Original Article

Spectrophotometric Determination With Anticancer Drugs, Proton Pump Inhibitors And Antihypertensive Drugs In Non Polar Medium

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Abstract

Spectrophotometric methods for the analytical determination of organic, inorganicand biological substances are generally based on development of colour by reagents and identifying such reagents is often cumbersome and time consuming. In this respect, spectrophotometric determination of drugs may be facilitated by their ability to from coloured charge transfer complexes with electron acceptors. In the present investigation, a variety of drugs acting as electron donors e.g. anticancer drugs (Altretamine, Imatinib, Letrozole, Irinotecan) and proton pump inhibitors (Ilaprazole, Omeprazole, Rabeprazole, Lansoprazole, Pantoprazole, Ranitidine)have been used for spectrophotometric determination in a relatively non polar medium.

Keywords: Spectrophotometric methods, anticancer drugs, PPI, Antihypertensive drugs etc.

INTRODUCTION

The large equilibrium constants of complex formation and the colour stability are the main advantage. A couple of neuroleptics e.g. haloperidol and droperidol have likewise been determined, in polar media, through CT interaction with I_2, TCNQ, DDQ, TCNE and bromanil in highly polar media [1]. While these investigations are useful, the highly polar media such as acetone and acetonitrile are likely to form CT complexes with the acceptors and so their conclusions are in doubt.

The literature survey has shown that studies for the analytical determination of drugs have mainly been focused on

- UV-Visible spectrophotometric methods where the characteristicabsorption maximum (λmax) was used for the determination of the drugs [2-35].
- UV-Visible spectrophotometric methods wherein the drug is converted to coloured species through some reaction through charge transfer complex formation,oxidation or reduction of the drug complexing with coloured species like dyes, diazotization reaction in the case of primary and secondary amine moieties containing compounds [36-47].

Most of the chromatographic methods not only allow the detection and determination of the pure drug but also the impurities present along with the drug. So, mostly chromatographic methods are being used for analysis of purity of drug andimpurities present in the drug simultaneously. All chromatographic methods are performed using costly instruments, and the running and maintenance cost are also high compared to UV-Visible

spectrophotometric method. In this respect, UV-Visible spectrophotometric methods can be used for the analysis of different drugs.

Keeping this point in view, the author developed UV-Visible spectrophotometric methods taking advantage of intense coloured charge transfer complex formation between the drug and selected acceptors. In present study examine the Spectrophotometric determination with anticancer drugs, proton pump inhibitors and antihypertensive drugs in non polar medium.

METHODOLOGY

The selected drugs are divided into two groups, anticancer and proton pump inhibitor. The drug molecules selected for the study are presented in Table 1 to 2. All drug moleculesare referred to asdonors. The selected drugmolecules in pure form were obtained on request from quality control laboratories of Mylon Laboratories, Hetero Drugs Limited, Laurus Labs, all in Hyderabad, India and few of them werefrom sigmaAldrich, USA or E. Merck,Germany. The list of acceptors selected for the study arepresented in Table 3. All these compounds werefrom, E. Merck, Germany, SigmaAldrich, USA or British Drug House, BDH, England. The drugs & acceptors were stored in separate vacuum desiccators. HPLC grade or Spectroscopy grade solvents cyclohexane, acetonitrile, dichloromethane and boron trifluoride diethyl etherate (BF3.OEt2) are from E. Merck, Germany or Sigma Aldrich, USA, were further distilled before use after drying them over anhydrous sodium sulfate. All the drugs are of 99.8% pure or above. Majority of drugs were obtained in pure base form & remaining as hydrochloride, sodium and mesylate form. The drugs in pure base form were directly dissolved in the selected solvent. Preparation of knownconcentration of solution was done bydissolving known weight of drug in a known volumeof solvent. The drugs in hydrochloride and sodium forms, were converted to base form using the following extraction procedure.

