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Complexation of Ciprofloxacin with Paracetamol and Zinc in Aqueous Medium

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Abstract

Concurrent administration of more than one drug is a common practice in medical science and in such case one drug may affect the pharmacology of another drug. Ciprofloxacin is a commonly used antibiotic in Bangladesh and frequently prescribed with paracetamol and zinc salt for concomitant use in patients suffering from infections. Therefore, the interaction of ciprofloxacin with paracetamol and zinc salt was studied *in vitro* at pH 1.2, 6.8 and 7.4 which are related to gastric, intestinal juices and blood, respectively. Analysis of drug-drug and drug-metal complexation was carried out by using UV/VIS spectrophotometer as well as the conductometric titration. It was observed that ciprofloxacin formed complex with paracetamol and zinc at pH 1.2.

Keywords: Ciprofloxacin; Paracetamol; Zinc sulfate; Drug-drug interaction; Drug-metal interaction; Complexation.

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1. Introduction

Hospitalized patients suffering from complicated conditions such as kidney / heart transplantation or failure, diabetes mellitus, hypertension, anemia, bone and lipid disorders and so on are frequently prescribed numerous medications. Concomitant use of a large number of medications may have an increased risk for drug interactions. Drug interactions are classified as pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions include those that result in additive or antagonistic pharmacological effects. Pharmacokinetic interactions involve induction or inhibition of metabolizing enzymes in

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the liver or elsewhere, displacement of drug from plasma protein binding sites, alterations in gastrointestinal absorption, or competition for active renal secretion [1, 2]. Therefore, drug interactions definitely alter the pharmacological effects. The effects of a moderate interaction may cause deterioration in the patient's clinical status, resulting in additional treatment, hospitalization, and/or an extended hospital stay. The effects of a major interaction are potentially life-threatening or can lead to permanent damage [3, 4]. Ciprofloxacin is indicated in the treatment of upper and lower respiratory infections, bone and joint, lung, urinary or digestive system, skin infections [5-8]. The drug inhibits DNA gyrase which is a type II topoisomerase, essential enzyme for forming DNA supercoils of bacteria [9, 10]. Paracetamol (Acetaminophen) is commonly used for the relief of pain, fever, headaches and other minor aches. It exhibited antipyretic action by acting on the hypothalamic heat-regulating centre and analgesic action by elevating the pain threshold [7, 9]. Zinc sulfate is used in the treatment of malnutrition, peptic ulcers and in the prevention of common cold [7, 9].

These drugs are indicated together to the patient sufferings from bacterial infections with fever, pain and weakness. So it has a chance of complexation among them during concomitant use. Therefore, we carried out the research work to have an idea about the concomitant use of these drugs. We evaluated the interactions by monitoring UV and conductometric titration analyses of ciprofloxacin with paracetamol and zinc sulfate at the ratio of 1: 1 at different pH. All the data showed interaction with ciprofloxacin.

2. Materials and Methods

2.1. *Apparatus*

UV spectrophotometer (Analytik Jena-SPECORD 205), FTIR (Shimadzu, Japan), conductometer (Hanna Instruments, USA), centrifuge machine were used for the analysis.

2.2. *Drugs and chemicals*

The working standards of ciprofloxacin and paracetamol with 99.10% and 99.6% potency, respectively were the kind gift of Healthcare Pharmaceuticals, Dhaka, Bangladesh. Potassium dihydrogen orthophosphate, orthophosphoric acid, potassium hydroxide, sodium hydroxide, hydrochloric acid (37%) were purchased from Active Fine Chemicals Ltd., Bangladesh. Zinc sulfate, sodium chloride, potassium bromide and heparin were purchased from local markets.

2.3. *Preparation of buffer solutions* [11, 12]

pH 1.2: To prepare 1 liter of pH 1.2 buffer, 2 g of sodium chloride and 0.1M HCl were taken in a 1000 mL volumetric flask and dissolved in 600 mL of distilled water. Finally the volume was made up to the mark with distilled water. The pH was adjusted to 1.2 by using HCl.

pH 6.8: To prepare 1 liter of pH 6.8 phosphate buffer, 6.8 g of monobasic potassium phosphate and 77 mL of 0.2M sodium hydroxide were taken in a 1000 mL volumetric flask and dissolved in 600 mL of distilled water. Finally the volume was made up to the mark with distilled water. The pH was adjusted to 6.8 by using HCl or NaOH as necessary.

*pH 7.4:*To prepare 1 liter of pH 7.4 phosphate buffer, 65.4 mL of 0.02M monobasic potassium phosphate and 289.7 mL of 0.001M dibasic sodium phosphate were taken in a 1000 mL volumetric flask and dissolved in 600 mL of distilled water. Finally the volume was made up to the mark with distilled water. The pH was adjusted to 7.4 by using dilute phosphoric acid.

