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Sensitive and Selective Spectrophotometric Methods for the Determination of Cisaprid, Metoclopramide Hydrochloride, Sulphadoxine and Sulphamethoxazole

Mohsina Begum[1], Isa Baba Koki[2], Mohammad Rizwan[3], Akheel Ahmed Syed[4,*]

[1]Department of Chemistry, Maharani's College, Mysuru - 570005, India
[2]Department of Chemistry, Northwest University Kano, PMB, 3220 Kano, Nigeria
[3]Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia
[4]Department of Studies in Chemistry, University of Mysore, Manasa Gangotri, Mysuru - 570006, India

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Abstract

Two simple, sensitive and selective spectrophotometric methods were developed for the determination of cisapride (CPD), metoclopramide hydrochloride (MCP), sulphadoxine (SDX) and sulphamethoxazole (SMX) containing aromatic primary amino group. The methods are based on the interaction of diazotised drugs with iminodibenzyl (IDB) and 3-chloroiminodibenzyl (Cl-IDB) (new spectrophotometric reagents) in hydrochloric acid medium to yield violet or red colored product with maximum absorption at 570 or 500 nm, respectively. The commonly encountered excipients and additives along with the drug do not interfere with the determination. These drugs can be determined in the range of 0.2-8.0 µg/mL, with a maximum relative standard deviation of 1.10% and 1.40% for IDB and Cl-IDB, respectively. Results of the analysis of some preformulations and commercial tablets (Perinorm, Amalar and Bactrim DS for MCP, SDX and SMX respectively) by these methods agree well with those determined by the official methods.

Keywords: Iminodibenzyl, 3-chloroiminodibenzyl, cisapride, metoclopramide hydrochloride, sulphadoxine, sulphamethoxazole

1. Introduction

Iminodibenzyl (IDB) and 3-chloroiminodibenzyl (Cl-IDB) belong to dibenzazepine class of tricyclic compounds having a central ring constituted of seven atoms (Figure 1a and 1b). These are precursors to dibenzoazepine derivatives, such as imipramine hydrochloride, desipramine hydrochloride and clomipramine hydrochloride, which are classified as benchmark antidepressant agents [1, 2]. IDB and Cl-IDB have been reported as spectrophotometric reagents for the determination of Hg(II), Ni(II), Cu(II) and Co(II) [3]. Further, we tried these as spectrophotometric reagents in the determination of certain pharmaceutical drugs containing amino group. Cisapride (CPD), metoclopramide hydrochloride(MCP), sulphadoxine (SDX) and sulphamethoxazole (SMX) are chemicals containing aromatic primary amino group, which depending on their structure exhibit varied medicinal properties[4].

* Corresponding author:
akheelahmed54@gmail.com
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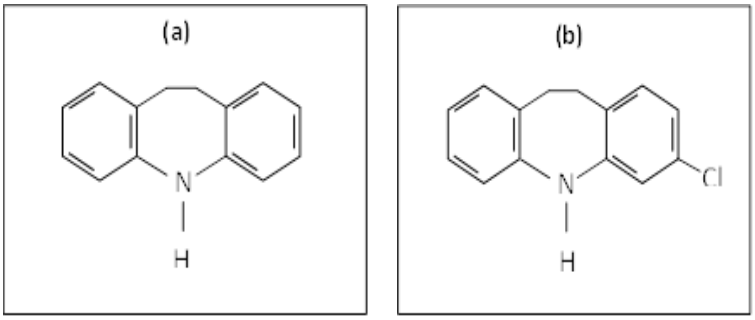


Figure 1. Structure of IDB (a) and Cl-IDB (b)

