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SPECTROPHOTOMETRIC DETERMINATION OF CODEINE IN PHARMACEUTICAL PREPARATIONS *

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SUMMARY

A spectrophotometric method for determination of codeine is described. The method is based on the reaction of codeine with bromocresol green. The yellow complex formed was extracted with chloroform at pH 3.8. The solution of complex in chloroform showed maximum absorbance at 418 nm. The complex was stable up to 10 days and obeyed Beer's law over the concentration ranges of 3–12 μg/ml. The ratio of codeine to bromocresol green was 1 : 1. Excipients, coloring matter, flavoring agents and some other compounds likely to be present in the codeine-containing preparation did not interfere in the determination. The interferences can be eliminated by preliminary TLC separation.

INTRODUCTION

Different methods have been developed for determination of codeine (I) and its compounds in pharmaceutical preparations. Non-aqueous titration (Buskova et al., 1971), ion exchange separation (Jeannin and Verain, 1969), potentiometric titrations (USP, 1973; Aldarova and Dolbeeva, 1966; Sell and Teodorczuk, 1973), complexiметric determination (Gayeueska, 1973), GLC (Ryabtseva et al., 1972), fluorometric (Theron, 1973), and several spectrophotometric methods (Smith, 1966; Fabrizio, 1968; Bertha and Knut, 1976) are among such examples. These methods mostly lack sensitivity, simplicity and selectivity for routine analysis. Furthermore, some of these need preliminary separation by thin-layer chromatography.

Bromocresol green (II) has been used for determination of small amounts of long-chain tertiary and quarternary ammonium salts (II). It has also been used for spectrophotomet-

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ric determination of thebaine (Maghsoudi and Fawzi, 1978) and diphenylhydramine hydrochloride (Maghsoudi et al., 1977).

The present method describes the determination of codeine in pharmaceutical preparations using II as a reagent. This method is based upon complexation reaction of I and II followed by extraction with chloroform.

MATERIALS AND METHODS

Reagents and chemicals

All solutions were prepared from reagent grade [2] chemicals. pH 3.8 (BP standard) buffer solution, 10^{-4} M of I buffer solution, 10^{-4} M of I (69.84 mg was dissolved in 2 ml of 0.1 N NaOH, and diluted to 1 liter with buffer solution).

General procedure

Three ml of solution I was pipetted into a 50 ml separatory funnel. 20 ml of solution II was added and a yellow complex was extracted by vigorous shaking with 5, 3 and 2 portions of chloroform. The extracts were combined in a 10 ml volumetric flask and the volume adjusted with chloroform. The absorbance [1] was measured at 418 nm against chloroform as blank.

Sample assay

A standard solution containing 100 μg of I plus the various compounds commonly present with I in pharmaceutical preparations was analyzed by the described method. Compounds that may interfere in the determination of I can be separated by TLC method as follows: a known volume of the pharmaceutical preparation containing about 4 mg of I was alkalized by 4 N NaOH solution and extracted 5 times with 10 ml portions of chloroform. The extracts were chromatographed by TLC method (silicagel, ethyl acetate–methanol–ammonia 75 : 15 : 10). The codeine fraction was separated, dissolved in 0.1 N HCl, neutralized with 0.1 N NaOH and made up to volume with buffer solution in a 250 ml volumetric flask. A known volume of this solution was then analyzed by the described procedure.

RESULTS AND DISCUSSION

In the present work I reacts with II to form a yellow complex.

The yellow I–II complex in chloroform showed maximum absorbance at 418 nm (Fig. 1).

The complex formation and extraction were studied in the pH ranges from 1 to 14. The best result was obtained at pH 3.8.

The absorbance of the complex in chloroform was measured at selected intervals of time and it was constant up to 10 days.

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[1] A Beckman DB–GT spectrophotometer with 1-cm glass cell and a Beckman H_3 type pH meter were used.

[2] Analar.

