Journal of Pharmaceutical & Biomedical Analysis
Vol. 9, No. 3, pp. 219–224, 1991
Printed in Great Britain

0731–7085/91 $3.00 + 0.00

Spectrophotometric determination of some pharmaceutical amides through charge–transfer complexation reactions

GAMAL A. SALEH* and HASSAN F. ASKAL

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Assiut University, Assiut, Egypt

Abstract: A spectrophotometric method is described for the assay of fenpipramide hydrochloride, isopropamide iodide, trimethobenzamide hydrochloride, morphazinamide hydrochloride and tolazamide. The method is based on the formation of a charge–transfer complex between the drug as *n*-donor and iodine, a σ-acceptor. The product exhibits absorption maxima at 295 and 365 nm; measurements are made at 365 nm for fenpipramide and at 295 nm for the other compounds. Beer's law is obeyed in a concentration range of 1–120 μg ml^{-1}. The method is rapid, simple and sensitive and can be applied to the analysis of some commercial and laboratory prepared tablets without interference. A more detailed investigation of the complex was made with respect to its composition. association constant and free energy change.

Keywords: *Fenpipramide; isopropamide; trimethobenzamide; morphazinamide; tolazamide; charge–transfer complex.*

Introduction

Trimethobenzamide hydrochloride (antihistaminic), isopropamide iodide (antispasmodic), tolazamide (oral hypoglycaemic), morphazinamide (tuberculostatic and leprostatic) and fenpipramide hydrochloride (used for inducing normal labour for veterinary purposes) are widely used in pharmaceutical practice (Scheme 1).

Official compendia in the USA describe a non-aqueous titration for isopropamide, trimethobenzamide hydrochloride and tolazamide [1]. Among methods described for the determination of these drugs are titrimetric [1, 2], chromatographic [3, 4] and colorimetric [5–8] procedures. Since these methods are time consuming and depend upon measuring fairly concentrated solutions, they lack simplicity and sensitivity.

Amines are excellent *n*-donors and charge–transfer complexes of these compounds with halogens and pseudo-halogens have been reported [9–12]. The proposed method is based on the interaction between the tertiary amine moiety of the chosen compound as the *n*-donor and iodine, the σ-acceptor, in 1,2-dichloroethane to form a stable charge–transfer complex. In addition, the association constant, the molar ratio of reactants, and the free energy change (ΔG°) were determined.

Experimental

Instrument

A Uvidec-320 spectrophotometer (Jasco, Tokyo, Japan) with 10-mm quartz cells was used.

