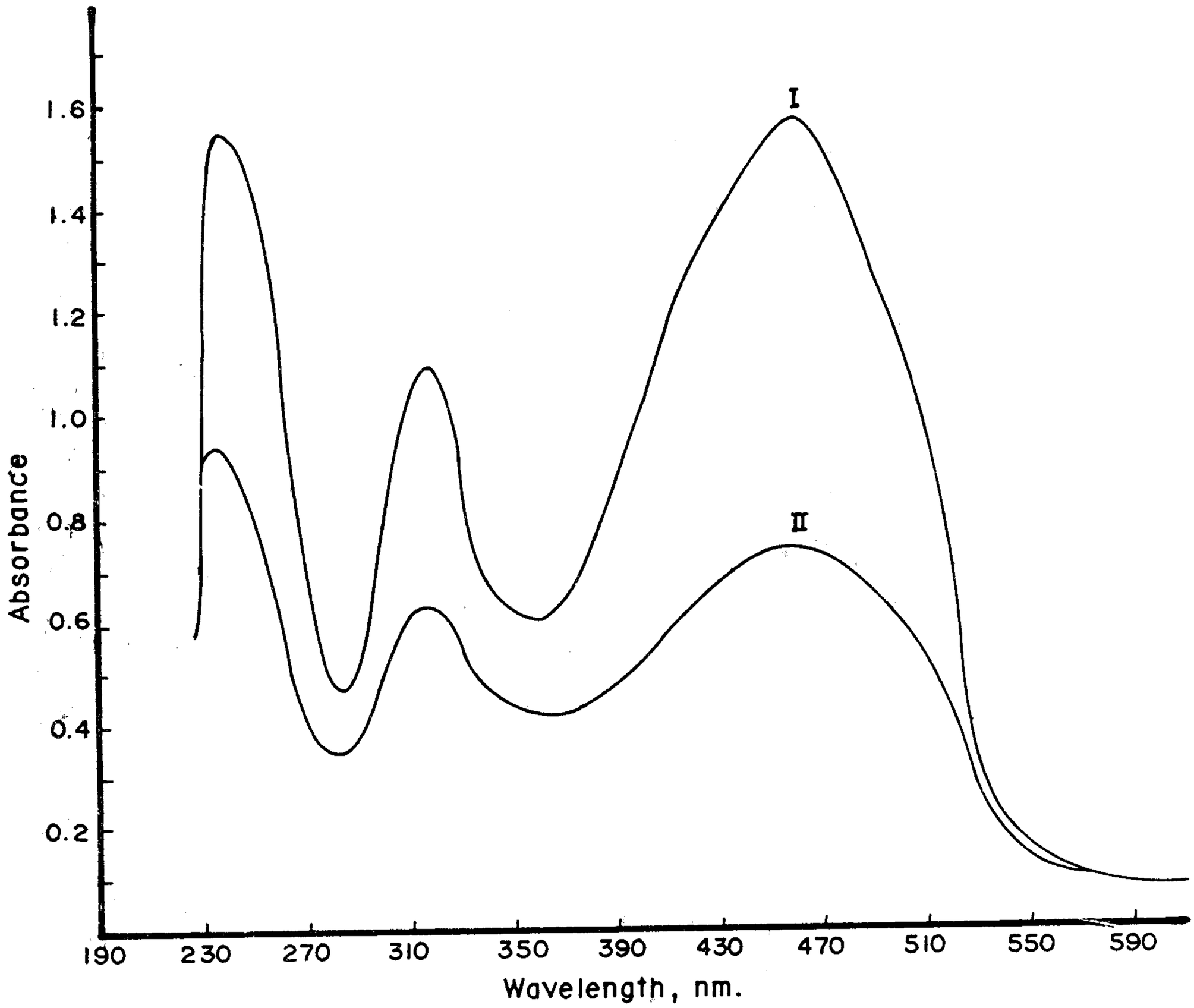


Fig.(1): Spectra of interaction products produced from mebendazole–NBS (I) and flubendazole–NBS (II).

