Journal of Bioanalysis & Biomedicine

Sultana et al., J Bioanal Biomed 2013, 5:5
DOI: 10.4172/1948-593X.1000092

Research Article Open Access

Synthesis and Spectrophotometric Determination Ibuprofen Charge Transfer Complexes with P-Chloranil, 7,7,8,8-Tetracyanoquinodimethane, Bromothymol Blue, Methyl Orange and Picric Acid

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Abstract

Three simple, sensitive and inexpensive spectrophotometric methods have been described for the assay of ibuprofen in bulk drugs and pharmaceutical formulations. The developed methods are based on the formation of colored charge transfer complexes of ibuprofen with p-chloranil, 7,7,8,8-tetracyanoquinodimethane, bromothymol blue, methyl orange and picric acid in acetonitrile as solvent. These newly formed complexes were found to absorb at 438, 394, 403, 418, 374 nm respectively. Optimizations of various experimental conditions are described. Beer's law obeyed in the concentration range6-54, 2-24, 4-28, 3-21 and 4-28 μgmL^{-1} with correlation coefficient >0.998 in each case and lower limit of detection values were 76, 90, 234, 63 and 189 ng mL^{-1}, respectively. The association constants and standard free energy changes were studied using Benesi-Hildebrand plots. Oscillator's strength, ionization potential and energy of complexes in the ground state for all the complexes have been calculated. For further confirmation, solid charge transfer complexes were synthesized and characterized by IR and ^{1}H-NMR spectroscopy. The applicability of the method was demonstrated by the determination of studied drugs in commercial tablets with satisfactory results. No interference from excipients was observed in the formulations.

Keywords: Charge transfer complexes; ibuprofen; π-acceptors; dyes; Benesi-Hildebrand plots

Introduction

Ibuprofen (IBU) (Figure 1), 2[4-(2-methyl propyl) phenyl] propanoic acid, is member of non-steroidal anti-inflammatory drug (NSAID), known to relief symptoms of arthritis, primary dysmenorrhea, fever and also possess mild antiplatelet effect. It is useful in sepsis-induced acute pneumonia [1], in retarding metastases of mammary carcinoma [2] and in preventing oxidative lesions of lungs caused by phosgene [3]. High doses of ibuprofen slow down the evolution of lung disease [4]. It also protects prostaglandin H synthase of human endothelial cells from hydrogen peroxide [5].

Charge transfer complexes are intensively studied because of the unique nature of interaction between donor and acceptor species. This type of complexation is widely applied since last decade to analyze and characterize many of organic compounds like carboxylic acids [6], amines [7] and so on. These are of great importance for determining a number of parameters like ionization potential [8], dipole moment [9], oscillator's strength [10] and resonance energy [11]. They are known to take part in many chemical reactions like addition, substitution and condensation reaction [12,13]. These complexes can be used as photo catalysts [14] and dendimers [15]. 2,3,5,6-tetrachloro-1,4-benzoquinone (p-chloranil) (CHL), 7,7,8,8-tetracyanoquinodimethane (TCNQ), bromothymol blue (BTB), methyl orange (MO) and picric acid (PA) are known to behave as electron acceptors and result in charge-transfer complexation and radical anions formation with a variety of electron donors [16-19].

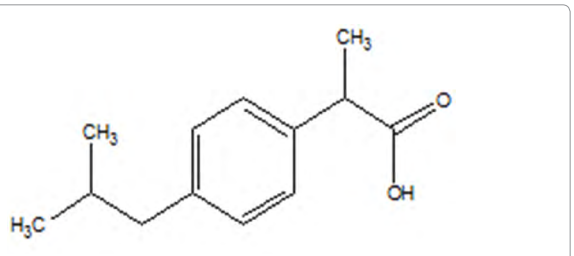

Figure 1: Ibuprofen.

