

SELECTIVE SPECTROPHOTOMETRIC DETERMINATION OF PROMETHAZINE HYDROCHLORIDE AND THIETHYLPERAZINE MALEATE IN PHARMACEUTICAL PREPARATIONS

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ABSTRACT

A new spectrophotometric method for the determination of promethazine HCl and thiethylperazine maleate is presented. The method is based on the interaction of each drug with benzocaine and N-bromosuccinimide at room temperature to produce a blue colour. Optimum conditions for colour development and possible interferences have been studied. The proposed method has been applied to the analysis of both drugs in pharmaceutical preparations, the results of which are in good agreement with those obtained by the official methods of B.P. and U.S.P.

INTRODUCTION

Among the methods used to assay promethazine.HCl and thiethylperazine maleate in bulk or in pharmaceutical preparations are titrimetric¹, chromatographic², polarographic³, ultraviolet⁴ and visible^{5,6} spectrophotometric procedures. The official methods generally include non-aqueous titration for bulk drugs and ultraviolet spectrophotometric methods for dosage forms^{7,8}.

It has been observed in these laboratories that phenothiazine drugs can be detected on TLC plates by applying a solution of amine (primary or secondary, aliphatic or aromatic) followed by N-bromosuccinimide (NBS) solution to give a characteristic colour⁹. The purpose of this study was to adapt a combination of an amine (benzocaine) and NBS solution as a new analytical reagent for the determination of promethazine.HCl and thiethylperazine maleate. The experimental variables of the assay have been optimized to yield a simple, rapid sensitive, accurate and specific method for the determination of the title drugs either in pure form or in pharmaceutical preparations.

EXPERIMENTAL

Apparatus:

Ultraviolet-visible spectrophotometer, PM2 DL (Zeiss, Oberkochen, West Germany) was used for all absorbance measurements with 1-cm matched glass cells.

Pharmaceutical Compounds:

Promethazine hydrochloride (Bayer) and thiethylperazine maleate (Sandoz) were used as working standards without further treatment. Both drugs were subjected to TLC identification¹⁰, purity being considered 100%.

Reagents and Solutions:

N-Bromosuccinimide Solution (NBS):

Prepare 0.4% NBS (Merck,Darmstadt) in distilled water by continuous stirring for 5 minutes.

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Benzocaine Solution:

Prepare as 0.2% in ethanol.

Standard Promethazine HCl and Thiethylperazine Maleate Solutions:

Into separate 50-ml volumetric flasks, dissolve 100 mg of each drug in methanol and dilute to volume with the same solvent. Dilute 5 ml of each drug solution quantitatively with methanol to obtain 20 µg/ml of promethazine HCl and 100 µg/ml of thiethylperazine maleate. These solutions must be freshly prepared and protected from light.

Promethazine Sulphoxide Solution:

Prepare 20 µg/ml promethazine sulphoxide in water daily from promethazine HCl⁴.

Preparation of Tablet Solution

Weigh and powder twenty tablets. Transfer an accurately weighed quantity of the powder equivalent to 25 mg of promethazine HCl or thiethylperazine maleate to a 100-ml volumetric flask. Add about 50 ml methanol, shake for 2-3 minutes and dilute to volume with the same solvent. Filter, discard the first portion of the filtrate and dilute aliquot portions of this filtrate with methanol to contain about 20 µg/ml promethazine HCl and 100 µg/ml thiethylperazine maleate.

Preparation of syrup solution

Transfer into a 25-ml volumetric flask an accurately measured volume of the syrup equivalent to about 25 mg of promethazine HCl, complete to volume with methanol and mix well. Dilute this solution quantitatively with methanol to obtain 20 µg promethazine HCl/ml.

Procedure

Transfer one ml of either standard or sample phenothiazine solution into separate 10-ml volumetric flasks. Add 0.5 ml of benzocaine solution, followed by one ml of NBS solution. Mix well and allow to stand at room temperature for 40 minutes. Add one ml of either concentrated HCl in case of promethazine HCl or 70% perchloric acid in case of thiethylperazine maleate and complete to volume with methanol. Mix well and measure the absorbance at 672 nm for promethazine HCl and at 640 nm for thiethylperazine maleate against a blank treated similarly but using one ml methanol instead of the phenothiazine drug.

