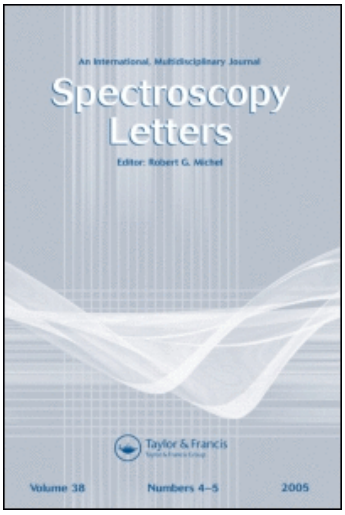

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Spectrophotometric Determination of Metformin via Charge-Transfer Complex with Iodine

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SPECTROPHOTOMETRIC DETERMINATION OF METFORMIN VIA CHARGE-TRANSFER COMPLEX WITH IODINE

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KEYWORDS: Metformin, Determination, Spectrophotometry.

ABSTRACT

A spectroscopic method is described for the determination of Metformin based on its formation of molecular complex with iodine in dichloroethane. Quantitative measurements are made at the maximum absorption of 295nm. The molar ratio of the formed metformin-iodine complex is 1:1 as revealed by Job's method. Beers' law is obeyed in the range 2-12 ug.ml^{-1} base solution. The proposed method is statistically comparable with the official B.P. method. When applied to pharmaceutical preparation, tablets, average percentage recovery of 99.97 ± 0.81 was obtained.

INTRODUCTION

Metformin (1,1-dimethylbiguanide) is an orally active hypoglycemic agent. Its hydrochloride salt is official in both BP 1973(1) and BP 1980(2). It lowers the blood sugar level to minimum physiological limit (3,4). The official assay method for the pure hydrochloride salt involves non-aqueous titration while the tablets official assay involves the reaction of the biguanide with nitroprusside and ferrocyanide in sodium hydroxide medium and measurement of the absorbance of the coloured product at 525nm (2). Several other procedures have been reported, including u.v. spectrometry (5,6), visible spectrophotometry (7,8) polarography (9) and fluorimetry (10,11). In addition to chromatographic procedures (12,13) in both pharmaceutical product and biological fluids. This paper describes a method involving the application of a charge-transfer complex for the spectrophotometric determination of microgram amounts

of metformin in both bulk and tablets dosage form. The investigation involved the determination of molecular ratio and different variables affecting the reaction.

EXPERIMENTAL

Apparatus

A Beckman, DU-7HS, UV spectrophotometer with 1 cm quartez cuvettes.

Materials and Reagents

(a) Authentic Metformin hydrochloride was kindly supplied by CID Pharmaceutical Chemical Industries, Cairo, A.R.E. The sample was used as a standard without further treatment. The melting range was 218.3-219.3°C, determined in a capillary tube according to BP 1973(1).

(b) Glucophage tablets, each claimed to contain 500 mg of Metformin hydrochloride, were purchased in local pharmacies.

(c) Spectrograde 1,2-dichloroethane.

(d) Iodine solution (10^{-3}M and 10^{-4}M) prepared by dissolving resublimed iodine in 1,2-dichloroethane.

(e) Aqueous solution of sodium hydroxide (10% w/v).

(f) Standard solution of Metformin: weigh accurately an amount of the salt calculated to contain 50mg base. Transfer into a 60ml separating funnel containing 5 ml of 10% solution sodium hydroxide. Extract with three 15 ml portions of 1,2-dichloroethane, passing the separated organic layer through 2 g. of anhydrous sodium sulphate supported by glass wool in a small funnel into a 50 ml volumetric flask. Rinse the sodium sulphate with dichloroethane. Collect in a 50 ml volumetric flask the washings and the filtrate. Complete to the mark with the same solvent. The working solution is then prepared to contain 100 ug.ml^{-1} of Metformin base.

PROCEDURES

For Pure Authentic Substances

In separate 10-ml volumetric flasks, transfer an aliquot (0.2-1.2ml) of the prepared working solution of Metformin base equivalent to 20-120 ug of standard base. Add to each flask 1 ml of iodine reagent (10^{-3}M), mix and then dilute to volume with 1,2-dichloroethane. Measure the absorbances after 20 mins. at 295 nm using dichloroethane as a blank.