There are several methods reported for the determination of IBU in pharmaceutical formulations and body fluids including chromatographic [20], spectrophotometric [21], spectrofluorimetric [22] and electrochemical methods [23]. Research on IBU have also been carried out in our laboratory by our research colleagues and a number of methods have been reported for its determination [24-28]. Present investigation aims to describe simple, fast and accurate spectrophotometric methods based on the interaction between IBU as donor and CHL, TCNQ, BTB, MO and PA forming colored CT complexes rapidly, which absorb radiation in the visible region. The optimum reaction conditions of the developed methods have been established, besides, the oscillator strength (f), dipole moment (μ), ionization potential (I_p), energy of CT complex (E_{CT}) and resonance energy (R_N) were evaluated. The association constant (K_c) and standard free energy changes (ΔG°) have also been determined. The solid complexes were synthesized and then characterized by IR and ^{1}H NMR spectroscopy. The excipients of formulations did not found to interfere in the assay of IBU in pharmaceutical formulations.

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Received October 26, 2013; **Accepted** November 26, 2013; **Published** November 29, 2013

Citation: Sultana N, Saeed Arayne M, Ali SN (2013) Synthesis and Spectrophotometric Determination Ibuprofen Charge Transfer Complexes with P-Chloranil, 7,7,8,8-Tetracyanoquinodimethane, Bromothymol Blue, Methyl Orange and Picric Acid. J Bioanal Biomed 5: 122-129. doi:10.4172/1948-593X.1000092

Experimental

Materials

Pure IBU was obtained from Abbott laboratories (Pakistan) Ltd and pharmaceutical formulation Brufen®200 mg was purchased from the local pharmacy (Karachi, Pakistan). CHL and TCNQ were purchased from Merck Schuchardt OHG, Darmstadt, Germany, MO and BTB were purchased from Merck (Darmstadt, Germany) and PA was purchased from Sigma Aldrich Chemie GmbH. Analytical grade acetonitrile was used throughout the research.

Instruments

Electronic spectra of IBU and its complexes were recorded in the region 200-800 nm using Shimadzu 1800 double beam UV–visible spectrophotometer version 2.32 software using quartz cells of 1.0 cm path length. The FT-IR spectra were obtained from KBr discs using Shimadzu Prestige-21200VEC version 1.2 software and ^{1}H NMR spectra were measured on BrukerAMX 500MHz spectrophotometer using TMS as internal standard and MeOD as solvent.

Standard solutions

A stock standard solution of 100 μgmL^{-1} was prepared by dissolving pure 10 mg of IBU in 100 mL acetonitrile. Working standard solutions were prepared by suitable dilutions of stock standard solution with same solvent. Solutions of 1000 μgmL^{-1} CHL, TCNQ, BTB, MO and PA were prepared fresh daily in the same solvent.

General procedure

Into different series of 10 mL volumetric flasks, aliquots of IBU solutions were transferred to get final concentration ranges 6-54, 2-24, 4-28, 3-21 and 4-28 μgmL^{-1} for CHL, TCNQ, BTB, MO and PA respectively. To each flask, 1 mL of 1000 μgmL^{-1} respective reagents was added.The colored CTC of IBU with CHL and TCNQ were formed immediately, whereas to attain complete complexation of IBU with other reagents, the solutions were vortexed for 5 minutes at room temperature (25°C). The volumes of flasks were brought to mark to get the above concentrations by acetonitrile and absorbance was measured against reagent blank treated similarly. Standard calibration graph was prepared by plotting absorbance of CTC against concentration of IBU.

Pharmaceuticals formulations

Twenty tablets of Brufen® were finely triturated into pestle and mortar. The powder equivalent to 10 mg mL^{-1} was dissolved in100 mL acetonitrile and shaken well for proper mixing. This solution was allowed to stand for 30 min and then sonicated for complete solubilization of drugs. The contents were filtered to separate the insoluble excipients and volume was completed with same solvent to get the solution of 1000 μg mL^{-1} IBU. The procedure was followed as described under the general procedure.

Synthesis of solid CT complexes

Equimolar quantities (1:1) of IBU and CTC agents were dissolved in 10 ml acetonitrile and refluxed on a water bath for 1.5 hrs. The reaction was continuously monitored by TLC using methanol and chloroform (9:1) solvent system. When all the reactants changed into product, they were collected by filtration and excess solvent was evaporated to dryness. The resultant solid material was thoroughly washed to remove the remaining traces of reactant. These materials were then dissolved and re-crystallized in acetonitrile. Pure CT complexes were characterized by UV-visible, FT-IR and ^{1}HNMR spectroscopy.