CPD is a gastrointestinal stimulant, effective in relieving gastrointestinal or esophagus disorders and in the promotion of gastric emptying of a gastrointestinal motility. Although CPD has been voluntarily withdrawn in the U.S. by Janssen Pharmaceutica, it was available till July 14, 2000 and for a limited period thereafter for meeting specific criteria. The background to this development points to certain adverse effects caused by cisapride. The regulatory authorities in India have not officially announced the discontinuation of cisapride from the Indian market [5]. CPD is a substituted piperidinyl benzamide and a prokinetic agent is chemically related to MCP. MCP prevents nausea and vomiting which are the most common adverse effects of cancer chemotherapy and often contribute to patients' reluctance to undergo treatment. In practice, clinical oncologists aggressively advocate antiemetic therapy to prevent chemotherapy-induced nausea and vomiting in an attempt to improve patients, psychological behavior and acceptance of treatment [6]. SDX is a long-acting sulphonamide; it has been used in the treatment of various types of infections. SDX exhibits synergistic effect with pyrimethamine, which acts against folate metabolism at different points of the metabolic cycle. SMX is commonly used to treat uncomplicated urinary tract infection, particularly those caused by *Escherichia coli*. The therapeutic importance of these drugs justifies development of a selective, rapid, sensitive and accessible method for their assay in industrial quality control and drug control department.

Many contemporary analytical methods including amperometry [7], potentiometry [7], voltammetry [8], ion selective electrodes [9, 10], fluorimetry [11], chromatographic methods [12-15] and UV-Visible spectrophotometry [16-20] have been utilized to determine these drugs in different matrices. However, these methods have proved to be deficient with respect to specificity, sensitivity, simplicity and/or short analysis time. For example, MCP is a subject of British Pharmacopoeia monograph, which adopts the potentiometric titration as the official assay for the bulk drug. The utilization of the titration method in dosage form in analysis has proven inadequate due to interference by additives. The low cost combined with the ease of operation of potentiometric instrumentation and use of ion selective electrode make the potentiometric method for drugs a highly desirable alternative. However, the method lacks reproducibility and the sensitivity is low. Voltammetry demands extensive selectivity regarding the solvent and the electrode material used is costly and is a cumbersome process. Ion selective electrodes lack reproducibility and the sensitivity is low. Chromatographic methods are valuable techniques for identification of impurities in preformulations or of metabolites in biological matrices, but are not preferred for routine quantitative analysis. Further, the instrument cost is relatively high and maintenance demands sophistication. Thus, for routine pharmaceutical analysis, spectrophotometry seems to be the most attractive analytical approach as it is convenient, simple and is relatively inexpensive.

Visible spectrophotometric methods used for the determination of CPD, MCP, SDX and SMX are of five types. Type I is based on the use of suitable aldehyde to form the Schiff's base [16]; the reactions of type II use electron acceptor and electron donor and the resulting product is a colored charge-transfer complex which is measured spectrophotometrically; type III is based on the diazotization of the substrate (drug) and subsequent coupling with reagents containing amino or phenolic group and spectrophotometric measurement of resulting azo dye; methods under type IV are based on ion-pair formation, and extraction of the ion pairs from the aqueous phase into an organic solvent, and measuring the resulting color by spectrophotometric method. Type V involves the oxidative coupling of the drug with an electrophilic reagent in the presence of oxidant and measuring the resulting chromophore [20]. The shortcomings of the existing procedures are presented in Table 1. Furthermore, no simple and direct visible spectrophotometric method for the determination of SMX is reported so far. These deficiencies have encouraged the authors to develop new and novel spectrophotometric methods for the determination of certain pharmaceutical drugs containing amino group.

The present work is an attempt to meet an ever-increasing demand for the analytical control of some pharmaceuticals, by developing sensitive and selective spectrophotometric methods. The products tried include, CPD, MCP, SDX and SMX in preformulation and dosage forms. The methods involve coupling of diazotized drugs with IDB and Cl-IDB in acidic medium to produce a violet or red color.

2. Material and Methods

2.1. Apparatus and Reagents

A Jasco UV-VIS spectrophotometer UVIDEC-610 type with 1.0-cm matched cell was employed for measuring the absorbance values. High purity reagents were used which include; Cisapride (USV Ltd., India), metoclopramide hydrochloride (IPCA Laboratories Ltd., India), sulphadoxine and sulphamethoxazole (Glaxo Smithkline Pharmaceuticals, India) iminodibenzyl and 3-chloroiminodibenzyl (Max Pharma, India). All other chemicals and solvents used were of analytical grade. Double distilled water was used throughout the analysis. 1.0% (*w/v*) of aqueous sodium nitrite, 3% (*w/v*) sulphamic acid, 10N sulphuric acid, 5 N hydrochloric acid, and 10 N acetic acid were prepared. Solutions of 0.05% (*w/v*) IDB and 0.2% (*w/v*) Cl-IDB were prepared in alcohol and used. The standard solutions of CPD, MCP, SDX and SMX were prepared by dissolving 0.1 g of each drug in 100 mL of appropriate solvent (distilled water for MCP; 1 M acetic acid for CPD; 1 M hydrochloric acid for SDX and SMX). Working standard solutions were prepared by appropriate dilution of the stock solution with distilled water.