Reagents

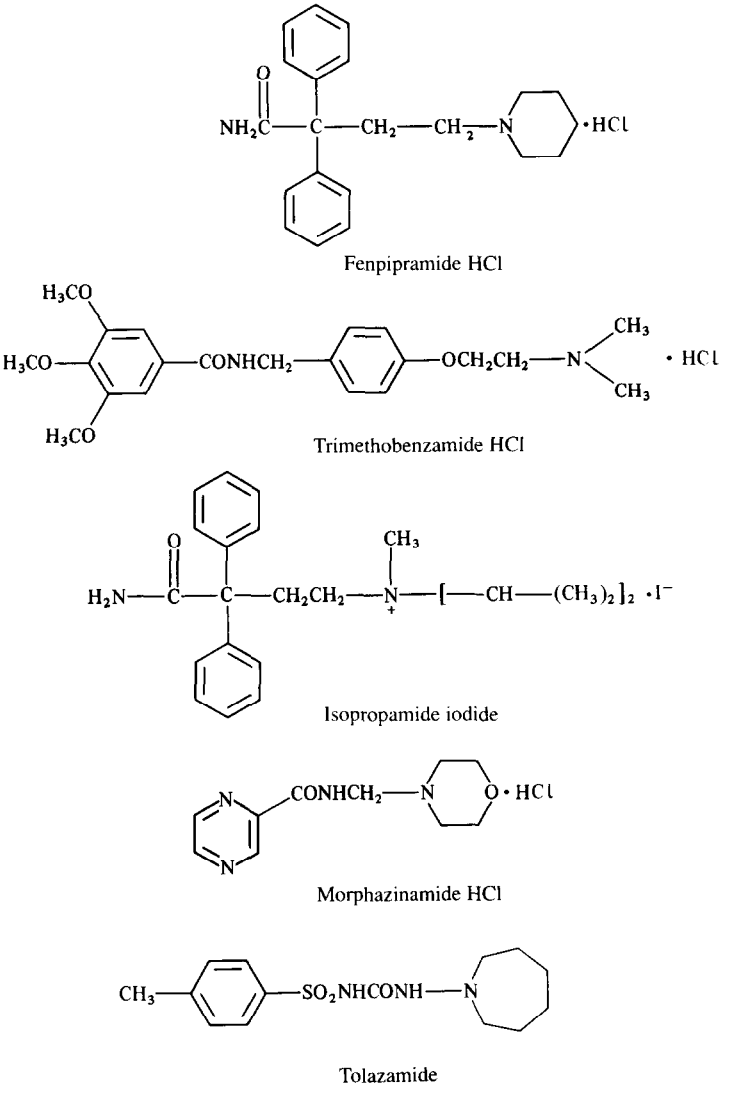
Pharmaceutical grades of fenpipramide hydrochloride (Hoechst), isopropamide iodide (SK & F Laboratories, UK), trimethobenzamide hydrochloride (The Nile Co., Cairo, Egypt), morphazinamide hydrochloride (Bracco Industria Chemica, Milano, Italy) and tolazamide (Upjohn Co., USA) were used as working standards.

Iodine solution (10^{-3} M) was prepared in 1,2-dichloroethane; this solution was stable for 1 week at 4°C. All reagents were of analytical grade.

Standard solutions

For fenpipramide, trimethobenzamide and morphazinamide hydrochlorides. A solution was prepared by dissolving an accurately weighed amount of the drug salt, equivalent to

*Author to whom correspondence should be addressed.



Scheme 1

100 mg of the base, in about 20 ml of water. The solution was quantitatively transferred to a separating funnel, made alkaline with ammonia solution and shaken with five 20-ml portions of 1,2-dichloroethane. The combined extracts were passed through 5 g of anhydrous sodium sulphate supported by glass wool in a small funnel into a 100-ml standard flask and diluted to volume with 1,2-dichloroethane to provide a standard 1 mg ml^{-1} solution of the base.

For tolazamide base and isopropamide iodide. An accurately weighed amount of the drug was dissolved in 1,2-dichloroethane in a 100-ml standard flask and diluted to volume with the same solvent to obtain a standard 0.5 mg ml^{-1} solution of the drug. For tolazamide the procedure was applied to 1 ml of this solution. For isopropamide iodide, 5 ml of solution was transferred by pipette into a 100-ml standard flask and diluted to volume with 1,2-dichloroethane. The procedure was applied to 1 ml of this solution.

Procedure

One millilitre of the working standard or sample solution was transferred by pipette into a 10-ml standard flask; 1 ml of iodine solution was added and the solutions were mixed well and allowed to stand at 25 ± 1°C for 60 min for tolazamide, or 15 min for the other drugs. The solution was diluted to volume with 1,2-dichloroethane. The absorbance was measured

in 10-mm cells against a reagent blank at 365 nm for fenpipramide, or at 295 nm for the other drugs.

Vomigan tablets. Twenty tablets were weighed and powdered. An accurately weighed quantity equivalent to 50 mg of trimethobenzamide base was placed in a separating funnel containing 20 ml of water. The base was extracted as described above, transferred to a 100-ml standard flask and diluted to volume with 1,2-dichloroethane. 5 ml was transferred by pipette to a 100-ml standard flask and diluted to volume with 1,2-dichloroethane. The procedure was applied to 1 ml of this solution.

