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Polarographic and Pharmacological study of Zn (II)-Paracetamol complex.

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Abstract
The formation of complexes of paracetamol and Zn (II) was studied in aqueous media at pH 7.2±0.1 by polarography and spectroscopy. The polarogram indicated formation of complexes between paracetamol and Zn (II). Paracetamol produces a well-defined direct current polarogram and differential pulse polarogram in 1M Britton Robinson buffer (supporting electrolyte) at pH 7.2±0.1. The stoichiometry of the Zn (II)-Paracetamol complex is 1:1. Analgesic studies on the drug and its metal complex have been performed in albino mice. Revealing the complex to be more potent in analgesic activity compared to the parent drug.

Key Words
Paracetamol, DCP, DPP, tail flick method, zinc complex.

Introduction

The word acetaminophen and paracetamol both come from chemical names for the compound. Para-acetylaminophenol and para-acetylaminophenol[1,2]. In some contexts, it is simply abbreviated as APAP, for N-acetyl- para- aminophenol. Paracetamol is a widely used over-the counter analgesic (pain reducer) and antipyretic (fever reducer)[3,4,5]. It is commonly used for the relief if fever, headaches, and other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. In combination with non- steroidal anti- inflammatory drugs and opioid analgesics[6]. Paracetamol is used also in the management of more severe pain (such as cancer of postoperative pain)[7] Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties[,8,9] was quickly introduced in to medical practice under the name of antifebrin by A. Cahn and P. Hepp in 1886. Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para[1,4] pattern[10,11]. The amide group is acetamide (ethanamide), it is an extensively conjugated system, as the lone pair on the hydroxyl oxygen the benzene pi cloud, the nitrogen lone pair, the p-orbital on the carboxyl carbon, and the lone pair on the carbonyl oxygen are all conjugated[12,13].

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Experimental

Instrumentation

Polarography: All polarograms were recorded on Micro-processor (µp) polarographic analyzer model CL-362. An Elico digital pH meter model 335 was used for pH measurement. The polarographic cell consisted of a three-electrode assembly with a saturated calomel electrode (reference electrode) as working electrode.

Spectroscopy: The IR spectrum of solid complex was recorded using KBr pellets on a model 8400s IR-spectrophotometer Shimadzu, Japan.

Chemicals: Paracetamol chemical used for the present work were of CDH grade. Stock solutions of the reagents were prepared in requisite amount of distilled water.

Preparation of complex

Qualitative and quantitative studies on coumarin were carried out using direct current polarography (DCP) and differential pulse polarography (DPP). The pH of the test solution was adjusted to 7.2±0.1 to avoid a matrix effect for electrochemical behavior of Paracetamol. Paracetamol (0.230g) was dissolved in 100mL water and a set of solution containing varying concentration of paracetamol were prepared in 0.01M overall concentration of Britton Robinson buffer at pH 7.2±0.1. For study of stoichiometry and formation of the complex, Lingane's polarographic method was used, a simple method over the entire range of ligand concentration. Experimental solutions were prepared by keeping overall zinc (metal ion) and Britton Robinson buffer

concentration fixed at 0.2M and 1M respectively, while varying the ligand concentration from 0 to 15mM. The pH was adjusted to 7.2±0.1, and the solution was deaerated with purified H_2 gas. Polarogram was recorded keeping the initial potential set to -1100mV.

Synthesis of solid complex

A white solid was synthesized by refluxing 1:1 aqueous solution of zinc sulfate and paracetamol in water for about 4h. The complexation was marked by precipitation after reducing the volume to one fourth of the original volume. The product was filtered, washed, dried over P_4O_{10} and stored.

In-vivo study on Zn (II)-Paracetamol complex

Pharmacological study [Analgesic activity: Tail flick Method]

Screening of analgesic activity: - Analgesia is defined as a state of reduced awareness to pain and analgesics are substances which decrease pain sensation by increasing threshold to painful stimuli. The commonly used analgesic is aspirin, Paracetamol (non-narcotic type).Tail flick response method with albino rats was adopted for the evaluation of analgesic activity.

Procedure: - 12 rats both male and females were selected. The average weight was 100gm. They were divided in to four groups including one control group. Each rat was placed in the rat holder and tail was protruded out through the slot in the lid and placed on a hot wire (3 ampere). Time taken to flick the tail known as the normal reaction time was noted. Test dose 1.5mg/kg animal body weight was administered orally to albino rats of respective group excluding control group. Same response was again noted after subsequent intervals of 30,60,90 and 120 minute of administering the drug.

Results and Discussion

The direct current polarogram (DCP) and differential pulse polarogram (DPP) of the authentic sample solution of paracetamol in Britton Robinson buffer (1M) at pH 7.2±0.1, produced a well-defined polarographic wave/peak with $E_{1/2}$ / E_p= -1.18V/-1.20V vs SCE. Paracetamol is polarographically active in both acidic and basic environments.

Polarographic study of M:L complexation equilibrium

Both Zn (II) and its complex with paracetamol produce a reversible two-electron reduction wave in 1M Britton Robinson buffer at pH 7.2±0.1. Complex formation between Zn (II) and paracetmol (Supplementary Material) was revealed by the shift in half-wave potential and peak potential to a more negative value and decrease in the height of the diffusion current with gradual increase of the paracetamol concentration. Plots of $\Delta E_{1/2}$ (shift in the half wave potential). $\Delta E_{1/2} = (E_{1/2})_c - (E_{1/2})_s$ against log Cx (Logarithm of the concentration of the ligand) resulted in a linear plot (Figure 2), showing formation of a single complex in solution. Lingane treatment of the observed polarographic data revealed 1:1 Zn (II)-paracetamol complex with formation constant log β_1= 4.7.