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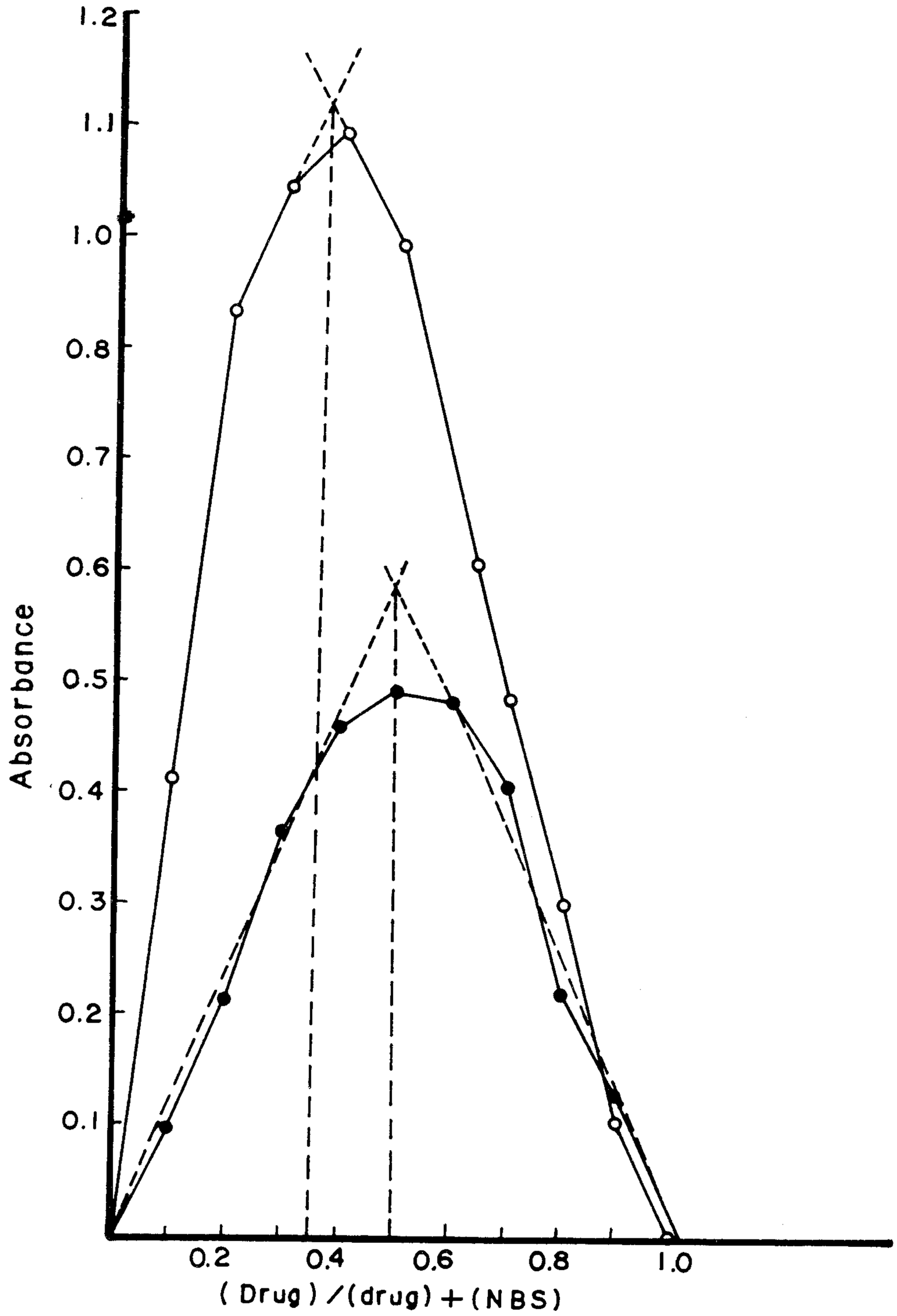

Fig.(2): Continuous variation plots obtained from solutions of mebendazole (•) or flubendazole (○) and NBS (2×10^{-4} M)

REFERENCES

1) The United States Pharmacopeia, USP XX th. Revision , Mack Easton, PA, 1980 p. 465.

2) A.M. Wahbi and S. Onsy, Talanta, 25, 716 (1978).

3) A. Kar., Analyst, 110, 1031 (1985).

4) K.B. Alton, J.E. Patrick and J.L. McCuire, J. Pharm. Sci., 68, 880 (1979).

5) F. Abdel-Fattah, W. Baeyens and P. De Moerloose Anal. Chem Acta, 154, 351 (1983).

6) W. Baeyens, F. Abdel-Fattah and P. De Moerloose J. of Pharm. Biomed, Anal. 3, 317 (1985).

7) W. Baeyens, F. Abdel-Fattah and P.De Moerloose Anal. Lett. 18 (B 17), 2105 (1985).

8) M.Z. Barakat and M.F. Abdel-Wahab, Anal. Chem. 24, 1973(1954).

9) J. Rose "Advanced physico-Chemical Experiments", Pitaman, London (England) 1964. p. 59.

التحلـــــــيل العيـارى والطيفى لـمركب الميبـند ازول والفلـوبـند ازول باستعمـال الن ـ بـروموسكسينـميـــــــد

فـردوس عبـد الفتـاح محمد ـ مديحة بخيت سـيدهم ـ سميحة عبـد الرحمـــن حسين
قسم الكيميـاء الصيدلـية ـ كلـية الصيدلـة ـ جامعة اسيوط

فى هذا البحث تم استعمـال الن ـ بـروموسكسينـميد فى التقدير الكمى العيـارى والطيفى لكل من مركب الميبـند ازول والفلـوبـند ازول فى صورتهم النقية وفـــــــى المستحضرات الصيدليـــة .

وتعتمد الطريقة الاولى على اضافة كمية زائدة من محلول ن ـ بروموسكينميد العيـارى وبعد المدة المحددة تتم معيـارة الجزء المتبقى بطريقة يودية وتســـــمح الطريقة بتعيين من ٣ الـــى ٣٠ مجم من العقـــار .

وتعتمد الطريقة الثانية على قياس اللون الاحمر بعد التفاعـــــــل مـــع ن ـ بروموسكسينميد (عند طول موجى قدره ٤٦٥ ن م) ويتميز التفاعل بالسرعـــة وانه يتم عند درجة حرارة الغرفة .

وقد ظهر ان نسبة تفاعل الكاشف للعقار ١:١ فى حالة الميبنـــــــــد ازول ـ ن بروموسكسينميد ١ : ٢ فى حالة الفلوبند ازول ـ ن بروموسكسينميد باســـتعمال كل من الطريقتيت .

وقد تم تطبيق الطريقتان فى تحليل بعض المركبات الصيدلية لكل من المركبيـن بنسبة استعادة قدرها ٩٧٠٧ ٪ ± ١٫٠٦٥ الى ١٠١ ٪ ± ٢٨٠

وتمت مقارنتها بالطريقة الدستورية المعروفة للميبند ازول ووجدتا مطابقتين

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