Results and Discussion

Strategy to develop and design the proposed method

The proposed method was designed to develop charge transfer complexation reaction between IBU as donor and CHL, TCNQ, BTB, MO and PA as acceptors. The absorbance of formed CT complexes was measured by UV/visible spectrophotometer. Selection of drug was based on its protective and therapeutic effect [29], where as complexing agents CHL, TCNQ, BTB, MO and PA are reported to form CT complex instantaneously [Repeat]. The mechanism of reaction is based on the transfer of electron from electron rich donor having lone pair of electron to electron deficient acceptors, which further dissociates due to high ionizing power of the polar solvent, and leads to the formation of radical ions. The proposed reactions are illustrated in scheme 1.

Reaction and spectral characteristics

The structure of IBU marks its acidic nature which suggests the possibility to treat IBU with basic compounds or acceptors. IBU shows maximum absorbance at 220 nm in the UV region and does not absorb in visible region where as acceptors/dyes added for complexation showed insignificant absorbance. IBU gives red, bluish green, green, red and yellow coloration with CHL, TCNQ, BTB, MO and PA respectively. These colorations are not associated with any of the reactants. The newly formed complexes exhibit absorption bands at 438, 394, 403, 418 and 374 nm respectively. Their electronic absorption spectra are shown in Figure 2.

Optimization of reaction conditions

Optimum conditions necessary for quick CT formation were established by investigating a number of parameters and observing their effect on absorbance of the colored product. Solvents like acetonitrile, methanol and ethanol were tested, in which all the drugs and acceptors showed absorbance at almost similar wavelength, though the molar absorptivity values were higher in acetonitrile solvent. The effect of reagent was measured by taking constant volume of drug and varying the amount of reagent. It was established that there was no effect of increasing volume of reagent above 1.0 mL of 1000 μg mL^{-1}. The optimum reaction time was determined by monitoring the absorbance of the developed colored complex at different time intervals at ambient temperature (25 ± 5°C) for all the reagents. Complete color development was attained instantaneously for CHL and within 5 min for all the other reagents. The complexes were found to be stable for 24 hr at -20°C. Optimum reaction conditions are summarized in Table 1.