RESULTS AND DISCUSSION

The absorption spectra for the chromogen products of promethazine HCl and thiethylperazine maleate with benzocaine and NBS reagents are shown in Fig. 1. The wavelengths of maximum absorption at 672 and 640 nm for promethazine HCl and thiethylperazine maleate, respectively were adopted in all subsequent experiments.

A- Effect of benzocaine concentration:

Different concentrations of benzocaine ranging from 0.5 to 3.5 g% w/v were added to a constant amount of promethazine HCl or thiethylperazine maleate and applying the developed procedure. From Fig. 2, it is evident that maximum absorbance is obtained by using 0.5 ml of 2% benzocaine solution. Further decrease or increase in benzocaine concentration resulted in lower absorbances.

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B- Effect of NBS concentration

The influence of NBS concentration was studied by carrying out the developed procedure, using fixed concentrations of promethazine HCl and thiethylperazine maleate and varying NBS concentration. Fig. 3 indicates that one ml of 0.4% NBS solution is necessary for maximal absorbance. Lower or higher concentrations of NBS decrease the absorbance.

C- Effect of heating and Reaction time

The optimal reaction time was determined for the interaction of both drugs with benzocaine and NBS reagents by following the colour development at ambient temperature (around 26°C) and in a thermostatically controlled water bath at 50°C. At the latter temperature, the colour developed immediately then rapidly disappeared. At ambient temperature, the colour intensity reached its maximum after 30 minutes and remained constant for another 40 minutes as shown in Fig. 4. In this work a time of 40 minutes was selected to be the suitable reaction time for full colour development.

Upon dilution of the interaction coloured products of both drugs with water, methanol, ethanol, isopropanol, n-butanol or dioxane, a marked decrease in absorption intensity was observed and the colour disappeared totally within few minutes. Attempts have been made to stabilize the developed colours before dilution with the selected solvent. This was done by using citrate-phosphate-borate buffer of pH range 2-10¹¹. It was observed that the colour intensity and stability increased by decreasing

the pH of the solution, Table 1. Further trials have been made by using various acids in different concentrations. The highest stability of the developed colours was observed with concentrated acid solutions. Hence, different volumes from each of concentrated sulphuric, nitric, perchloric, hydrochloric and glacial acetic acid were tested. Maximum colour intensity and stability were obtained with hydrochloric acid in case of promethazine HCl, and with perchloric acid in case of thiethylperazine maleate Table 2. It was found that a constant absorbance was obtained by adding the proper acid in the range of 0.2 to 2.0 ml. However; one ml of either hydrochloric or 70% perchloric acid is recommended in this work.

D- Effect of dilution by different solvents

Dilution of the interaction coloured products of both drugs by different solvents showed no significant effect on the position of λ_{\max} , while the intensity of absorption is affected. Methanol was found to be the best solvent as it gave the highest absorption intensity, Table 3. After dilution of the interaction coloured products with methanol, the absorbance remained constant for at least ten hours.

Adherence to Beer's law:

Calibration curves of absorbance versus concentration were constructed from eight points over a concentration range from 0.2-8.0 μg promethazine HCl/ml, and from 3.0-40 μg thiethylperazine maleate/ml. The parameters and correlation coefficients of the calibration plots, expressed as regression lines of the form of $Y = a + bx$, are listed in Table 4. These data indicate a linear relationship between absorbance and concentration and negligible intercepts.

Specificity and Precision

The specificity of the developed procedure was checked by applying it for the determination of promethazine.HCl in presence of its sulphoxide as well as in presence of the commonly encountered excipients and additives such as starch, talc, lactose, and magnesium stearate. No interference from these compounds was observed.