For Tablets Dosage Form

Accurately weight twenty tablets and pulverise in a small morter. In a 60 ml separating funnel, suspend the weight equivalent to 50 mg Metformin base in

5 ml 10% sodium hydroxide solution, extract with 1,2-dichloroethane and complete as directed under preparation of the standard solution.
Transfer quantitatively 1 ml of the obtained extract (equivalent to 1 mg metformin base) to a volumetric flask of 100 ml capacity. Complete to volume with the same solvent. Mix well and transfer 4 ml of the obtained final dilution to a measuring flask of 10 ml capacity, add 1 ml of iodine reagent (10^{-3}M solution) and complete as directed under authentic substance.

RESULTS AND DISCUSSION

The immediate change of the violet colour of iodine in dichloroethane to yellowish purple upon reaction with metformin base suggested charge-transfer complex formation. The spectrum of charge-transfer complex produced by the reaction of metformin with iodine by the suggested procedure is shown to possess a blue-shifted iodine and charge transfer bands at 360 and 295 nm respectively, (Fig. 1).

Development of the optimum conditions for the charge-transfer complex formation involves proper selection of the experimental conditions namely solvent, the concentration of iodine solution and time of reaction. Four of the most commonly used solvents: chloroform, carbon tetrachloride, dichloromethane and 1,2 dichloroethane were tried to choose the most suitable solvent for the complex formed. Among the solvent tested, dichloroethane was selected for the highest intensity of complex absorbance obtained. While, chloroform and carbon tetrachloride failed to give successful results. This is probably due to the decreased tendency of 1,2 dichloroethane to form contact charge-transfer pairs(14) with the nitrogen of the base because of the low ratio of chlorine to carbon atoms in its molecule as compared to chloroform or carbon tetrachloride(14). By testing the effect of iodine solution concentration on the developed charge-transfer absorption band, fig. 2 indicates that 0.8 ml of 10^{-3}M of iodine in 1,2-dichloroethane is sufficient for maximum absorbance and complete reaction. Complexation between iodine (as a σ acceptor) and metformin donor started at room temperature and the reaction rate increased markedly by time. The optimum time for the maximum development of absorbance intensity was twenty min. The complex formed was found to be stable for more than one hour as shown in fig. 3.

To ascertain the stoichiometry of the reaction between metformin and iodine, Job's method(15) was applied using 10^{-4}M solutions of the drug base and iodine. The results indicated a molar ratio of 1:1 under the optimum conditions obtained, fig. 4. Beer's law was obeyed in the concentration range of 2.0-12.0 ug.ml^{-1}, the results are calculated from a calibration curve (fig. 5) representing the