In a separating funnel, a knownweight1 of drug hydrochloride was dissolved in 100 mL distilled water, to which 20 mL of 0.1 M sodium hydroxide solution and 20 mL of dichloromethane were added and promptly extracted. The hydrochloride medicines were extracted with dichloromethane. This extraction method was performed four times using new 20 mL of dichloromethane each time. The extracted dichloromethane was poured into a beaker. Anhydrous sodium sulphate was used to dissolve any remaining water in the solvent. A 100 mL solution of dichloromethane was prepared. The concentration of was determined using the published molar extinction coefficient at the UV-peak maximum of the specific drug molecules and the weight of the hydrochloride form of drug. A known weight of Sodium form of drugs was dissolved in 100 mL distilled water in a separating funnel to which 20mL of 0.1M hydrochloric acid solution and dichloromethane were added and extraction was carried out immediately. This extraction technique was rapidly repeated four times using fresh 20 mL of dichloromethane each time. The portions of dichloromethane extracted were transferred to a beaker. Anhydrous sodium sulphate was used to eliminate the water. A 100 mL solution of dichloromethane was prepared. Since medicines degrade in acidic or basic solutions, the extraction operation was completed in as little as 10-15 minutes. The drug concentration was determined using the weight of the dissolved Sodium form of the drug and the published molar extinction coefficient at the UV-peak maximum of that particular medication. The above approach was used to treat the drug's mesylate form.

Thermo Electronics Unicam UV-500 recording double beam spectrophotometer with a grating of 0.2 nm band width and temperature regulated cells (water peltier system) with an accuracy of + 1 0C was used to record all UV and visible spectra. The spectra were recorded using matched quartz quvettes of 1.0, 0.5, and 0.1 cm with air tight teflon lids. The ^{1}H, ^{13}C and ^{11}B percentage (%) natural abundance of nuclei are 99.98, 1.108, 80.42 respectively. NMR spectra was recorded at NMR Research Centre, Andhra University, Visakhapatnam, using Bruker AV-400 multinuclear NMR spectrometer. The ^{1}H and ^{13}C chemical shifts (δ) were measured relative to Me_4Si and ^{11}B shifts were with reference to $Et_2O.BF_3$ standards respectively.

Table 1Details of the selected anticancer drugmolecules (donors)

Name of Compound	Structure of Compound	Molecular Formula	M.W (g/mol.)	M.P (^{0}C)	CAS No

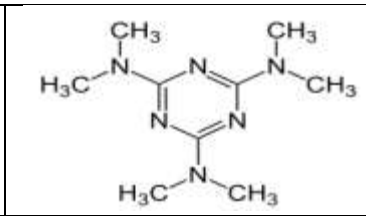
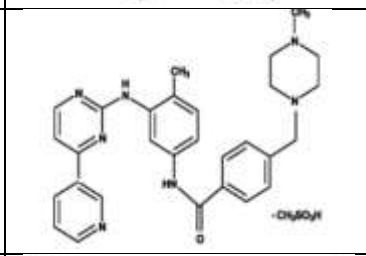
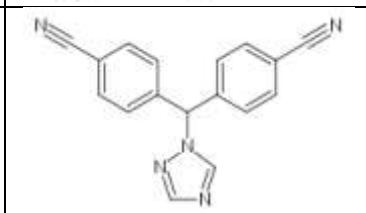
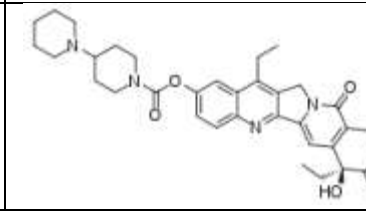
Altretamine		C9H18N6	210.2	172-174°C	645-05-6
Imatinib mesylate		C29H31N7O	589.7	226 °C	220127-57-1
Letrozole		C17H11N5	285.3	184 - 185°C	112809-51-5
Irinotecan HCl		C33H38N4O6	586.6	223 °C	100286-90-6

Table 2 Details of selected proton pump inhibitor drug molecules (donors)