Table 1. Comparison of Visible Spectrophotometric Methods for the Determination of Cisapride, Metoclopramide and Sulphadoxin

S/N	Reagent	Colored species	λ_{max} (nm)	Range of determination μgmL^{-1}	ε $1.mol.^{-1} cm^{-1}$	Remarks
1	*Cisapride, p-dimethyl amino cinnamaldehyde*	Schiff's base	525	50-110	Not reported	Reaction carried out in methanol
2	Iodine and catechol	Charge transfer complex	490	20-180	2.30×10^3	Precipation time with iodine 30 min reaction time with catechol 45 min
3	Chromotropic acid	Dye	530	1-10	3.48×10^4	-
4	Phloroglucinol	Dye	450	1-14	2.62×10^4	-
5	NEDA	Dye	540	1-14	3.11×10^4	-
6	Suprachem Violet – 3B	Ion association complex	595	2.5-40.0	1.21×10^4	Extraction in chloroform
7	Erioglaucine A	Ion association complex	640	0.5 – 5.0	4.56×10^4	Extraction in chloroform
8	Naphthalene blue 12BR	Ion association complex	620	2.5-17.5	1.69×10^4	Extraction in chloroform
9	Tropaeolin 000	Ion association complex	500	2.5 – 25.0	1.98×10^4	Extraction in chloroform
10	Wool fast blue BL	Ion-association complex	600	1-12	2.42×10^4	Extraction in chloroform
11	Metanil yellow	Ion pair	408	4-16	not reported	Extraction in chloroform
12	Dimethyl formamide (DMF)	Not reported	274.4	2-20	4.55 x 104	-
13	Metoclopramide Phloroglucinol	Dye	420	1-10	Not reported	-
14	Sodium 1,2-naphthoquinone-4 sulfonate (NQSA)	Orange red reaction product (N-alkyl amino naphthoquinone)	470	5-80	Not reported	Heating at 100°C for 10 min, blank is yellow
15	Bromothymol blue	Dye complex	Blue filter	1-10	Not reported	Extraction in $CHCl_3$
16	8-anilino-1- naphthalene sulphonic acid	Not reported	540	10-70	1.77 x 103	Reaction completed in 10 min
17	Resorcinol	Dye	430	1-9	2.83 x 103	Reaction completed in 10 min
18	β - naphthol	Dye	495	5-30	1.06 x 103	Reaction completed in 10 min
19	Chromotropic acid(CTA)	Dye	540	0.6-12	2.20 x 104	Colour intensity increases slightly in first 10 min
20	MBTH	Oxidative coupling	560	2-24	0.41 x 104	Colour intensity increases slightly in first 15 min
21	Sulphadoxine 1,2-napthaquinone -4-sulphonic acid, sodium salt	Not reported	485	10-50	4.66 x 103	Maximum color intensity after 20 min
22	o-chloranil	Charge transfer complex	525	20-70	3.62 x 103	Reaction time 20 min
23	Metol-Cr(VI)	Charge transfer complex	520	4-32	4.29 x 103	Maximum color intensity after 20 min
24	Phloroglucinol	Dye	415	2-10	1.18 x 104	Maximum color intensity after 30 min

2.2. Procedures

Aliquots of standard solution of CPD (10-160 μg), MCP (5-90 μg), SDX (5-100 μg) and SMX (5-80 μg) were transferred into a series of 25 mL calibrated flasks. 3 mL of 5 N HCl was added and the flask were cooled in ice bath for 5 min. Sodium nitrite solution (2 mL) was added, swirled and allowed to stand for 5 min; next 1 mL of sulphamic acid was added, mixed well and allowed to stand for 5 min. Next 1 mL of 0.05% IDB was added and allowed to stand for 10 min, diluted to the mark with 10 N acetic acid for CPD, SDX, SMX and 10 N sulphuric acid for MCP. After thoroughly mixing the solution the absorbance was measured at 570 nm against the corresponding reagent blank and calibration graphs were constructed.