Stelabid tablets. Twenty tablets were weighed and powdered. An accurately weighed amount equivalent to 50 mg of isopropamide iodide was placed in a separating funnel containing 20 ml of water and 1 ml of 0.01 M hydrochloric acid. The mixture was shaken with five 20-ml portions of 1,2-dichloroethane. The combined extracts were passed through 5 g of anhydrous sodium sulphate supported by glass wool in a small funnel into a 100-ml standard flask and diluted to volume with 1,2-dichloroethane. 5 ml of the filtrate was diluted to volume in a 50-ml standard flask. The procedure was applied to 1 ml of this solution.

Laboratory prepared tolazamide tablets. Tablets were prepared according to Remington [13]. An accurately weighed amount equivalent to 100 mg of tolazamide was placed in a 100-ml standard flask, shaken with 70 ml of 1,2-dichloroethane, diluted to volume and filtered, rejecting the first 20 ml of the filtrate. The procedure was applied to 1 ml of this solution.

Laboratory prepared morphazinamide hydrochloride tablets. Tablets were treated in the same manner as that described under Vomigan tablets.

Stoichiometric relationship

Master equimolar solutions of iodine and the different amides in 1,2-dichloroethane were prepared. The concentrations of these solutions were: 4×10^{-5} M for trimethobenzamide; 1×10^{-6} M for isopropamide iodide; 1.8×10^{-4} M for morphazinamide; 5×10^{-5} M for fenpipramide; and 1×10^{-3} M for tolazamide. A series of 10-ml volumes of mixtures containing the master solution and 1,2-dichloroethane in different proportions (0:10 to 10:0) were prepared in 10-ml volumetric flasks. After the flasks had been allowed to stand at 25 ± 1°C for the specified time required to give maximum readings for each drug, the absorbance was measured at 365 nm for fenpipramide and at 295 nm for the other compounds.

Association constant and free energy change

Trimethobenzamide solutions in 1,2-dichloroethane were prepared (0.9, 1.8, 2.7, 3.6 and 4.5×10^{-5} M) and 5 ml of each solution was mixed rapidly with 5 ml of iodine solution in the same solvent (0.8×10^{-5} M). The absorbance of each solution was determined immediately at 295 nm.

Results and Discussion

The immediate change in colour of iodine in halogenated solvents from violet to lemon yellow upon reaction with each of the investigated compounds is due to a charge–transfer complexation reaction between the *n*-donor amine and the σ-acceptor iodine followed by the formation of a tri-iodide ion-pair that exhibits strong absorption maxima at 295 and 365 nm; this agrees with reports on similar reactions [14, 15].

$$\underset{\text{outer complex}}{R{-}N + I_2 \rightarrow R{-}N{\cdot}I_2 \rightarrow [R{-}\overset{+}{N}{-}I]I^-} \xrightarrow{I_2} \underset{\text{tri-iode ion pair}}{[R{-}\overset{+}{N}{-}I]I_3^-}$$
inner complex

Further confirmation of the charge–transfer nature of the reaction was obtained by extracting the drug from the complex by shaking with aqueous mineral acid; the colour of iodine in 1,2-dichloroethane was restored to violet. The following compounds were tested and gave positive responses: fenpipramide, isopropamide iodide, trimethobenzamide, morphazinamide and tolazamide. The absorption spectrum of iodine in 1,2-dichloroethane (Fig. 1) showed only one peak with maximum absorption at 520 nm. However, the charge–transfer complex with the tested compounds exhibited blue-shifted iodine bands at 295 and 365 nm;