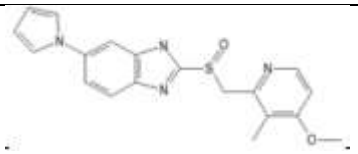
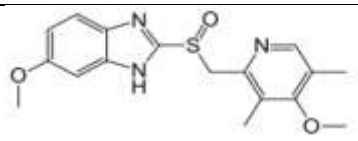
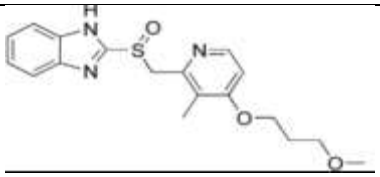
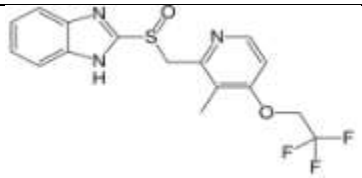
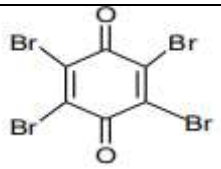
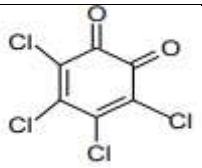
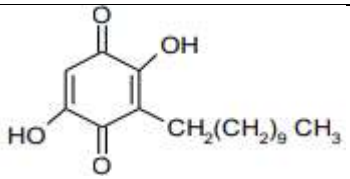
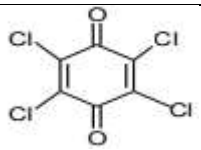
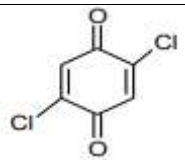
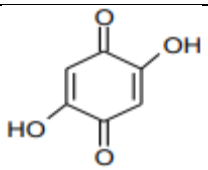
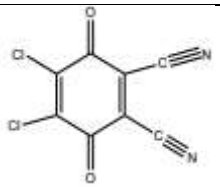
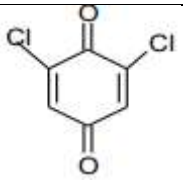
Name of the Compound	Structure of Compound	Molecular Formula	M.W (g/mol.)	M.P (^{0}C)	CAS No
Ilaprozole		C19H18N4O2S	366.1	150-155 °C	172152-36-2
Omeprazole		C17H19N3O3S	345.4	156 °C	73590-58-6
Rabeprazole sodium		C18H21N3O3S	359.4	140-141°C	117976-90-6
Lansoprazole		C16H14F3N3O2S	369.3	178-182 °C	103577-45-3

Table 3 Details of selected acceptors

σ- Acceptor		
S.No.	Name of compounds	Structure of compound
1	Iodine	I_2

π-Acceptors		
2	Bromanil	
3	o-Chloranil	
4	2,5-Dihydroxy-3-undecyl-2,5- cyclohexadiene-1,4-dione(Embelin)	
5	p-Chloranil	
6	2,5-Dichloro-pbenzoquinone	
7	2,5-Dihydroxy-pbenzoquinone	
8	2,3-Dichloro-5,6-dicyano-1,4- benzoquinone	
9	2,6-Dichloro-pbenzoquinone	

RESULTS AND DISCUSSION

The experimental details are as presented in chapter II. All experiments were conducted at room temperature (27 ^{o}C).

ANTICANCER DRUGS

When a drug, e.g. imatinib is mixed with an acceptor 2, 5-DHPBQ in dichloromethane solvent an intense colour developed and remained stable for about ten minutes (Fig 1). The acceptor was maintained, in the all the cases, in excess of the drugs concentration to ensure a 1:1 complex. The mixture shows an absorption maximumat 486 nm. The absorbance was constant for the actual period of measurements. The new transition was not present in either donor or acceptor. No bandswere present due to formation of radical ions of the acceptor. The 485 nm band was therefore assigned tentatively to a charge transfer from the drug to an acceptor.

A plot of the absorbance with concentration of drug, imatanib is linear in the range 30-200 ppm (Fig 2)

showing the validity of Beer's law. Similar results were obtained with other anticancer drugs. The data for altretamine, imatinib and irinotecan areshown in tables 4 to 5 and 6. Since the interaction of letrozole with π-acceptors is weak no investigation has been carried out to determine letrozole by spectrophotometric method.