The above procedure was repeated with Cl-IDB using CPD (10 –200 μg), MCP (10 –200μg), SDX (10 –120 μg) and SMX (5–90 μg). The diazotized drugs were coupled with 1mL of Cl-IDB (0.2%) and allowed to stand for 10 min, for CPD and MCP and for SDX and SMX heated for 10 min and cooled, diluted to the mark with alcohol for CPD and with 10 M acetic acid for MCP, SDX and SMX. After thorough mixing of the solution the absorbance was measured at 500 nm for CPD/MCP and at 570 nm for SDX/SMX against the corresponding reagent blank and calibration graphs were constructed.

(Addition of 5 N HCl was not required for the determination of CPD with Cl-IDB and MCP in both the methods).

2.3. Pharmaceuticals Preparations

Twenty tablets of MCP, SDX and SMX were finely powdered in a small dish. An accurately weighed portion of the powder equivalent to 10 mg of drug was dissolved in ~ 20 mL of 1 N HCl and filtered through a Whatman No. 42 filter paper. The resulting filtrate was made up to the mark with distilled water in a 100 mL volumetric flask. Working standard solutions were obtained by appropriate dilution of the stock solution with distilled water. An aliquot of this solution was analyzed for the determination of the above drugs as per the methods described earlier.

3. Results and Discussions

The method involves the coupling of the diazotised drugs with IDB or Cl-IDB to produce violet or red color with maximum absorption at 570 nm or 500 nm. For the diazotisation process, the NH_2 group in the drug gets readily diazotised in hydrochloric acid medium (~0.5 N). The diazonium group then reacts with IDB or Cl-IDB, by electrophilic substitution at the 4-position of the reagent to produce a violet or red azo dye. In a study on the determination of sulfamethoxazole based diazotization of sulfonamide with sodium nitrite using coupling reaction of diazo compound with thymol, a linear range for the determination and the detection limit was found to be 1-10 µg/L and 0.008 µg/L respectively [21]. Simple and sensitive Spectrophotometric methods for the quantitative estimation of sulfadoxine using Methylene blue was developed and revealed a very high sensitivity of the method [22], some methods used acetonitrile with organic modifier [23-24]. Cisaprid was determined spectrometrically by its reaction with bromocresol green and bromophenol blue at a pH of 2.5 where linearity was achieved in the range of 5- 22.5 µg/mL cisaprid with bromocresol green and bromophenol blue [25]. Similarly, metoclopramide hydrochloride and sulphamethoxazole were determined using different coupling reagents and medium. Furthermore, SDX and SMX were applied in the spectrophotometric determination of anarcadic acid and cardol using sulfanilamides [26-27].

In this study, the factors affecting the color development – such as reproducibility, sensitivity and adherence to Beer's Law were investigated for each drug separately.

3.1. Spectral Characteristics

A violet or red colored product with maximum absorption at 570 nm or 500 nm was formed when the diazotised drugs reacted with IDB or Cl-IDB.

3.2. Optimization of Analytical Variables

The choice of an appropriate solvent/medium has profound influence on the sensitivity and reproducibility of the results. Hydrochloric acid as the reaction medium for diazotization was found to give better results than sulphuric acid. Full color development and maximum sensitivity was achieved with 3-7 mL of 5 N HCl, 1-3 mL of sodium nitrite (1.0%), 1-3 mL of sulphamic acid (3.0%), 1-3 mL of IDB (0.05%) or 1-2 mL of Cl-IDB (0.2%). Hence, 3 mL of HCl (5 N), 1 mL of sodium nitrite, 1 mL of sulphamic acid and 1 mL of IDB or 2 mL of Cl-IDB were recommended.

Table 2 shows the linear calibration ranges and equation parameters for these methods. Separate determinations at different concentrations of each drug gave a coefficient of variation not exceeding 2%.