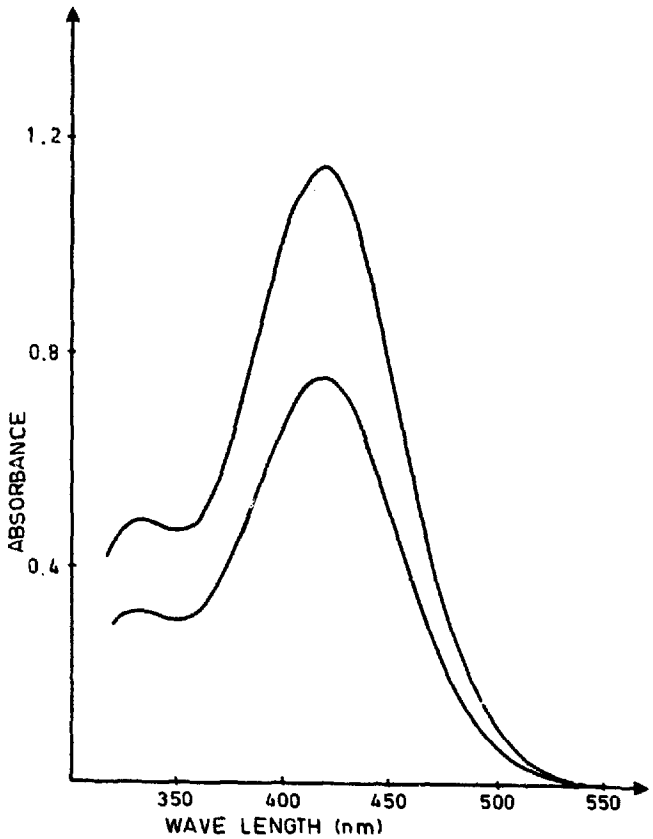

Fig. 1. Absorption spectra of chloroform solutions of I–II complex.

Nature of complex

The composition of the I–II complex was studied by the mole ratio method (Yoe and Jones, 1944) and the continuous variation method (Jobe, 1928; Jobe, 1936). In the first method, as shown in Fig. 1, the ratio of I–II was 1 : 1, but the required ratio for complete complexation and extration was 1 : 3. In the second method, as indicated in Fig. 2, the ratio of I–II was 1 : 1.

The complex followed Beer's law over the concentration ranges of 3–12 μg/ml.

Effect of other compounds

The following compounds did not interfere up to indicated amounts: acetysalysilic acid [3] (20 mg), phenacetolin [3] (50 mg), caffeine [3] (100 mg), acetaminophen [4] (20 mg), phenobarbitol [3] (20 mg), phenylephrine hydrochloride [4] (2 mg), ammonium chloride [4] (30 mg), potassium guiacolsulfonate [4] (50 mg), menthol [4] (30 mg), sodium benzoate [4] (15 mg), amaranth [4] (20 mg), saccarin sodium [4] (30 mg), glycerol [4] (10 mg), alcohol [4] (5 mg). Other compounds that may be combined with codeine in pharmaceutical preparations, such as ephedrine hydrochloride, antipyrine, antihistamines and compounds with

[3] Present with I in tablet form.
[4] Present with I in syrup form.

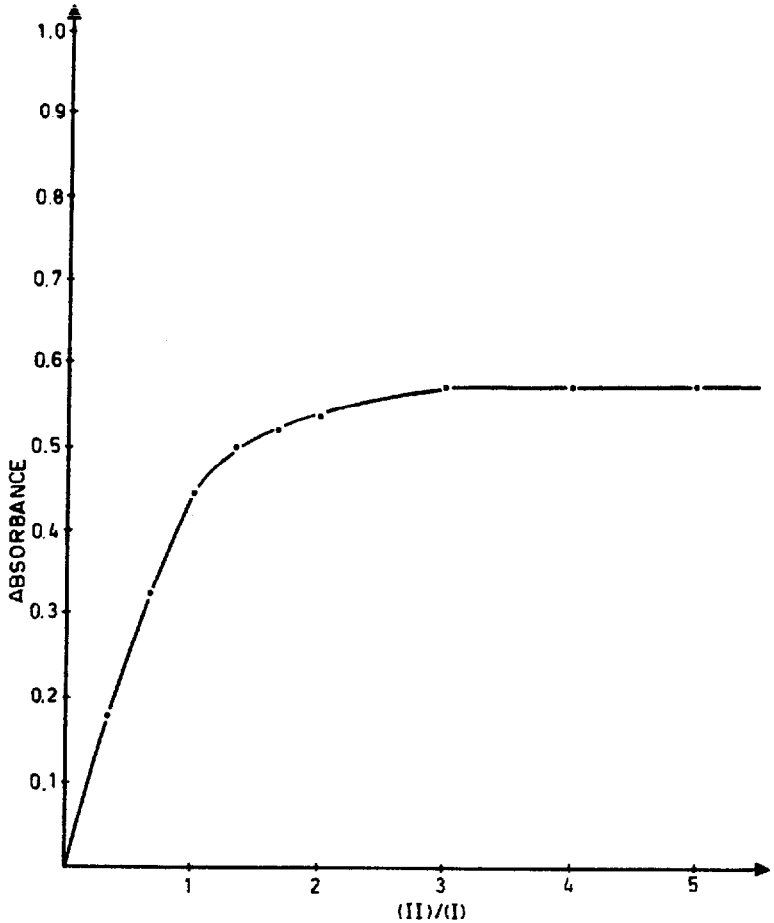

Fig. 2. Variation of the absorbance vs the mole rate of II to I at 418 nm. The final concentration of I was 3×10^{-4} M.