IR spectral analysis of Zn (II)-Paracetamol Complex

On comparing the IR spectra of paracetamol and its Zn (II) complex, it was observe that the band at 1730 cm^{-1} due to C=O group in the spectrum of pure drug and this band disappear in the spectrum of its Zn (II) complex. The sharp –OH signal at 3620 cm^{-1} is observed in paracetamol. This band is shifted to 3639 cm^{-1} in the spectrum of Zn(II)-paracetamol complex, which confirms involvement of C=O and -OH in the complexation of Zn(II). Thus on the basis of polarographic and IR studies a tentative structure to 1:1, Zn (II)-paracetamol complex may be as under:

Paracetamol Zn(II)-Paracetamol Complex

Screening of analgesic activity

Analgesic activity of the complexes was measured by tail flick method using Analgesiometer. Doses were administered orally as suspension in distilled water. The activity was found to be in the following order Zn (II)-Paracetamol>Paracetamol (Parent drug). The observed analgesic results are tabulated below (Table-1).

Table 1: Screening data for analgesic activity of Paracetamol and its complexes with Zn (II).

S. No.	Group	Dose	Tail flick time in sec.					% Analgesic activity after 120 minutes.
			Normal (before dose)	After dose administration				
				30 min	60 min	90 min	120 min	
1	Control	-	6.4	6.4	6.2	6.2	6.2	-
2	Paracetamol (authentic drug)	1.5mg/kg	6.2	6.6	6.9	7.2	7.5	17%
4	Zn(II)-Paracetamol complex	1.5mg/kg	6.2	6.7	7.3	7.9	8.3	25%

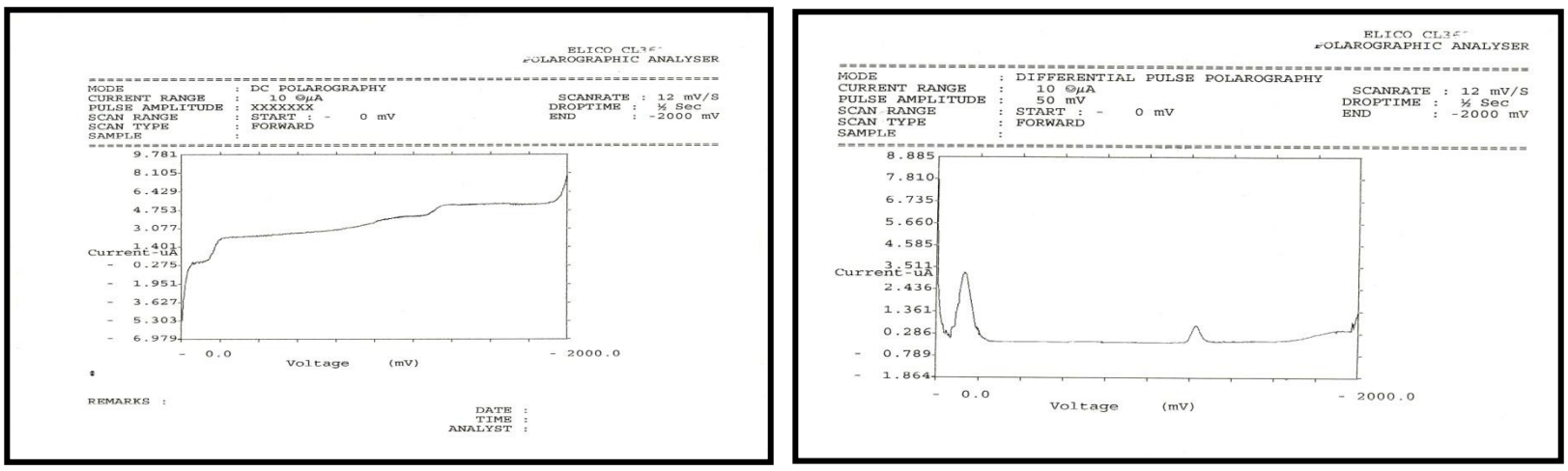

Figure 1: Direct current Polarogram and Differential pulse Polarogram of Zn (II) - paracetamol complex in Britton Robinson buffer (1M) at pH 7.2±0.1.

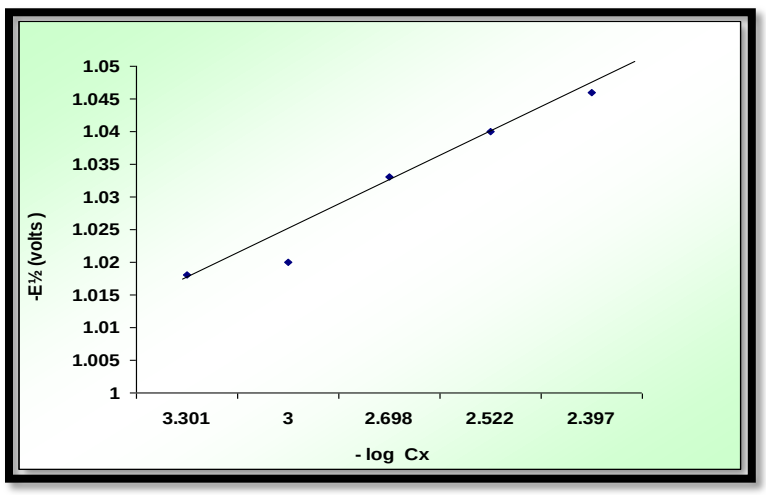

Figure 2: Zn (II) - Paracetamol Complex (Plot of $E_{1/2}$ vs log Cx)

Conclusion

The data show stoichiometric ratio of 1:1 for the Zn (II) paracetamol complex. The polarographic method is used for qualitative and quantitative analysis of paracetamol and is recommended for quality control in the drug industry. The increased potency of the complex may allow use as a potent analgesic drug.

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