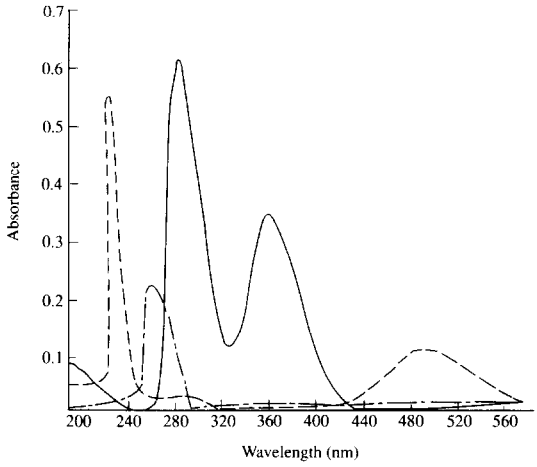


Figure 1
Absorption spectra of trimethobenzamide hydrochloride, 4 μg ml^{-1} (—·—); iodine, 2 × 10^{-3} M (---); and their reaction product in 1,2-dichloroethane (——).

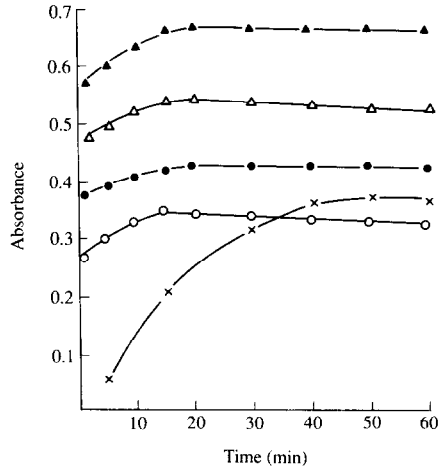


Figure 2
Rate of complex formation, △, fenpipramide (10 μg ml^{-1}); ▲, isopropamide iodide (5 μg ml^{-1}); ●, morphazinamide (37.5 μg ml^{-1}); ○, trimethobenzamide (2 μg ml^{-1}); and ×, tolazamide (70 μg ml^{-1}).

that the first peak was more intense than the second is characteristic of the *n*-donor–iodine charge–transfer complexes.

Although the complex was formed rapidly, constant absorbance readings were obtained after 1 h for tolazamide or after 15 min for the other compounds. The readings remained constant for at least one additional hour (Fig. 2).

Standard curves for the different compounds were constructed by plotting absorbance (A) versus concentration (C) (μg ml^{-1}). Beer's law was obeyed in the range 1–10 μg ml^{-1} of fenpipramide and isopropamide, 0.5–5 μg ml^{-1} of trimethobenzamide, 5–50 μg ml^{-1} of morphazinamide and 10–120 μg ml^{-1} of tolazamide. Regression equations [16] were derived using the method of least-squares and correlation coefficients (r) were calculated: Fenpipramide, $A_{365} = 0.0481 + 0.0621C$ (SE of slope = 0.0019, n =8, r = 0.9990); isopropamide $A_{295} = -0.0610 + 0.144C$ (SE of slope = 0.0028, n = 8, r = 0.9975); trimethobenzamide $A_{295} = -0.0055 + 0.166C$ (SE of slope = 0.0026, n = 8, r = 0.9989); morphazinamide $A_{295} = -0.0065 + 0.019C$ (SE of slope = 0.000635, n = 8, r = 0.9952); and tolazamide $A_{295} = -0.007 + 0.005C$ (SE of slope = 0.000064, n = 8, r = 0.9990).

The slopes of the calibration curves reflect the sensitivity of the procedure. The highest slope is that for trimethobenzamide, the compound of greatest basicity (pK_a = 8.3) [17]. Being less basic, the other compounds gave lower slopes.

Using Job's method of continuous variation [18] the ratio of iodine to each of the tested compounds was 1:1 (Fig. 3). This finding was expected because of the presence of one basic or electron-donating tertiary amine moiety.