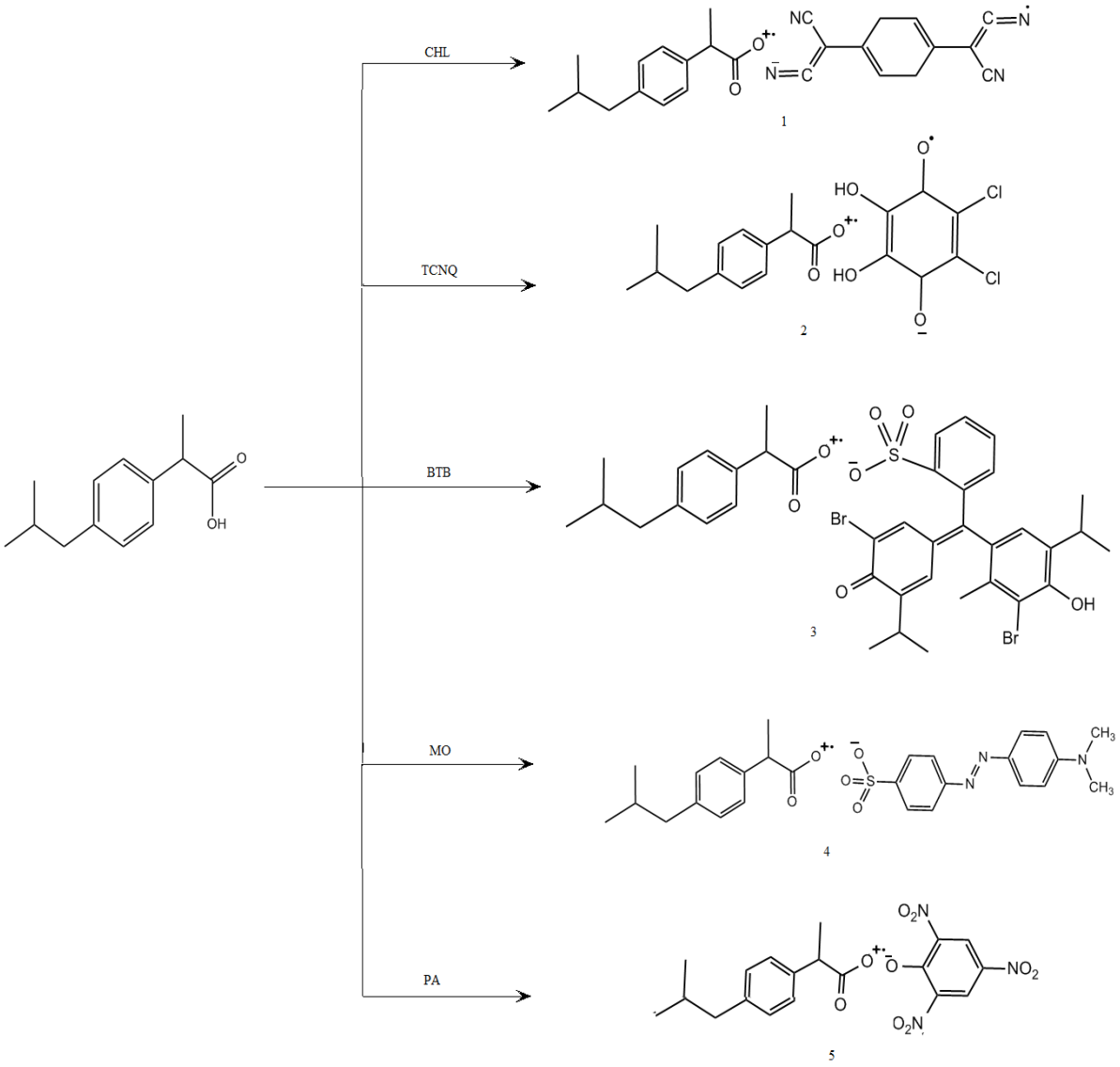
The composition of CT complexes of IBU with acceptors was determined spectrophotometrically by applying

Stoichiometric relationship

Job's method [30] using equimolar solution. Into eleven volumetric flasks of 10 mL capacity, donor and acceptor were mixed in the ratio of 0:10, 1:9…… 10:0 and allowed to stand for 5 min. for complete complexation. The absorbance was measured and the graph plotted between mole fraction vs. absorbance. In both cases, mole fraction value indicated that the CT interaction of ibuprofen occurs on equimolar basis (1:1) (Figure 3).

Method validation

Linearity: Under the described experimental conditions, calibration curves were constructed between concentration of ibuprofen verses



Scheme 1: Reaction pathway of IBU and its complexes with (1) CHL, (2) TCNQ, (3) BTB, (4) MO and (5) PA complexes.

absorbance of complexes, which were found to be linear in the Beer's law limits of 6-54, 2-24, 4-28, 3-21 and 4-28 μgmL^{-1} for CHL, TCNQ, BTB, MO and PA respectively. Linear regression equation, slope, intercept, correlation coefficient, standard error and standard error of estimate are given in Table 1. Further, molar absorptivity values were calculated for each method. It was established that the molar absorptivity of IBU complexes with CHL<TCNQ<PA<BTB<MO.

Sensitivity: The sensitivity of method was determined according to ICH guidelines [31] using formulae;

LLOD=3.3 S/b

LLOQ=10 S/b

where, S is the standard deviation of absorbance of blank solutions taken under the same analytical conditions and b is the slope of calibration curve. The LOD values were found to be 63<76<90<189<234 for MO, CHL, TCNQ, PA and BTB respectively and are shown in Table 1.

Precision: The assay was repeated six times at six concentration levels within the day to determine the precision of method. It is described in terms of percent relative standard deviation which was found to be <2% for each method showing the good repeatability. The data of % RSD for each complex is tabulated in Table 2.

Accuracy: The accuracy of developed method was indicated by means of excellent recovery of IBU in dosage formulation i.e. 98.44-102.02% and also by the percent relative error, calculated by formula;

% Err=(Found - Added)* 100/Added

The percent relative error was found to be less than 2.89% assuring the accuracy of method. The % recovery and % error values are presented in Table 3.