The application of this method for the determination of other phenothiazine drugs such as promazine HCl, alimemazine tartrate, mepazine HCl, perazine maleate, prochlorperazine maleate, chlorpromazine HCl, levomepromazine maleate, thioridazine HCl, fluphenazine dihydrochloride, triflupromazine HCl, thioproperazine, pericyazine maleate, and butaperazine maleate (up to 100 µg phenothiazine drug/ml) gave no absorption under the above described experimental parameters. The method is thus specific for the determination of promethazine HCl and thiethylperazine maleate.

The precision of the method was evaluated by analysis of ten replicate samples of promethazine HCl (2 µg/ml), and thiethylperazine maleate (10 µg/ml). At these concentration levels, the relative standard deviation was 0.31 for promethazine HCl and 0.36 for thiethylperazine maleate.

Analysis of Dosage Forms

The validity of the procedure for the determination of promethazine HCl and thiethylperazine maleate in tablets and syrups was assessed by applying the method to three commercially available preparations and adding known

amounts of the corresponding drug to tablets or syrups followed by its determination. Compared to the BP and USP methods, the proposed method gave results of equal accuracy (t-test) and reproducibility (F-test), (Table 5.)

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Table 1 - Effect of pH on Colour Intensity of Promethazine HCl and Thiethylperazine Maleate.

pH	Absorbance of	
	Promethazine HCl ^x at λ max 672 nm	Thiethylperazine maleate ^{xx} at λ max 640 nm
2	0.155	0.100
4	0.135	0.096
6	0.120	0.092
8	0.060	0.030
10	0.000	0.000

Final Concentrations, 2 μ g/ml (x) and 10 μ g/ml (xx)

Table 2 - Effect of Acids on Colour Intensity

Volume added, ml	HCl		HClO ₄		HNO ₃		H ₂ SO ₄		Glacial ⁺ CH ₃ COOH	
	P	T	P	T	P	T	P	T	p	T
0.1	0.270	0.080	0.185	0.225	0.102	0.092	0.090	0.051	0.075	0.047
0.3	0.275	0.085	0.185	0.225	0.090	0.100	0.080	0.040	0.050	0.049
0.5	0.275	0.070	0.185	0.225	0.080	0.060	0.070	0.040	0.040	0.030
1.0	0.275	0.000	0.185	0.225	0.020	0.030	0.020	0.000	0.000	0.000
2.0	0.275	0.000	0.185	0.225	0.000	0.000	0.000	0.000	0.000	0.000

P Absorbance of promethazine HCl (2 μ g/ml) at 672 nm

T Absorbance of thiethylperazine maleate (10 μ g/ml) at 640 nm

+ The colour disappears immediately.

Table 3- Effect of Dilution by Different Solvents on the Absorption Intensity
of the Interaction Products of Both Drugs with Benzocaine and NBS Reagents

Solvent	Promethazine HCl		Thiethylperazine maleate	
	2 ug/ml	10 ug/ml		
	λ_{max}	A^x	λ_{max}	A^x
Methanol	672	0.275	640	0.225
Ethanol	672	0.264	640	0.218
Isopropanol	675	0.242	640	0.201
n-Butanol	675	0.219	640	0.185
Dioxane	677	0.211	640	0.176

x Average of 4 determinations.

Table 4-- Experimental Parameters of the Interaction Coloured Products of Both
Drugs with Benzocaine and NBS Reagents

Drug	Concentration		Slope	Intercept	Correlation coefficient
	λ max	ϵ range $\mu\text{g/ml}$			
Promethazine HCl	672	4.30×10^4 0.2-8.0	0.072	0.0054	0.9934
Thiethylperazine maleate	640	1.31×10^4 3.0-40	0.018	0.0032	0.9990

Table 5- Determination of Promethazine HCl and Thiethylperazine Maleate in Certain
Pharmacrutical Preparations by the Proposed and Official Methods

Sample	Claimed		Found ^x	Added		Recovered		Official method
	mg	mg	Percent	mg	mg	Precent	Precent	
<u>Promethazine HCl</u>								
<u>Phenergan tablets^a</u>								
	25/tab	24.45	97.80+1.04	25	24.72	98.88+1.56	97.15+0.54 ¹	
			t ^{xx} = 1.009					
			F ^{xxx} = 3.700					
<u>Promantine syrup^b</u>								
	6/5 ml	5.70	95.00+0.98	6	5.80	96.67+1.06		²
<u>Thiethylperazine maleate</u>								
<u>Torecan tablets^c</u>								
	6.5/tab	6.25	96.15+0.89	6.5	6.40	98.46+1.02	96.11+0.68 ³	
			t ^{xx} = 0.104					
			F ^{xxx} = 1.714					