2.4. ***Preparation of stock solutions***

Ciprofloxacin: 100 mL stock solution of 0.01M was prepared by dissolving 0.367g of ciprofloxacin HCl in demineralized water and made the volume up to 100 mL with the same solvent.

Paracetamol: 100 mL stock solution of 0.01M was prepared by dissolving 0.151g of Paracetamol in demineralized water and made the volume up to 100 mL with the same solvent.

Zinc sulfate: 100 mL stock solution of 0.01M was prepared by dissolving 0.287g of zinc sulfate in demineralized water and makes the volume up to 100 mL with the same solvent.

2.5. ***Methods*** [13, 14]

2.5.1. UV analysis

Aliquot of ciprofloxacin solution (10 mL) was taken in nine flasks and marked as 1 to 9. Same amount of previously prepared paracetamol was added in the flasks marked as 2, 5, 8 and zinc sulfate solutions was added in the flasks marked as 3, 6, 9. Then 15 mL of each of the buffers of pH 1.2, 6.8 and 7.4 were added to beakers marked as 1-3, 4-6, 7-9; respectively. The contents of each flask were mixed well and allowed to stand for few minute to complete the reactions. Then the absorbance was measured at the range of 190 to 400 nm. The experiment was repeated thrice.

2.5.2. IR analysis

Three beakers were taken and marked as 1, 2 and 3. 500mg of ciprofloxacin was taken in each beaker. Paracetamol (500 mg) and Zinc sulfate (500 mg) were added into beaker 2 and 3, respectively. Then 15 mL acidic buffer (pH 1.2) was added in each beaker and mixed well with glass stirrer for 5 to 10 min followed by heating for evaporation to

dryness by a water bath at below 60°C. After proper drying 2 mg samples from each of the beaker was taken out and individually prepared IR disc with 200 mg of dried KBr. Then the IR spectrums of the samples were recorded at the range of 400 cm^{-1} to 2000 cm^{-1}.

2.5.3. *Conductometric titration*

Conductometric titrations were done to detect the complex formation of ciprofloxacin with paracetamol and zinc as well as to find the molar ratios of the interacting species to the drug molecule in the complex. 40 mL of 0.00001M ciprofloxacin solution was taken in an 80 mL beaker and was titrated individually with gradual addition of 0.0001M solution of paracetamol and zinc by a pipette. Reversely 40 mL each of 0.00001M paracetamol and zinc were titrated with gradual addition of 0.001M ciprofloxacin under similar conditions. The conductance values (ms) were plotted against molar ratios between the two species in the system. The titrations curves showed break at the points of possible interaction. All titrations were performed with solutions adjusted to pH 1.2, 6.8, and 7.4.

3. Results and Discussion

zIn UV ciprofloxacin, the drug-drug (ciprofloxacin and paracetamol) and drug-metal (ciprofloxacin and zinc) mixture at the ratio of 1:1 were studied at the pH of 1.2, 6.8 and 7.4 at the range of 190 to 400 nm (Figs. 1-3). The absorption maxima of ciprofloxacin were found to be shifted when the paracetamol and zinc sulfate were mixed separately with ciprofloxacin HCl. For the mixture with paracetamol the characteristics absorbance of ciprofloxacin was found to be prominent change from 280 nm to 245 at the pH of 1.2 and 7.4 (Fig. 1).

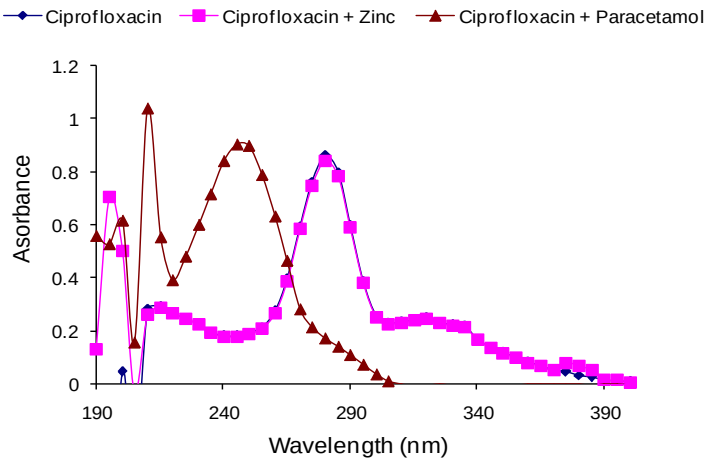

Fig. 1. UV spectrum of the interactions at pH 1.2.