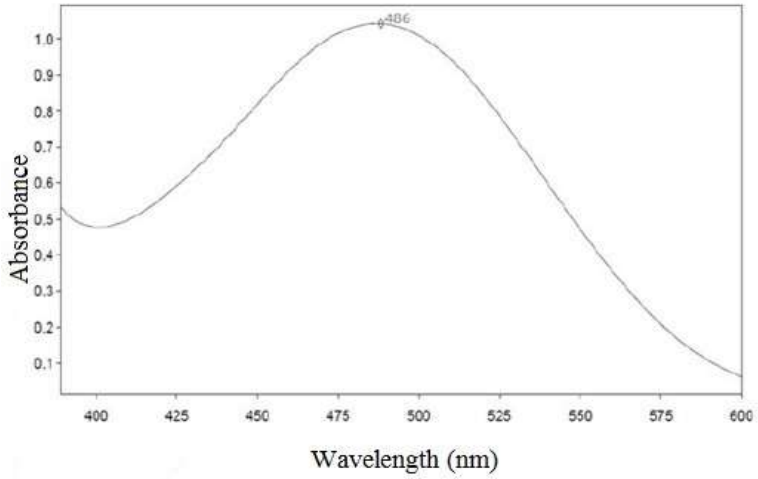


Fig 1 CT bandposition for imatinib -2, 5-DHPBQcomplex in CH_2Cl_2

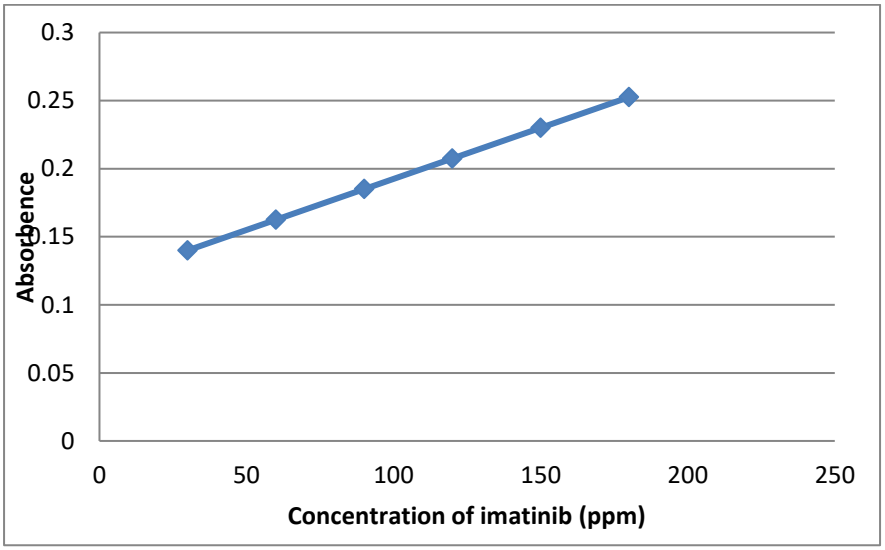


Fig 2 Beer's law plot of imatinib with 2, 5 DHPBQ in CH_2Cl_2

Table 4 Determination of altretamine with different π-acceptors.

S.No.	Acceptor	λmax (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	463	82	82-700
2	p-Chloranil	518	196	196-1200
3	Bromanil	523	171	171-1200
4	2,5-DHPBQ	483	51	51-360
5	2,5-DCPBQ	467	62	62-480

Note: Time required for stable complex formation is: 2 to 5 minutes

Table 5 Determination of imatinib with different π-acceptors

S.No.	Acceptor	λmax. (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	462	103	103-900
2	p-Chloranil	451	204	204-1200
3	Bromanil	460	162	162-1000
4	2,5-DHPBQ	485	32	32-200
5	2,5-DCPBQ	535	31	31-220

Note: Time required for stable complex formation is: 2 to 5 minutes.

Table 6 Determination of irinotecan with different π-acceptors

S.No.	Acceptor	λmax. (nm)	LOQ|ppm)	Linear dynamic range (ppm)
1	Embelin	505	64	64-420
2	p-Chloranil	534	84	84-700
3	Bromanil	423	92	92-800
4	2,5-DHPBQ	498	24	24-300
5	2,5-DCPBQ	486	55	55-350

Note: Time required for stable complex formation is: 2 to 5 minutes.