Products of a:Specia, b:Mir, and c:Swiss-Pharma pharmaceutical companies
x Average of 5 determinations+SD
xx Theoretical value: t= 2.78 at the 95% confidence level
xxx Theoretical value: F= 6.39 at the 95% confidence level
1 Analysis according to BP 1980 method
2 Not official
3 Analysis according to USP XX method.

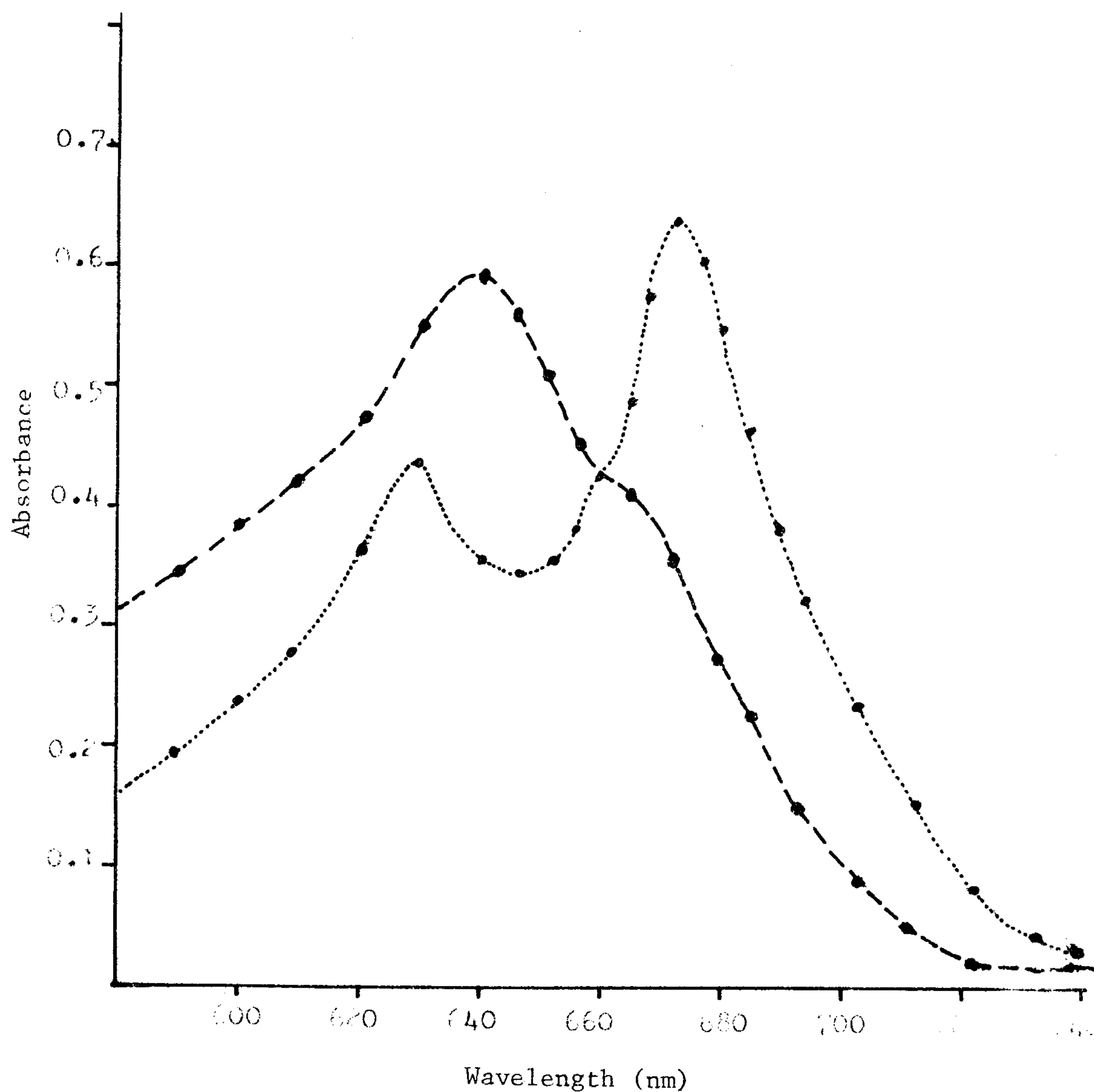


Fig. 1. Absorption spectra for the interaction of benzocaine and NBS reagents with 5 µg promethazine HCl/ml (—○—○—○—) and 25 µg thiethylperazine maleate/ml (●—●—●—●—).