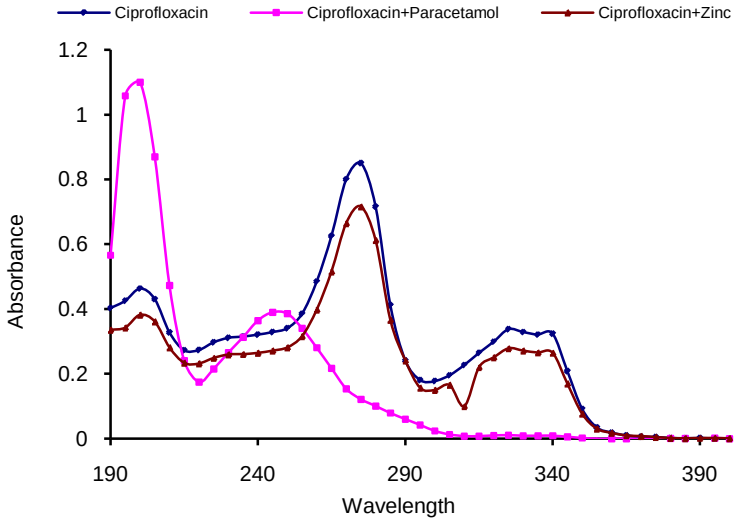

Fig. 2. UV spectrum of the interactions at pH 6.8

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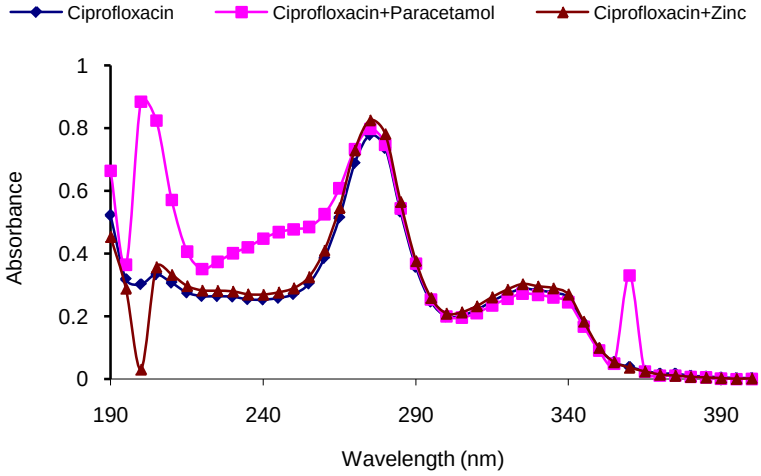

Fig. 3. UV spectrum of the interactions at pH 7.4.

In case IR observation of the interaction, the spectrums of the mixtures of ciprofloxacin with paracetamol and zinc showed some changes in comparison to the spectrum of ciprofloxacin itself (Figs. 4-6).

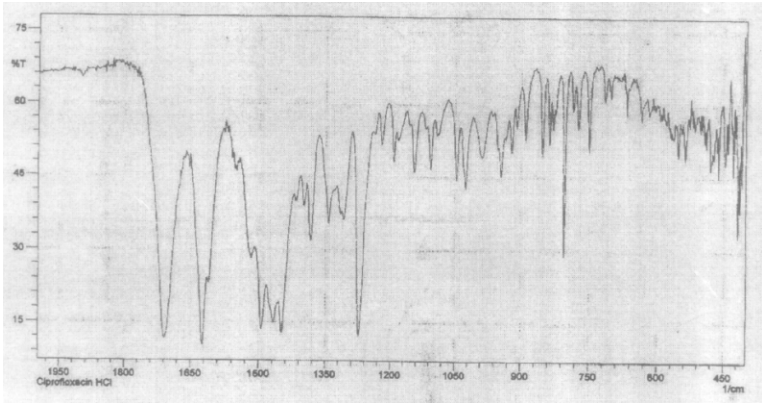

Fig. 4. IR spectrum of ciprofloxacin.