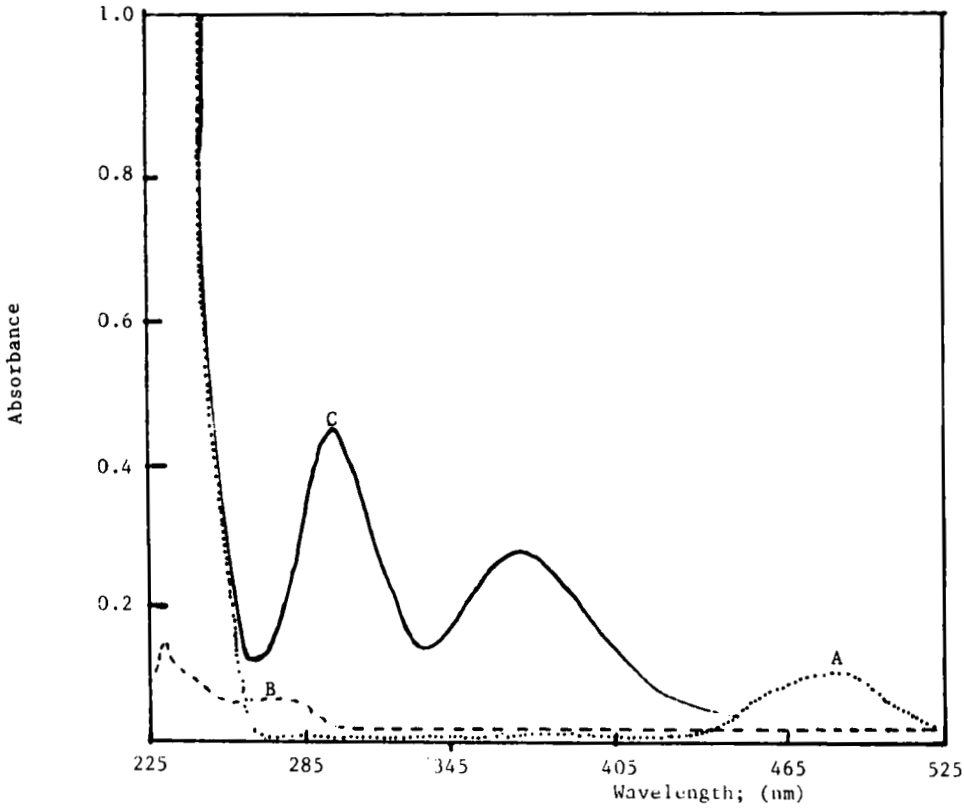

Figure 1: Absorption Spectrum of Metformin - Iodine Charge-Transfer Complex.

A = Iodine 1×10^{-4}M

B = Metformin base 10 ug.ml^{-1}

C = Metformin - iodine complex 10 ug,ml^{-1}

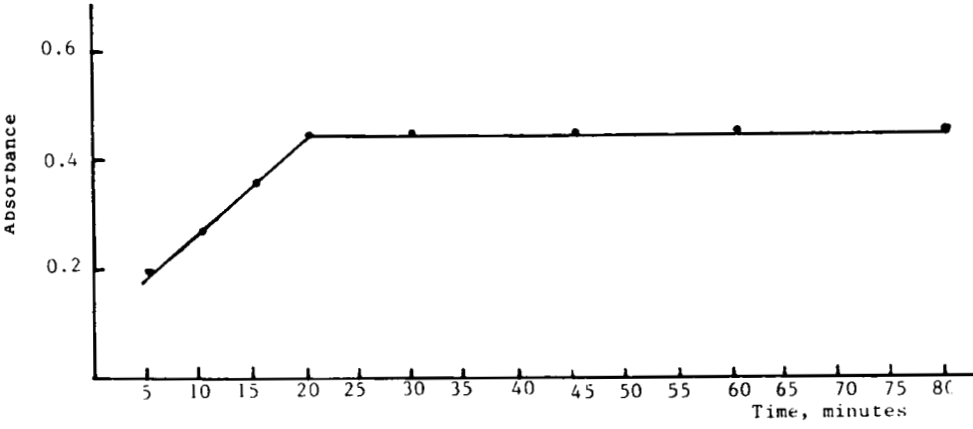

Figure (2): Effect of Time on Reaction of Metformin - Iodine Charge-Transfer Complexes. (10 ug, ml^{-1} Metformin in dichloroethane)

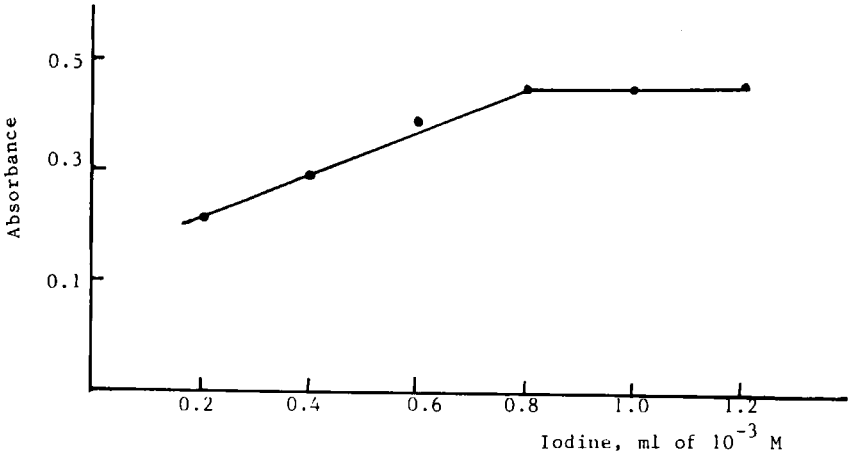

Figure (3): Effect of Iodine Concentration on Metformin - Iodine Charge Transfer Complexes. (10 ug.ml^{-1} Metformin in dichloroethane)