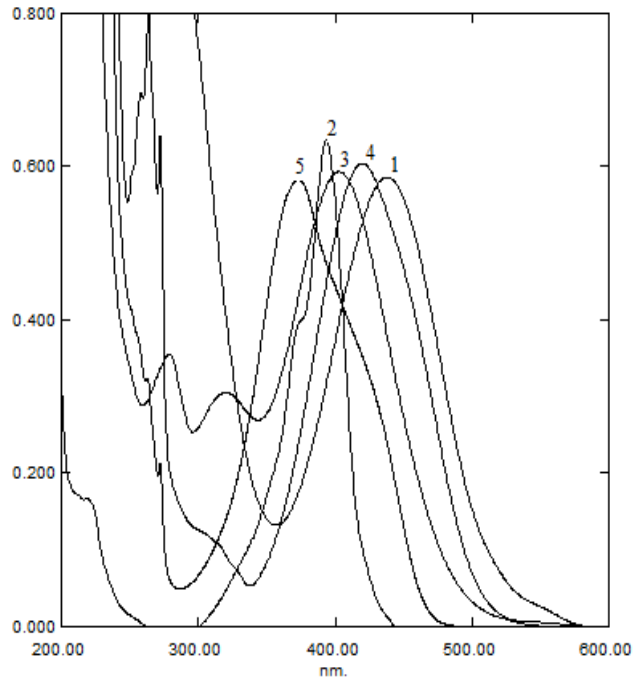


Figure 2: Absorption spectra of CTC complexes of IBU with CHL (1), TCNQ (2), BTB (3), MO (4) and PA (5).

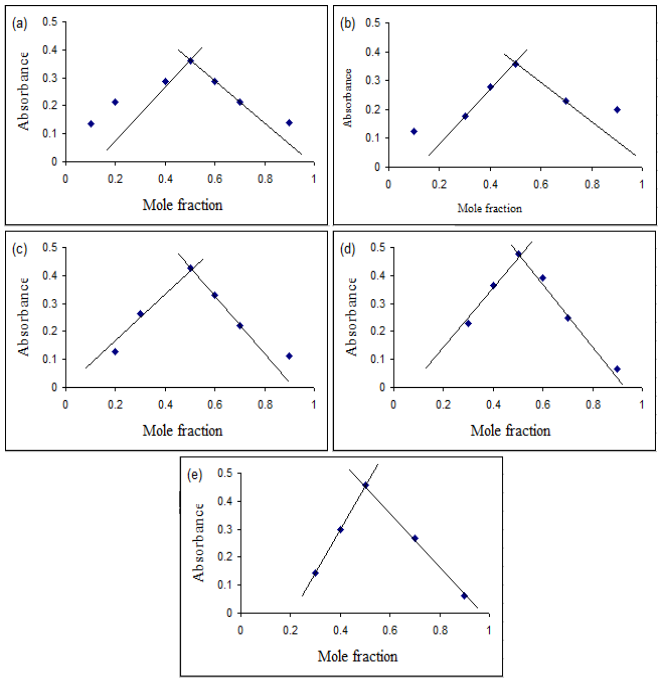


Figure 3: Job's plots for IBU with (a) CHL, (b) TCNQ, (c) BTB, (d) MO and (e) PA.

Effect of interference

For the evaluation of selectivity of the proposed method, the effect of standard excipients and fillers added into the formulations were tested by spiking active drug individually in lactose monohydrate (10%), magnesium stearate (10%), sucrose (10%), talc (10%) and starch (10%). It was found via good percentage recovery values (Table 4) that the presence of common excipients of tablet does not interfere in the determination of the ibuprofen.

Determination of oscillator strength (f) and transition dipole moment (μ)

The experimental oscillator strength (*f*) and transition dipole moment (μ) is calculated from CT spectra making use of equation (1) and (2) [9,10].

$$f = (4.319 \times 10\text{-}9)\ \varepsilon_{max}.\nu_{1/2} \quad (1)$$

$$\mu = 0.0958\ (\varepsilon_{max}.\nu_{1/2}/\nu_{max})^{1/2} \quad (2)$$

Where ε_{max} is the molar extinction coefficient at maximum absorbance, $\nu_{1/2}$ is the band-width at half absorbance in cm^{-1} and ν_{max} is wave number in cm^{-1}. The calculated values are reported in Table 5.