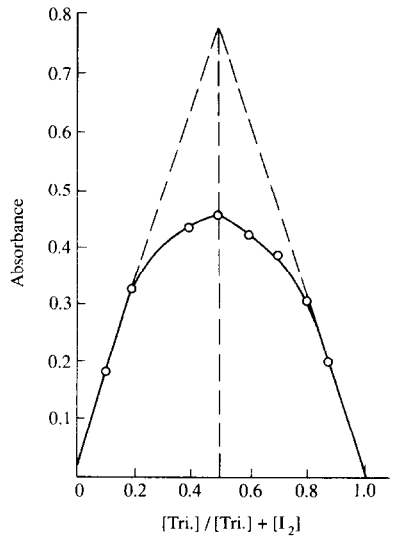


Figure 3
Continuous variation plot for trimethobenzamide–iodine complex (2 × 10^{-5} M).

A more detailed examination was made for the most sensitive compound, trimethobenzamide. The absorbance of the trimethobenzamide–iodine complex was used to calculate the association constant using the Benesi–Hildebrand equation [19]:

$$\frac{[A_o]}{A_\lambda^{AD}} = \frac{1}{\epsilon_\lambda^{AD}} + \frac{1}{K_C^{AD}\,\epsilon_\lambda^{AD}} \cdot \frac{1}{[D_o]}, \quad (1)$$

Table 1
Assay results of commercial tablets and laboratory prepared tablets

Preparation	Nominal content (mg/tablet)	% Found ±SD (n = 5)	
		Proposed method	USP-NFXXI method
Vomigan tablets*	250	99.23 ± 0.73	100.30 ± .035
Stelabid tablets*	5	99.63 ± 0.83	100.96 ± 0.63
Morphazinamide tablets†	500	99.17 ± 0.92	—
Tolazamide tablets†	500	99.60 ± 0.43	—

* Vomigan tablets (trimethobenzamide) were obtained from the Nile Co. for Pharmaceutical Industries (Cairo, Egypt). Stelabid tablets (isopropamide iodide with trifluoroperazine dihydrochloride) were obtained from Kahira/S.K. & F (Cairo, Egypt).
† Morphazinamide tablets and tolazamide tablets were prepared in the laboratory.

where $[A_o]$ and $[D_o]$ are the total concentrations of the interacting species, A_λ^{AD} and ϵ_λ^{AD} are the absorbance and molar absorptivity of the complex at 295 nm, and K_C^{AD} is the association constant of the complex. On plotting the values of $[A_o]/A_\lambda^{AD}$ versus $1/[D_o]$, a straight line was obtained which is described by the following regression equation:

$$\frac{[A_o]}{A_\lambda^{AD}} = 8.29 \times 10^{-5} + \frac{1}{[D_o]}(3.4 \times 10^{-10}). \quad (2)$$

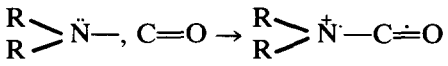
The SE of the slope = 1.04×10^{-10}, $n = 5$, and $r = 0.9997$. The intercept of this line with the ordinate is $(\epsilon_\lambda^{AD})^{-1}$; the slope equals $(\epsilon_\lambda^{AD} K_C^{AD})^{-1}$. From equation (2), the association constant is 2.43×10^5. The standard free energy [20] of complexation, $\Delta G°$ is related to the association constant by:

$$\Delta G° = -2.303\ RT \log K, \quad (3)$$

from which $\Delta G° = -7.34$ kcal.

The high value of the association constant is common to n-donors where the intermolecular overlap may be considerable [12].

Theoretically, one or more of the amido and amino nitrogens can participate as the donor centre in such an interaction. The amido nitrogen is not basic enough to play this rôle because the lone pair of electrons is not localized entirely on the nitrogen atom but rather is equally distributed between nitrogen and oxygen [21].



In contrast, dimethylacetamide was found to form a molecular addition compound with iodine; complexation occurs through the oxygen. However, no shifts in the IR carbonyl absorption band were observed. From the earlier discussion, it was concluded that complex formation between the investigation compounds and iodine proceeds via the tertiary nitrogen moiety.