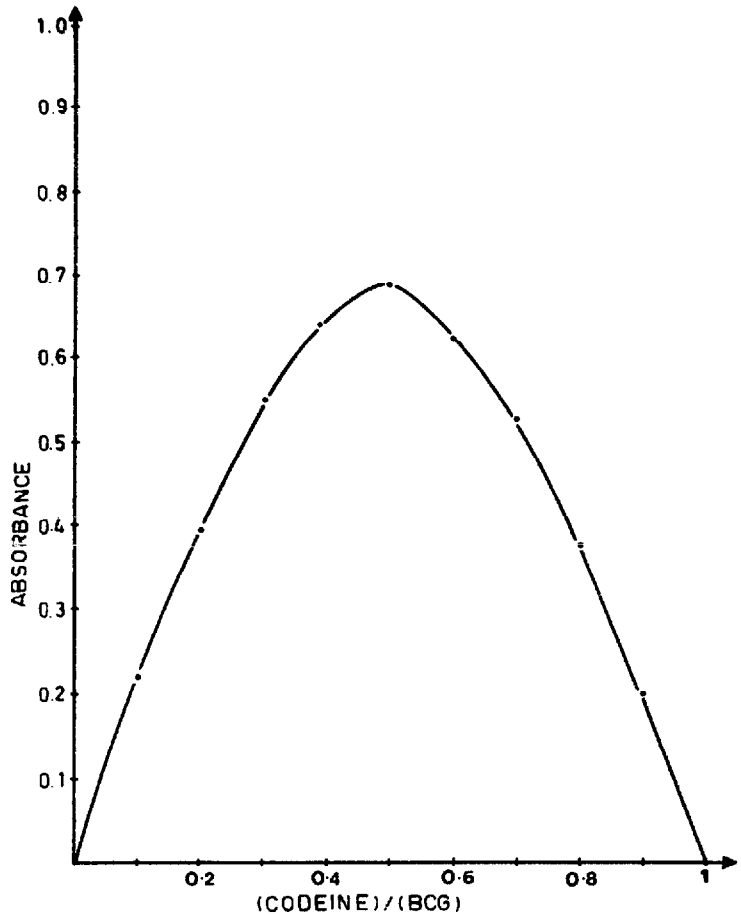

Fig. 3. Jobe's plot for the I–II system. The total concentration of I and II was 1×10^{-4} M.

TABLE 1

DETERMINATION AND RECOVERY OF CODEINE IN PHARMACEUTICAL PREPARATIONS

Preparation	μg codeine/sample taken			Recovery (%)
	Manufacturer's claim	Added	Determined	
Syrup A [a]	40	50	49.1	98.2
Syrup B [b]	60	80	81.1	101.25
Tablet A [c]	40	40	40.5	101.25
Tablet B [d]	80	40	39.1	97.75

[a] Senodin; Squibb–Iran, Tehran, Iran. (Ipecae fluid extract 0.13 ml, Sanguinaria fluid extract 0.013 ml, Senega fluid extract 0.025 ml, Sqill fluid extract 0.015 ml, codeine sulfate 7.300 mg, glycerin 0.25 ml, menthol 0.3 mg, in 5 ml of syrup, alcohol 8.5% v/v.)

[b] Ambenyl; Park-Davis, Tehran. (Codeine sulfate 10 mg, bromodiphenhydramine 3.75 mg, diphenhydramine-HCl 8.75 mg, ammonium chloride 80 mg, potassium guiacolsulfonate 80 mg, menthol 0.5 mg in 5 ml of syrup.)

[c] Dolviran; Bayer-Pharma, Tehran, Iran. (Salicylamide 200 mg, phenacetin 200 mg, caffeine 50 mg, phenobarbital 25 mg, codeine phosphate 10 mg, in a tablet.)

[d] Paxedin; Boots, GB–Khorak Co., Tehran, Iran. (Aspirin 259 mg, phenacetin 259 mg, codeine phosphate 8 mg, in a tablet.)

tertiary amine groups or quarternary ammonium salts can be separated by TLC method as described. The results obtained by TLC separation were quite consistent with the amounts claimed by the manufacturers.

To test the validity of the method, codeine was added to the pharmaceutical preparations and determined by the described method. Recovery of the added amounts of codeine is given in Table 1.

The advantages of this method are its simplicity and sensitivity; it can be used for the determination of codeine in many pharmaceutical preparations.

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