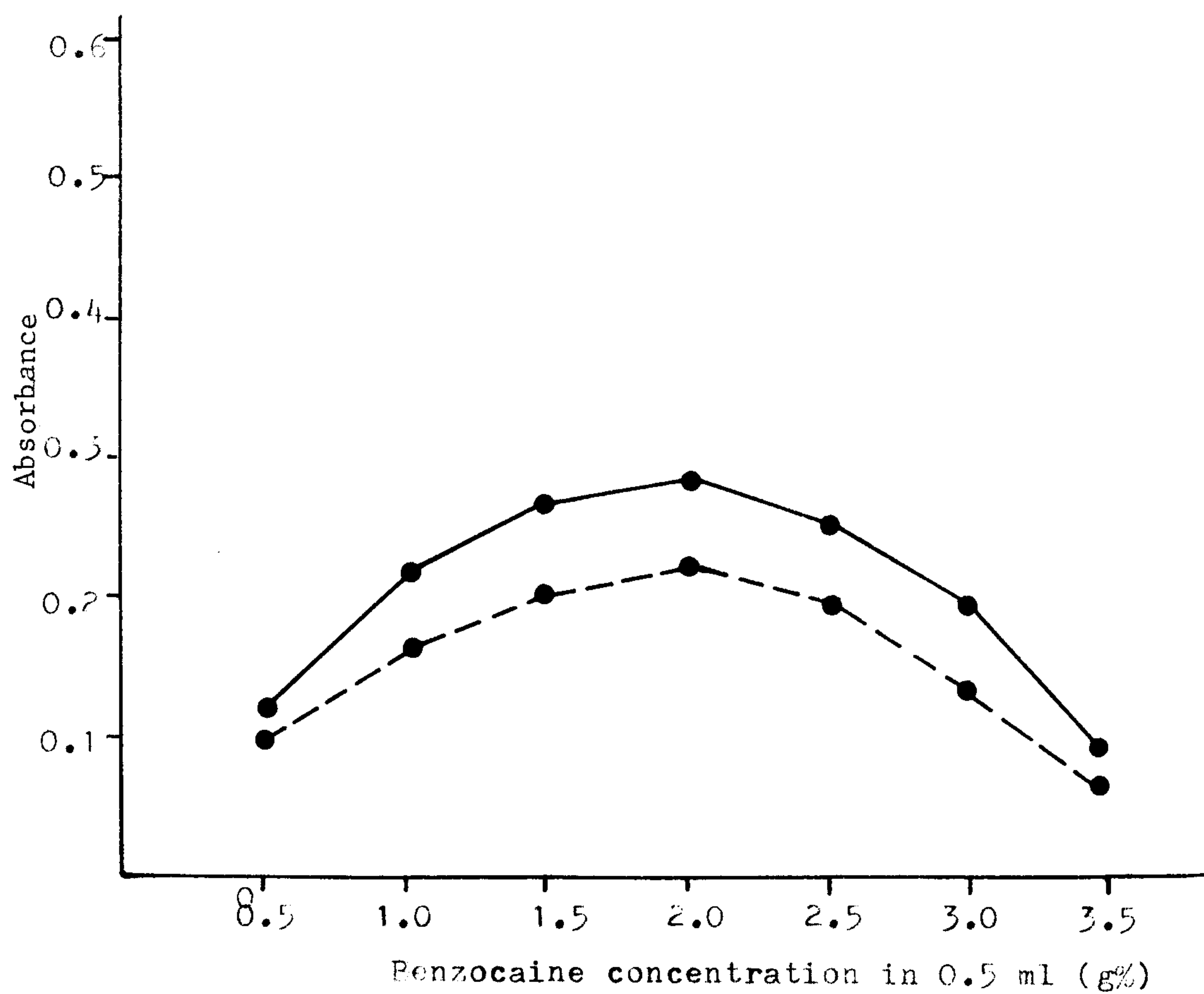


Fig. 2. Effect of benzocaine concentration on the absorption intensity of the interaction products of benzocaine and NBS reagents with 2 µg promethazine HCl/ml (—●—) and 10 µg thiethylperazine maleate/ml (---●---).