It is interesting to note, that all the anti cancer drugs except letrozole with 2, 5- DHPBQ and 2,5-DCPBQ show a dynamic range in low ppm range, the haloquinone acceptors do better in the high concentration ranges.

PROTON PUMP INHIBITORS

When a drug, e.g. ilaprazole is mixed with an acceptor embilin in dichloromethane solvent an intense colour developed and remained stable for about ten minutes Fig 3. The acceptor was maintained, in the all the cases, in excess of the drugs concentration to ensure a 1:1 complex. The mixture shows an absorption maximum at 501 nm. The absorbance was constant for the actual period of measurements. The new transition was not present in either the donor or acceptor. The 501 nm band is therefore due to a charge transfer from the drug to an acceptor. No further reaction took place.

A plot of the absorbance with concentration of drug, ilaprazole in the range 50- 450 ppm is shown in Fig 4. The plot is linear, showing the validity of Beer's law. Similar results were obtained with other Proton Pump Inhibitors. The data for ilaprazole, omeprazole, rabeprazole, lansoprazole, pantoprazole and ranitidine are shown in tables 7 to 12.

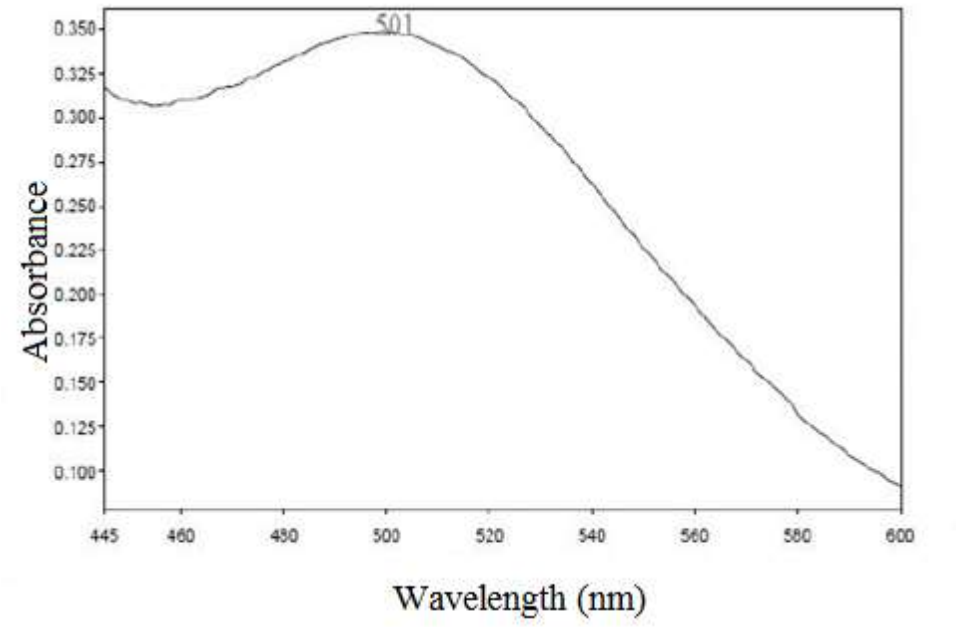


Fig 3 CT band position for ilaprazole- embilin complex in CH_2Cl_2

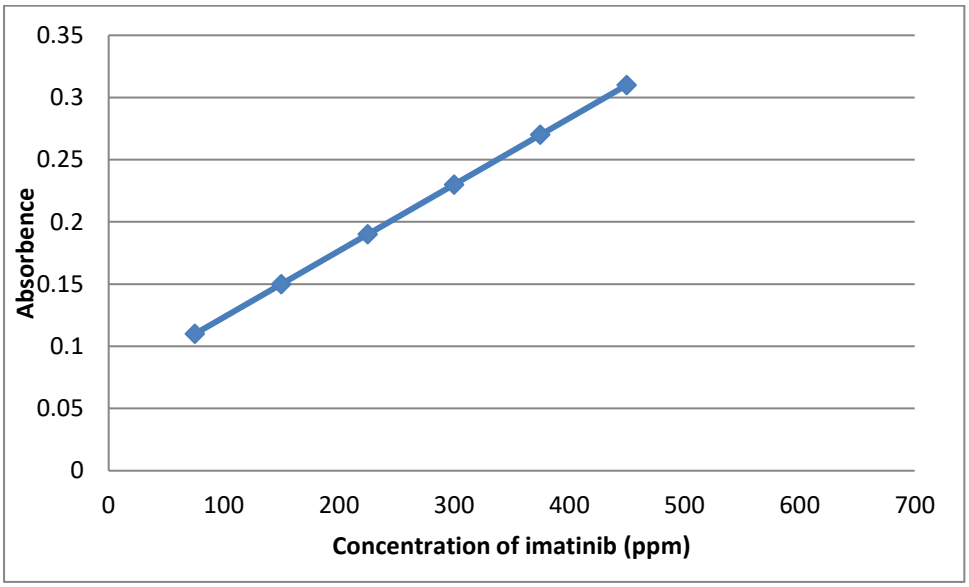


Fig 4 Beer's law graph of ilaprazole with 2, 5 DHPBQ in CH_2Cl_2.

Table 7 Determination of ilaprozole with different π-acceptors.

S.No.	Acceptor	λmax. (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	502	41	41-250
2	p-Chloranil	524	85	85-700
3	Bromanil	425	35	35-200
4	2,5-DHPBQ	497	51	51-480
5	2,5-DCPBQ	407	45	45-200

Note: Time required for stable complex formation is: 2 to 5 minutes.

Table 8 Determination of omeprazole with different π-acceptors.

S.No.	Acceptor	λmax. (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	497	91	91-600
2	p-Chloranil	428	94	94-700
3	Bromanil	414	52	52-450
4	2,5-DHPBQ	485	45	45-250
5	2,5-DCPBQ	477	35	35-250

Note: Time required for stable complex formation is: 2 to 5 minutes.

Table 9 Determination of rabeprazole with different π-acceptors