3.3. Stability

The development of the colored product was achieved within 20 min, which included the time for diazotisation and coupling reactions. The absorbance values were maximum and remained constant for 6-24 h (3h for SDX using Cl-IDB).

3.4. Effect of Diverse Ions

The effects of various substances that often accompany these drugs in pharmaceutical preparations were studied and the results are presented in Table 3. Commonly encountered additives and excipients such as glucose, starch, gum acacia, magnesium stearate and talc did not interfere. While, vitamin C, sodium lauryl sulphate and sodium alginate were found to interfere significantly.

3.5. Applications

The applicability of the method to assay pharmaceutical preparations was examined. Commercial tablets containing metoclopramide hydrochloride, sulphadoxine and sulphamethoxazole were analyzed with the proposed methods. The results obtained were compared favorably with those reported by BP 1999 method [28]. Simethicone, which generally acco-

Table 2. Optical Characteristics CPD, MCP, SDX and SMX

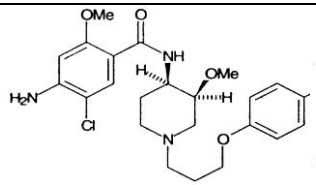
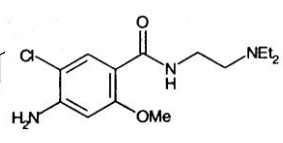
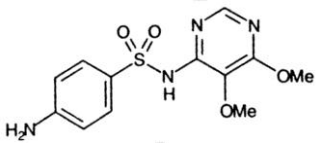
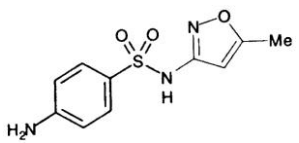
Structure								
Abbreviation used	**CPD**		**MCP**		**SDX**		**SMX**	
Reagent	IDB	Cl-IDB	IDB	Cl-IDB	IDB	Cl-IDB	IDB	Cl-IDB
Colour	Violet	Red	Violet	Red	Violet	Violet	Violet	Violet
λ_{max} (nm)	570	500	570	500	570	570	570	570
Stability(h)	6	>5	6	>24	>24	3	>24	>24
Beer's law(μgmL^{-1})	0.4-6.4	0.4-8.0	0.2-3.6	0.4-8.0	0.2-4.0	0.4-4.8	0.2-3.2	0.2-3.6
Molar absorptivity(ε) $l\ mol^{-1}cm^{-1}$	5.00×10^4	2.80×10^4	5.42×10^4	2.08×10^4	6.50×10^4	4.49×10^4	6.29×10^4	4.72×10^4
Sandell's sensitivity μgcm^{-2}	0.009	0.016	0.005	0.014	0.004	0.006	0.004	0.005
Regression equation*								
Slope(a)	0.121	0.062	0.156	0.061	0.209	0.145	0.244	0.170
Intercept(b)	-0.004	0.002	0.024	0.011	-0.003	-0.009	0.001	0.017
Correlation coefficient	1.000	1.001	0.998	0.971	0.995	1.000	0.998	0.997
R.S.D. %**	± 0.90	± 1.12	±0.60	± 1.22	± 1.10	± 1.40	± 1.10	± 1.20

Table 3. Determination of CPD, MCP, SDX and SMX in the Presence of Excipients and other Substances