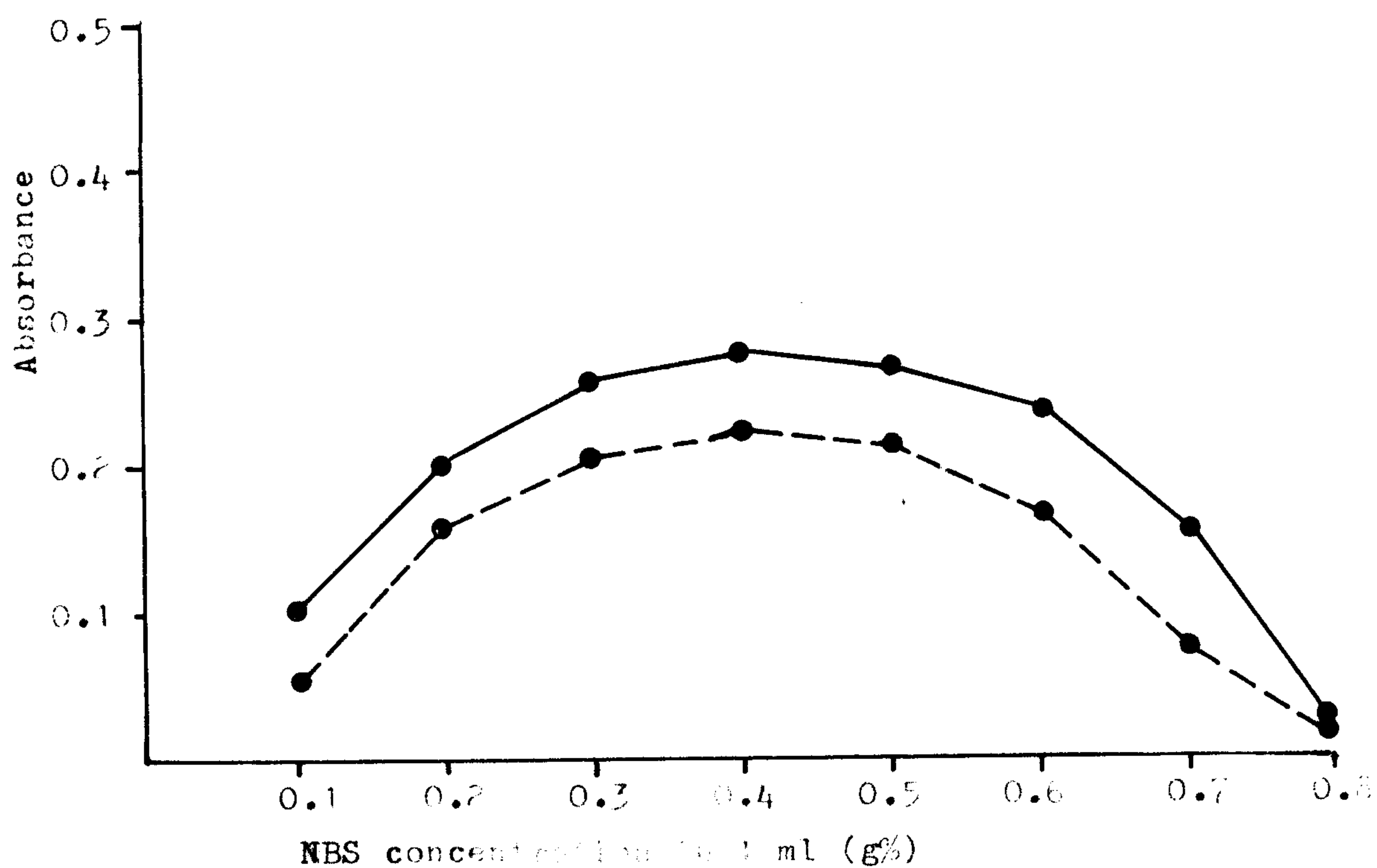


Fig. 3. Effect of NBS concentration on the absorption intensity of the interaction products of benzocaine and NBS reagents with 2 µg promethazine HCl/ml (—●—●—●—), and 10 µg thiethylperazine maleate/ml (---●---●---●---).