S.No.	Acceptor	λmax. (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	513	55	55-500
2	p-Chloranil	514	96	96-700
3	Bromanil	452	75	75-600
4	2,5-DHPBQ	405	67	67-550
5	2,5-DCPBQ	445	43	43-300

Note: Time required for stable complex formation is: 2 to 5 minutes.

Table 10 Determination of lansoprazole with different π-acceptors

S.No.	Acceptor	λmax. (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	493	22	22-140
2	p-Chloranil	405	32	32-200
3	Bromanil	431	23	23-140
4	2,5-DHPBQ	406	24	24-200
5	2,5-DCPBQ	448	13	13-70

Note: Time required for stable complex formation is: 2 to 5 minutes.

Table 11 Determination of pantoprazole with different π-acceptors

S.No.	Acceptor	λmax. (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	488	18	18-140

2	p-Chloranil	405	38	38-280
3	Bromanil	405	25	25-160
4	2,5-DHPBQ	404	36	36-240
5	2,5-DCPBQ	483	23	23-140

Note: Time required for stable complex formation is: 2 to 5 minutes

Table 12 Determination of ranitidine with different π-acceptors

S.No.	Acceptor	$\lambda_{max.}$ (nm)	LOQ (ppm)	Linear dynamic range (ppm)
1	Embelin	457	15	15-140
2	p-Chloranil	541	75	75-500
3	Bromanil	554	52	52-350
4	2,5-DHPBQ	481	25	25-180
5	2,5-DCPBQ	493	21	21-180

Note: Time required for stable complex formation is: 2 to 5 minutes

It is interesting to note, that the all proton pump inhibitors with 2, 5-DHPBQ and 2, 5-DCPBQ show a dynamic range in low ppm range, the haloquinone acceptors do better in the high concentration ranges.

CONCLUSIONS

The author observed that irinotecan, imatinib, pantoprazole, lansoprazole, carvedilol, irbesartan and valsartan gave intense colours with all the five selected acceptors. Using this, methods havebeen developed for spectrophotometric determinationof the selected drugs. As reported earlier the interaction of letrozole and azelnidipine with π-acceptors are weak i.e., they form weak complexes. So, for their interactions high concentrations the drugs are needed. So, the author has not carried out analysis of these two drugs.

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