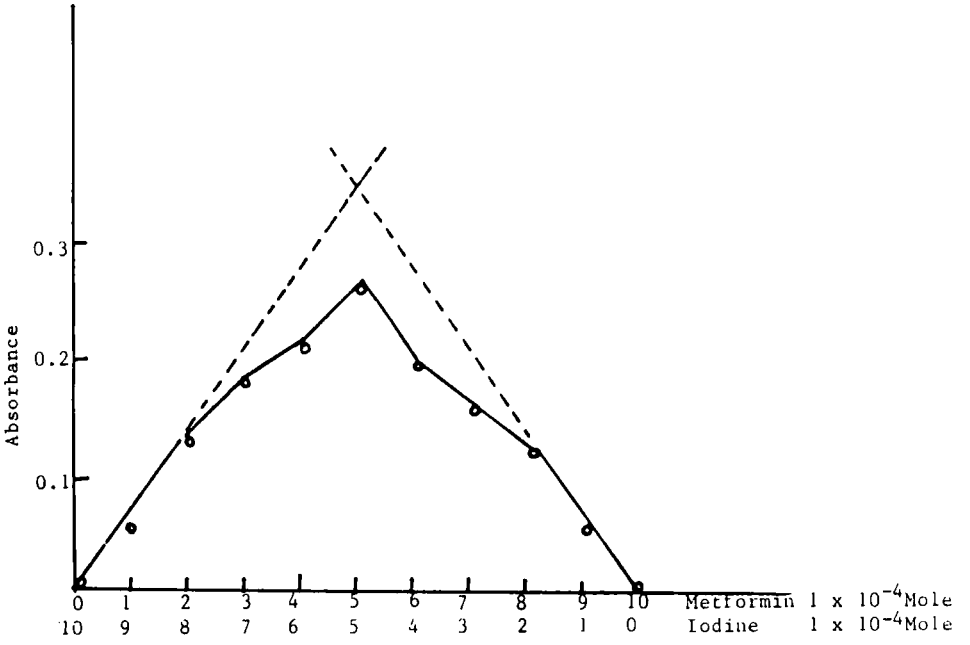

Figure (4): Stoichiometric Balance of the Reaction of Metformin and Iodine Solution in Dichloroethane