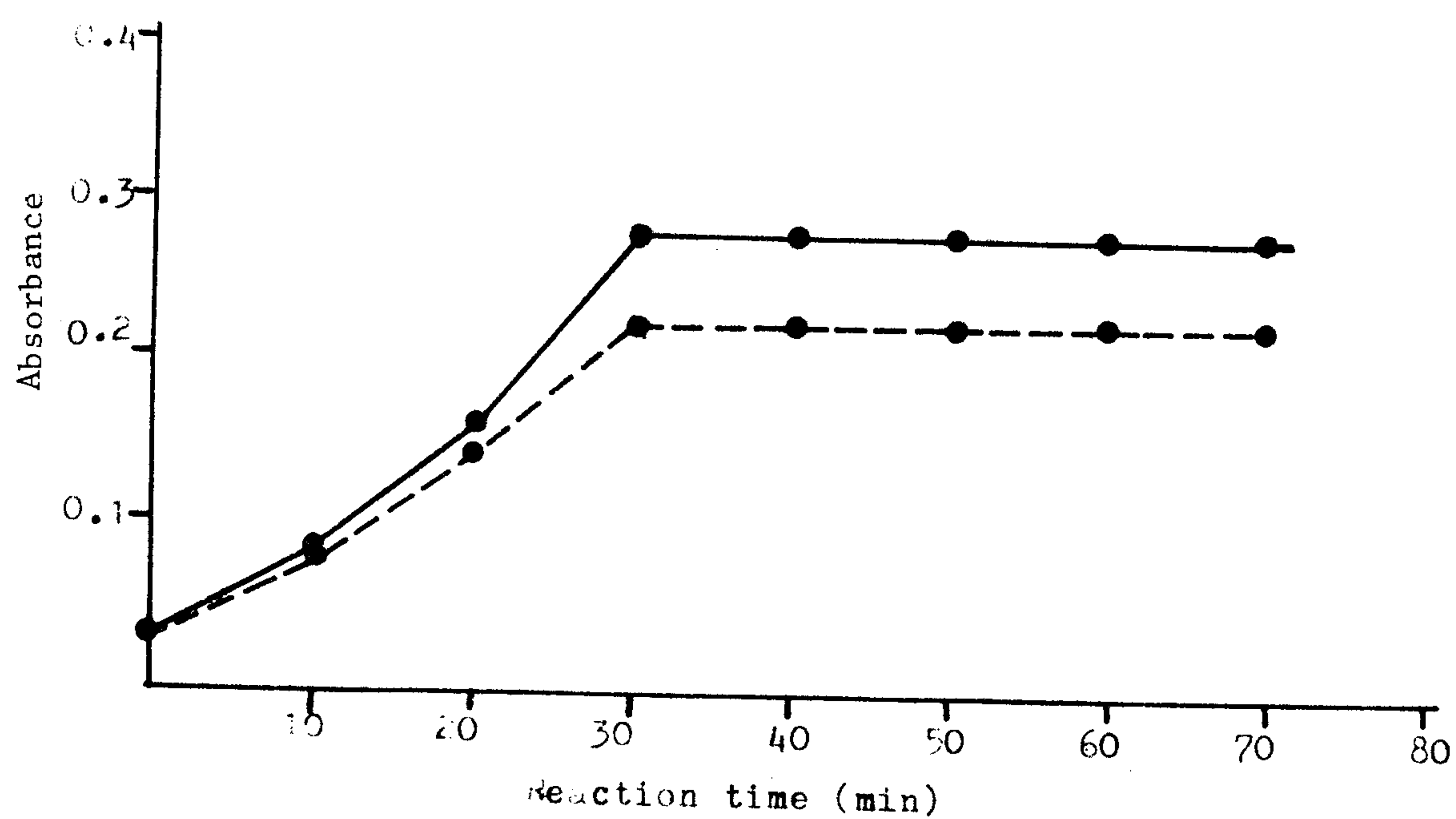


Fig. 4. Effect of the reaction time on the absorption intensity of the interaction products of benzocaine and NBS reagents with 2 µg promethazine HCl/ml (—●—●—●) and 10 µg thiethylperazine maleate/ml (-●-●-●) at ambient temperature.

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REFERENCES

- 1) M.I. Walash, M. Rizk, A. Abou-ouf and F. Belal, *Analyst*, 108, 626 (1983).
- 2) J.E. Wallace, E.L. Shimek, S. Stavchansky and S.C. Harris, *Anal. Chem.*, 53, 960 (1981).
- 3) M.M. Ellaithy, *Ind. J. Pharm Sci.*, 42, 41 (1980).
- 4) A.G. Davidson, *J. Pharm. pharmac.*, 28, 795 (1976).
- 5) A.S. Issa, Y.A. Beltagy and M.S. Mahrous, *Talanta*, 25, 710 (1978).
- 6) M. Stan, V. Dorneanu and G. Ghimicescu, *Talanta*, 24, 140 (1977).
- 7) *British Pharmacopoeia*, 1980 Her Majesty's stationary Office, London, UK, pp. 372, 813.
- 8) *The United State Pharmacopoeia 20th Rev. and the National Formulary 15th Rev.*, 1980, U.S. Pharmacop-eial Convention, Rockville, MD, p.790
- 9) S.R. El-Shabouri, A.F. Youssef, F.A. Mohamed, and A.I. Rageh, *Bull. pharm. Sci., Assiut university*, 8, 144 (1985).