Determination of ionization potential (Ip) of free donor

The ionization potential (Ip) of free donor was calculated by applying the relationship given in equation (3) [8]

$$I_p = 5.76 + 1.53 \times 10^{-4}\nu_{CT} \quad (3)$$

Where ν_{CT} is the wave number in cm^{-1}corresponding to the CT band of complex formed between donor and acceptor. The values thus determined are given in Table 5.

Determination of resonance energy (R_N) and energy of charge transfer complex (E_{CT})

The resonance energy of CT complex in the ground state is determined by Brieglab and Czekalla as given below [11]:

$$\varepsilon_{max} = 7.7 \times 10^{-4}/\ [h\nu_{CT}/\ R_N - 3.5] \quad (4)$$

The energy of CT complexes was calculated using the following equation (4) [26]:

$$E_{CT} = 1243.667/\lambda_{CT} \quad (5)$$

Where λ_{CT} is the wavelength of CT band. The R_N and E_{CT} values are tabulated in Table 5.

Determination of association constants and standard free energy changes

More detailed examination was made for newly formed complexes, by applying Benesi-Hildebrand plot [32]. Absorbance was measured on cells with optimum 1 cm path length, values of formation constants (Table 5) are calculated by using equation 1. The concentration of donor $[D_o]$ was varied and that of acceptor $[A_o]$ was kept constant.

$$[A_o]/A = 1/K\ [D_o].\varepsilon + 1/\varepsilon \quad (6)$$

where, K is the association constant, A is absorbance, ε is molar extinction coefficient and $[A_o]$ and $[D_o$ are the initial concentrations ofacceptor and donor respectively ($[A_o] >> [D_o]$). In both cases, sharp straight lines were obtained on plotting the values of $1/D_o$ versus A_o/A, as shown in Figure 4. The data obtained throughout this calculation is given in Table 6.

The standard free energy changes (ΔG°) associated with IBU-CHL, IBU-TCNQ, IBU-BTB, IBU-MO and IBU-PA complexation reactions were calculated from the association constants by applying equation (2) [33]. The values of ΔG° for each complex are given in Table 5.

Parameters	IBU-CHL	IBU-TCNQ	IBU-BTB	IBU-MO	IBU-PA
λ_{max} (nm)	438	394	403	418	374
Linearity range µgmL^{-1}	6-54	2-24	4-28	3-21	4-28
Molar absorptivity	2.43 x 10^3	6.37 x 10^3	10.16 x 10^3	10.35 x 10^3	9.86 x 10^3
Slope	1.23 x 10^{-2}	2.86 x 10^{-2}	3.29x10^{-2}	4.06x 10^{-2}	2.84 x 10^{-2}
Intercept	-0.69 x 10^{-2}	1.49 x 10^{-2}	0.1598	0.1208	0.2114
Correlation coefficient	0.9995	0.9980	0.9981	0.9992	0.9983
LOD ngmL^{-1}	76	90	234	0.063	0.189
LOQ µgmL^{-1}	0.230	0.270	0.709	0.192	0.573

Table 1: Optimum conditions and analytical parameters.

IBU-CHL		IBU-TCNQ		IBU-BTB		IBU-MO		IBU-PA	
% Rec	% Err	% Rec	% Err	% Rec	% Err	% Rec	% Err	% Rec	% Err
100.72	-0.72	98.84	1.16	102.89	-2.89	100.44	-0.44	100.38	-0.77
99.95	0.05	100.14	-0.14	98.44	1.56	100.55	-0.55	100.04	-0.09
100.35	-0.35	99.61	0.39	98.48	1.52	100.25	-0.25	100.69	-1.37
100.36	-0.36	99.70	0.30	99.63	0.37	100.37	-0.37	101.15	-2.29
100.07	-0.07	103.32	-3.32	98.99	1.01	100.16	-0.16	100.14	-0.28
100.86	-0.86	102.02	-2.02	100.17		100.02	-0.02	100.00	100.00

Table 2: Accuracy of method.