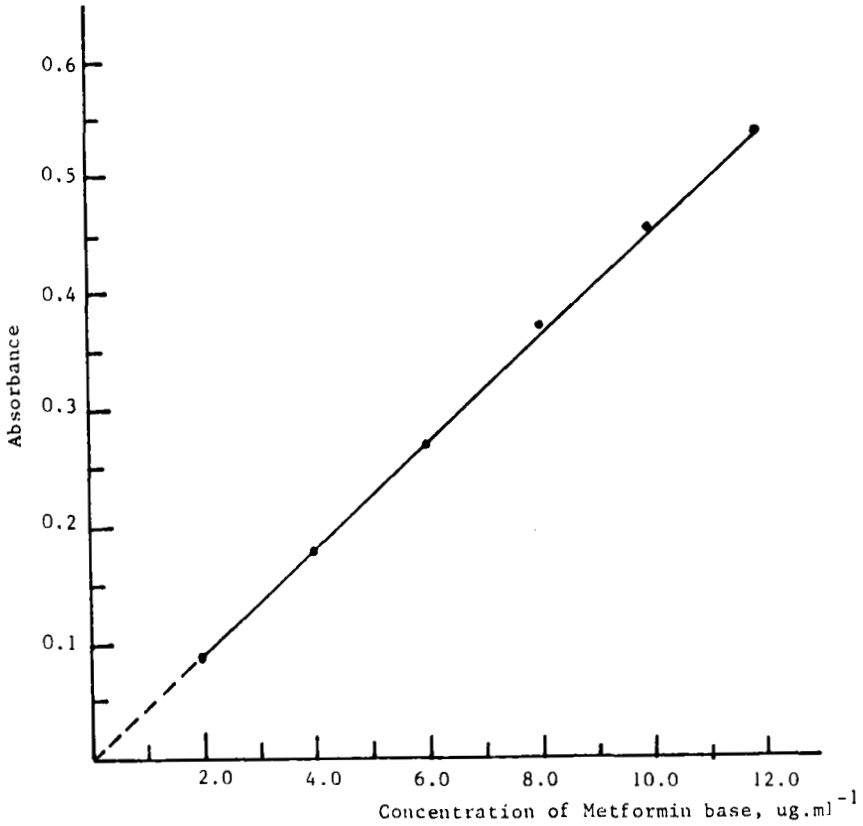

Figure (5): Calibration Graph of Metformin base using the Proposed Charge Transfer Complexes with Iodine.

absorbance of metformin base versus the concentration in ug.ml^{-1} or from the following linear regression equation.

$$A = 0.006 + 0.045\ C^*$$

$$r = 0.997 \qquad SD = \pm\ 0.245$$

C* is the concentration of metformin base in ug.ml^{-1}

Table (1) shows the percentage recoveries obtained when the proposed method is used for assay of authentic metformin base. The results demonstrated good precisions (average percent recoveries 100.05 ± 0.59).

Analysis of authentic metformin hydrochloride according to the BP 1980 is carried out by non-aqueous titration with acetous perchloric acid, the end point being determined potentiometrically while the official BP 1980 method

Table 1. Determination of authentic metformin base by the proposed charge-transfer complex with iodine.

Taken Metformin base $ug.ml^{-1}$	Found base* $ug.ml^{-1}$	Recovery %
2	1.98	99.00
3	3.01	100.33
4	4.03	100.75
5	4.99	99.98
6	5.98	99.67
8	8.05	100.62
9	9.02	100.22
10	10.01	100.10
12	11.97	99.75
	Mean	100.05
	(P=0.05)	± 0.59**

*The average of four experiments.

**Standard deviation.

Table 2. Statistical comparison of the results obtained by the proposed Charge-Transfer Method with the B.P. 1980 Method.

	B.P. Method	Proposed Method
Mean	100.15	100.05
(P = 0.05)	± 1.10	± 0.59
N	6	9
Variance	1.210	0.35
t	0.2299 (2.160)*	
F	0.289 (5.0)*	

*Figures in parentheses are the theoretical t and F values at P=0.05.

Table 3. Determination of Metformin in its tablets by the standard addition technique to the Charge-Transfer Method

Amount Labelled (ug)	Found (ug)	Standard Added (ug)	Standard Found (ug)	Recovery %
40	38.80*	-	-	-
		20	20.1	100.50
		40	40.4	101.00
		50	59.9	99.80
		60	60.1	100.17
		70	69.8	99.72
		80	78.9	98.63
		Mean		99.97
		(P=0.05)		± 0.81**

*Average of four experiments

**Standard deviation.

for determination of the drug hydrochloride salt in tablets dosage form depends on the reaction of the biguanide salt with nitroprusside and ferrocyanide in alkaline sodium hydroxide solution followed by measuring the absorbance of the colour formed at 525 nm. A comparison between the proposed method with the British Pharmacopoea 1980(2) method for pure authentic drug is shown in Table (2).

According to the variance ratio test (F. test) the calculated F value was 0.289 while the theoretical value is 5.0 (P=0.05, n=9). This means that there is no significant differences between the proposed method and BP method with respect of precision. Also the calculated t was found to be 0.2299 while the theoretical value of t was 2.160 (P=0.05). This indicates that there is no significant differences with respect to accuracy. The proposed method can be applied for the analysis of tablets dosage form with considerable accuracy and sensitivity as being assessed by the standard addition technique. The results in Table (3) shows a mean percentage recovery of 99 ± 0.81 (P=0.05) (n=6) for different added authentic samples range between 20-80 ug metformin base to powder tablets.

The proposed method has the advantage of being rapid, requires simple equipments and can be used for the determination of microgram amounts of drug, therefore, it is preferred over the official method when only small amounts of the drug is available for analysis. Amount of 0.25 g of pure drug being required for its analysis by the official BP 1980 method.

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