Material name	Used quantity (mg)	% recovery of drugs ± RSD**							
		CPD		**MCP**		**SDX**		**SMX**	
		IDB	Cl-IDB	IDB	Cl-IDB	IDB	Cl-IDB	IDB	Cl-IDB
		*2.4 μgmL^{-1}	*4.0 μgmL^{-1}	*2.0 μgmL^{-1}	*4.8 μgmL^{-1}	*1.2 μgmL^{-1}	*2.4 μgmL^{-1}	*1.6 μgmL^{-1}	*1.6 μgmL^{-1}
Glucose	50	101.97 ± 0.85	100.96 ± 1.00	102.06 ± 0.96	100.30 ± 0.75	100.00 ± 0.68	98.15 ± 1.20	101.08 ± 0.94	101.19 ± 0.78
Lactose	50	101.24 ± 0.80	102.80 ± 0.64	98.30 ± 0.75	102.00 ± 0.54	73.74 ± 1.01	#	101.87 ± 0.68	99.09 ± 0.62
Dextrose	50	105.69 ± 1.12	102.10 ± 0.70	98.08 ± 0.87	98.80 ± 0.92	98.70 ± 1.20	98.04 ± 0.68	99.17 ± 0.98	98.80 ± 0.76
Maltose	50	098.35 ± 0.92	102.12 ± 1.01	99.70 ± 0.63	101.40 ± 1.14	101.11 ± 0.83	99.16 ± 1.14	101.35 ± 1.36	97.93 ± 1.02
Starch	50	100.60 ± 0.62	098.02 ± 1.12	99.40 ± 0.62	98.20 ± 0.96	97.80 ± 1.14	104.98 ± 1.42	100.00 ± 0.82	97.06 ± 0.92
Gum acacia	50	98.47 ± 1.13	101.98 ± 1.42	99.17 ± 0.95	97.86 ± 1.32	99.43 ± 0.60	97.99 ± 1.36	98.41 ± 1.32	98.01 ± 1.46
Magnesium stearate	50	99.47 ± 1.34	98.57 ± 0.86	102.87 ± 0.98	101.86 ± 0.86	97.98 ± 1.13	98.15 ± 1.46	102.00 ± 1.45	102.80 ± 1.13
Talc	50	102.96 ± 1.00	98.41 ± 0.98	97.34 ± 1.14	98.25 ± 0.89	102.13 ± 1.46	101.97 ± 1.00	98.87 ± 1.23	100.96 ± 1.43
Vitamin C	50	086.92 ± 1.16	084.62 ± 1.06	#	#	66.32 ± 1.14	#	#	#
Sodium lanryl sulphate	50	051.24 ± 1.13	059.60 ± 0.97	49.61 ± 1.00	#	59.53 ± 1.34	54.60 ± 1.12	73.85 ± 1.40	87.15 ± 1.38
Sodium alginate	50	064.59 ± 0.96	#	#	148.47 ± 0.87	77.76 ± 0.86	75.36 ± 0.65	98.37 ± 1.14	91.87 ± 1.36

**Average of five determinations *Drug concentration #Colourless

mpanies cisapride in dosage form seriously, interferes with the methods. Besides, any compound containing primary amino group seriously interferes with the methods proposed. Hence, laboratory prepared tablets of cisapride, metoclopramide hydrochloride, sulphadoxine and sulphamethoxazole were used for analyses; the results are as shown in Table 4.

Table 4. Determination of CPD, MCP, SDX and SMX in Commercial and Laboratory Prepared Tablets by the Proposed and Official Methods

Drug	Label claim (mg / tablet)	Proposed method found ± RSD %		Analyte (mg)	Recovery[#] (%)		Official method[*] (found %)
		IDB	Cl-IDB		IDB	Cl-IDB	
Cisapride	10	99.6 ± 0.5	99.4 ± 0.7	10	100.5 ± 0.6	98.6 ± 0.6	99.4 ± 0.60
Perinorm tablet (metoclopramide hydrochloride)	10	99.8 ± 0.6	100.5 ± 0.6	10	100.0 ± 0.5	98.9 ± 0.9	99.8 ± 0.15
Amalar tablets (sulphadoxine hydrochloride	500	100.2 ± 0.4	100.3 ± 0.9	50	99.4 ± 0.7	100.5 ± 0.6	99.2 ± 0.09
Bactrim DS Tablet (sulphamethoxazole hydro-chloride)	800	99.6 ± 0.5	99.4 ± 0.8	50	100.4 ± 0.8	99.5 ± 0.9	99.6 ± 0.09

[#] Average ± standard deviation of 5 determinations

4. Conclusions

The procedure described meets most of the requirements of analytical chemistry, such as, simplicity, rapidity, sensitivity, selectivity and cost of analysis. Besides, the conditions for diazotization would seem applicable to methods using other drugs, which can act as coupling agent, as the diazotization forms a separate entity. It is evident from the results that the recommended procedure is well suited for the assay and evaluation of drugs, in pre formulation and dosage forms, to assure high standard of quality control. Such simple methods based on spectrophotometry have become an accepted analytical tool for the assay and evaluation of drugs.

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