IBU-CHL		IBU-TCNQ		IBU-BTB		IBU-MO		IBU-PA	
Conc	%RSD	Conc	%RSD	Conc	%RSD	Conc	%RSD	Conc	%RSD
6	0.36	2	0.75	4	0.24	3	1.02	4	0.54
12	0.03	4	0.59	8	0.61	6	0.29	8	0.06
18	0.18	6	0.32	12	1.59	9	0.14	12	0.97
24	0.21	8	0.20	16	1.14	12	0.18	16	1.60
36	0.05	12	0.16	20	1.28	15	0.10	20	0.20
48	0.46	18	1.69	24	0.39	18	0.10	24	0.79
54	0.12	24	1.30	28	0.98	21	0.53	28	0.55

Table 3: Precision of method.

Excipient	IBU-CHL	IBU-TCNQ	IBU-BTB	IBU-MO	IBU-PA
Lactose monohydrate	102.70	100.32	100.24	100.02	101.37
Cellulose	100.00	100.04	102.89	100.25	98.70
Sodium starch glycolate	99.10	101.03	100.90	98.33	100.84
Colloidal anhydrous	101.16	99.91	99.36	100.52	100.12
Magnesium	102.13	97.02	98.77	98.47	99.72
Sucrose	100.00	100.80	101.28	98.26	99.60
Talc	100.40	98.77	100.71	100.61	100.97
Starch	101.64	103.15	98.41	99.02	98.75

Table 4: Recovery of ibuprofen in presence of different excipients.

Complex	f	µ	Ip	E_{CT}	R_N	Kc x10^2 (lit/mol)	ΔG° (KCal)
IBU-CHL	1.15	10.37	9.25	2.84	0.81	2.52	-3.27
IBU-TCNQ	7.24	24.63	9.64	3.16	0.90	2.06	-3.15
IBU-BTB	4.82	20.32	9.56	3.09	0.88	6.47	-3.83
IBU-MO	4.86	20.77	9.42	2.98	0.85	3.50	-3.47
IBU-PA	6.98	23.55	9.85	3.33	0.95	3.09	-3.39

Table 5: Spectrophotometric results.

$$\Delta G^\circ = -2.303RT \log K_C \quad (7)$$

Where, ΔG° is the free energy change of the complex in KJ mol^{-1}, R is the gas constant (1.987 cal mol^{-1}deg^{-1}), T is temperature in Kelvin and K_c is the association constant of drug-acceptor complexes.

Spectroscopic studies

Spectroscopic studies of free donor and formed complexes were carried out to determine the structure of complexes. The IR spectra (Figure 5) were recorded using KBr discs and ^{1}H NMR spectra were measured at room temperature in MeOD. The infrared frequencies and band assignments are given in Table 7 and the chemical shift values for the detected peaks are mentioned in Table 8.

Conclusion

Spectrophotometric methods based on the charge transfer complex formation for the analysis of ibuprofen in its formulation have been

Complex	D (M) x 10^{-4}	A (M) x 10^{-3}	Abs	1/D x 10^{4}	A/Abs x 10^{-2}
IBU-CHL	0.29	4.08	0.0707	3.45	5.77
	0.58	4.08	0.1385	1.72	2.95
	0.87	4.08	0.2126	1.15	1.92
	1.17	4.08	0.2869	0.85	1.42
	1.46	4.08	0.3589	0.68	1.14
IBU-TCNQ	0.09	4.90	0.0628	11.11	7.80
	0.43	4.90	0.2793	2.33	1.75
	0.67	4.90	0.4288	1.49	1.14
	0.82	4.90	0.5217	1.22	0.94
	1.17	4.90	0.634	0.85	0.77
IBU-BTB	0.19	1.60	0.1949	5.26	0.82
	0.38	1.60	0.4257	2.63	0.38
	0.58	1.60	0.5920	1.72	0.27
	0.77	1.60	0.6943	1.30	0.23
	1.36	1.60	1.1468	0.74	0.14
IBU-MO	0.14	3.05	0.2549	7.14	1.20
	0.29	3.05	0.3634	3.45	0.84
	0.43	3.05	0.4778	2.33	0.64
	0.58	3.05	0.6033	1.72	0.51
	0.72	3.05	0.7346	1.39	0.42
IBU-PA	0.14	4.36	0.3002	7.14	1.45
	0.29	4.36	0.4579	3.45	0.95
	0.43	4.36	0.5748	2.33	0.76
	0.58	4.36	0.7457	1.72	0.58
	0.72	4.36	0.8841	1.39	0.49

Table 6: The values of $[A_0]$/Abs and 1/ $[D_0]$ for ibuprofen complexes.