- 10) E.G.C. Clarke, "Isolation and Identification of Drugs", Pharmaceutical press, London, 1969, p.49
- 11) *Documenta Geigy "Scientific Tables"*, J.R. Geigy, Basel, Switzerland, p. 314.
- 12) M. Pesetz and J. Bartos, "Colorimetric and Fluorimetric Analysis of Organic Compounds and Drugs" Marcel Dekker, Inc. New York, 1974, p.930.

طريقة طيفية متخصصة لتقدير هيدروكلوريد

البروميثازين والشاي ايثيل بيرازين ماليات فى المستحضرات الصيدلية

سلوى الشابورى - عادل فوزى - فردوس عبد الفتاح - عبد المعبود اسماعيل

قسم الكيمياء الصيدلية - كلية الصيدلة - جامعة اسيوط

فى هذا البحث تم استخدام طريقة طيفية جديدة لتقييم كل من مركب هيدروكلوريد البروميثازين ومركب الشاي ايثيل بيرازين ماليات امـا فى حالتها النقية او على هيئة مستحضرات صيدلية .

وتعتمد هذه الطريقة على معالجة هذين المركبين بكل من محلول البنزوكيين ون - بروموسكسينيميد عند درجة حرارة الغرفة ثم قياس اللون الازرق الناتج عند الطول الموجى ٦٧٢ ، ٦٤٠ ن.م على الترتيب .

ولقد استخدمت هذه الطريقة بنجاح فى تعيين بعض المستحضرات الصيدلية التى تحتوى على هيدروكلوريد البروميثازين والشاي ايثيل بيرازين ماليات كما تمت دراسة لمقارنة الطريقة المقترحة بطرق دستورية مثل دستور الادوية البريطانى والامريكى ووجد انها متطابقة معهم فى نتائجهم .

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