The proposed method was applied to the analysis of commercial tablets of trimethobenzamide (Vomigan) and isopropamide iodide (Stelabid) (Table 1). Potential interference caused by the presence of trifluoroperazine dihydrochloride together with isopropamide iodide in Stelabid tablets was eliminated by adopting an appropriate extraction method. Thus isopropamide iodide was extracted with 1,2-dichloroethane in a faintly acidic or neutral medium [22, 23]. The results obtained (Table 1) were comparable with those obtained by the official USP-XXI method. Since commercial products of the other drugs were not available, laboratory prepared tablets were analysed by the proposed method. The results (Table 1) further confirm the suitability of the charge–transfer spectrophotometric method for control analysis and unit-dose assay. No interference from excipients normally present in tablets was encountered. The proposed method offers the advantages of accuracy and time saving as well as simplicity of reagents and apparatus.

References

[1] The United States Pharmacopeia, XXI Rev., pp. 567–568, 1094–1095, 1067–1068. The National Formulary XVI Edition, The United States Pharmacopeial Convention, Inc. (1985).
[2] J. Mitchell and C.E. Ashly, *J. Am. Chem. Soc.* **67**, 161–164 (1945).
[3] K. Hentrich, *Pharmazie* **18**, 405–409 (1963).
[4] E. Sophoulies, *Egypt. J. Pharm. Sci.* **2**, 29–34 (1961).
[5] F. Bergmann, *Anal. Chem.* **24**, 1367–1369 (1952).

[6] S. Hestrin, *J. Biol. Chem.* **180**, 249 (1949).
[7] J.B. Polya and P.L. Tardrew, *Anal. Chem.* **23**, 1036–1037 (1952).
[8] S. Solway and A. Lipschitz, *Anal. Chem.* **24**, 898–900 (1952).
[9] A.I. Popov and R.H. Rygg, *J. Am. Chem. Soc.* **79**, 4622–4625 (1957).
[10] H. Yada, J. Tanaka and S. Nagakura, *Bull. Chem. Soc., Japan* **33**, 1660–1666 (1960).
[11] S. Kobinata and S. Nagakura, *J. Am. Chem. Soc.* **88**, 3905–3909 (1966).
[12] R. Foster, *Organic Charge–Transfer Complexes*, pp. 4, 23. Academic Press, London (1969).
[13] M.R. Gibson, *Remington's Pharmaceutical Sciences*, 14 edn, p. 1671. Mack Publishing Co., Easton (1970).
[14] A.M. Taha, N.A. El-Rabbat and F. Abdel-Fattah, *J. Pharm. Belg.* **35**, 437–444 (1980).
[15] A.M. Taha, N.A. El-Rabbat and F. Abdel-Fattah, *Analyst* **105**, 568–574 (1980).
[16] E.H. Girgis, Z. Gad and M. Maram, *J. Pharm. Sci.* **63**, 1764–1766 (1974).
[17] Wilson and Gisvold, *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 8th edn, p. 845. Philadelphia, London and New York (1982).
[18] P. Job, *Ann. Chim.* **16**, 97 (1936); through *Advanced Physicochemical Experiments*, 2nd edn, p. 54. Oliver and Boyd, London (1964).
[19] H.A. Benesi and J. Hildebrand, *J. Am. Chem. Soc.* **71**, 2703–2707 (1949).
[20] A.N. Martin, J. Swarbrick and A. Cammarata, *Physical Pharmacy*, 2nd edn, pp. 343, 360. Lee and Febiger, Philadelphia, PA (1969).
[21] J. Zabicky, *The Chemistry of Amides* (S. Patai, Ed.), p. 60. Interscience and Wiley, London (1970).
[22] E. Jungermann, *Cationic Surfactants*, Vol. 4, pp. 419–454. Dekker, New York (1970).
[23] A. Taha, A.K.S. Ahmed, C.S. Gomaa and H. El-Fatatry, *J. Pharm. Sci.* **63**, 1853–1857 (1974).

[*Received for review 7 July 1989*]