IBU	IBU-CHL	IBU-JTCNQ	IBU-BTB	IBU-MO	IBU-PA	Assignment
3150	-	-	-	-	-	v(OH)
2954, 2922	2954, 2922	2954, 2922	2954, 2922	2954, 2922	2956, 2924	v(C-H)
2870	2870	2870	2870	2870	2873	
-	-	2729, 2630	-	-	-	v(N-H)
-	-	2341, 2374	-	-	-	v(C≡N)
1720	1718	1720	1720	1720	1710	v(C=O)
-	-	-	-	-	1683	v(NO_2)
1653	1628	1654	1654	1654	1628	v(C=C)
1558, 1508	1552, 1498	1558, 1508	1562, 1508 1548, 1419	1562, 1508 1548, 1419	1562, 1508 1548	v(C-H) deformation
-	-	-	-	1361	1342	v(C-N)
1321	1324	1323	1323	1323	1321	v(C-C)
1184, 1121	1158	1168	1184	1184	1151	v(C-O)
-	-	-	-	-	-	v(C-Br)
-	-	-	-	-	-	v(S=O)
970, 935	989, 935	970	935	939	918	v(C-H) in plane
848	854	866	866	848, 823	866	δ_{rock} CH_2
740, 680	752, 690	746, 634	779	779	783	δ(COO)
-	-	-	-	-	704	v(NO_2)
-	-	-	669	667, 630	-	v(S-O)
588, 522	572	588, 522	588, 522	574, 522	522	ring deformation

Table 7: Infrared frequencies and their assignments.

Assignment	IBU	IBU-CHL	IBU-TCNQ	IBU-BTB	IBU-MO	IBU-PA
(d, CH_3)	δ 0.87	δ 0.87	δ 0.89	δ 0.87	δ 0.87	δ 0.85
(d, $4CH_3$)	-	-	-	δ 1.00	-	-
(d, CH_3)	δ1.41	δ1.43	δ1.41	δ1.41	δ1.43	δ1.41
(m, CH)	δ1.78	δ1.83	δ1.81	δ1.78	δ1.78	δ1.77
(s, CH_3)	-	-	-	δ 1.97	-	-
(s, CH_3)	-	-	-	δ 2.13	-	-
(d, CH_2)	δ2.43	δ2.42	δ2.44	δ2.42	δ2.42	δ2.41
(s, $2CH_3$)	-	-	-	-	δ3.09	-
(m, 2CH)	-	-	-	δ3.28	-	-
(m, CH)	δ3.62	δ3.62	δ3.64	δ3.62	δ3.61	δ3.60
(m, arayl)	δ7.07	δ7.09	δ7.20	δ 6.94-7.51	δ 6.81-6.84 δ 7.79-7.94	δ 7.05-7.19 δ 7.38-7.71
(s, COOH)	δ11.0	-	-	-	-	-

Table 8: ^{1}H NMR spectra.

established with great sensitivity and accuracy. The obtained association constants values reflect the strength of complexation. Moreover, the oscillator's strength, ionization potential and energy of complexes have been calculated. The FT-IR and ^{1}HNMR spectra of solid synthesized complexes assure the interaction between donor and acceptor.

Acknowledgments

Mrs Saeeda Khowaja acknowledges Higher Education Commission of Pakistan, for the financial support to conduct research work in the form of scholarship through Indigenous Ph.D. 5000 Scholarship Program Batch IV.

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Citation: Sultana N, Saeed Arayne M, Ali SN (2013) Synthesis and Spectrophotometric Determination Ibuprofen Charge Transfer Complexes with P-Chloranil, 7,7,8,8-Tetracyanoquinodimethane, Bromothymol Blue, Methyl Orange and Picric Acid. J Bioanal Biomed 5: 122-129. doi:10.4172/1948-593X.1000092

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