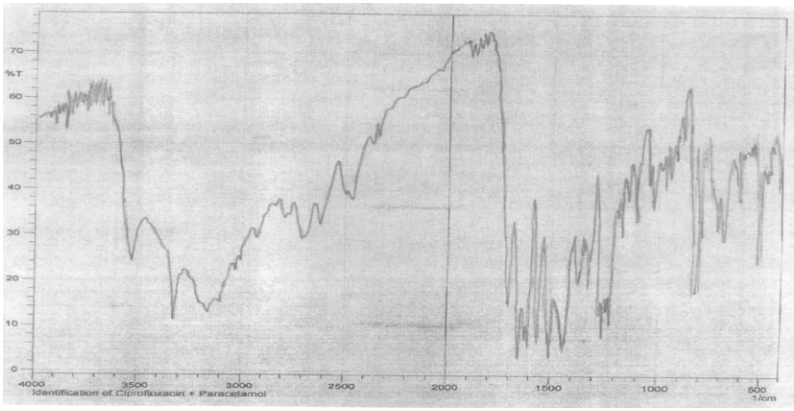

Fig. 5. IR spectrum of the mixture of ciprofloxacin and paracetamol

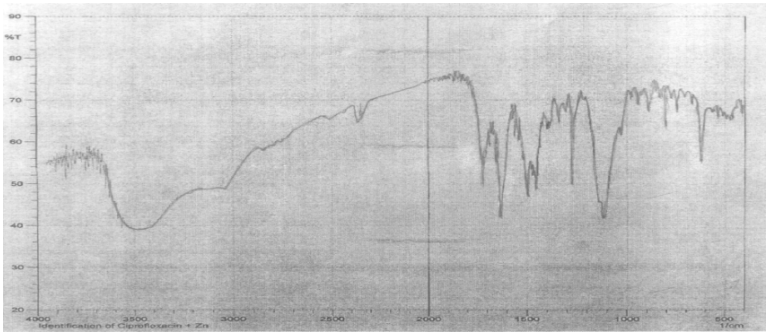

Fig. 6. IR spectrum of the mixture of ciprofloxacin and zinc.

The conductance of one species in solution may change due to interaction with other species. In this study, conductometric titration was carried out in demineralized water at different pH to find out the molar ratios at which complexation occurred. When ciprofloxacin was titrated with zinc and paracetamol individually at pH 1.2, a distinct break was observed at molar ratio 1:1 including few other breaks at different molar ratios corresponding to ciprofloxacin-zinc or ciprofloxacin-paracetamol complexes (Figs. 7 and 8).

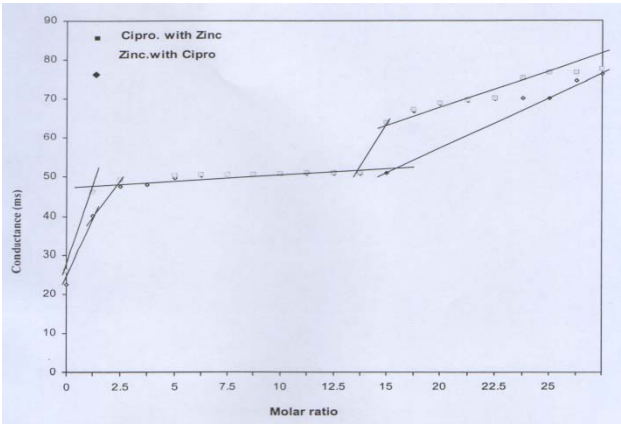

Fig. 7. Conductometric titration curve of ciprofloxacin with zinc and zinc with ciprofloxacin at pH 1.2.

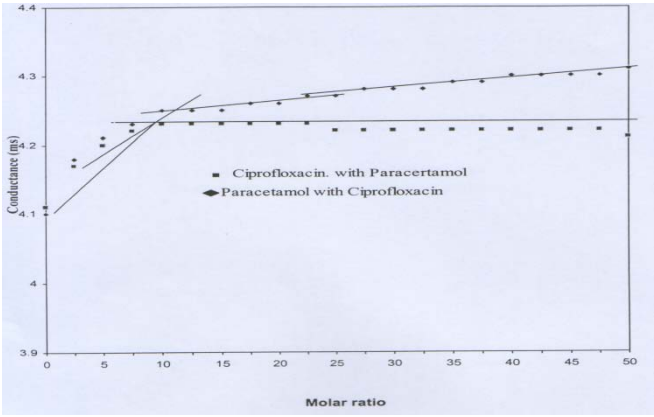

Fig. 8. Conductometric titration curve of ciprofloxacin with zinc and zinc with ciprofloxacin at pH 6.8.

The conductometric titration at pH 6.8 and 7.4 showed various breaks at different molar ratios. But there was no indication of the formation of stable ciprofloxacin-

paracetamol or ciprofloxacin-zinc complexes. Therefore, it was obvious that the conductometric titration showed stable complexes at pH 1.2. It has been found that along with stable complexes some unstable intermediates were also being formed between each of the two interacting molecules. But at pH 6.8 and 7.4 the situation became uncertain.

4. Conclusion

UV/VIS and IR spetrophotometric methods were used to analyze the drug content by measuring absorbance at the range of 190 to 400 nm and 400 cm^{-1} to 2000 cm^{-1}, respectively. The spectrum of ciprofloxacin and paracetamol was found to be different at pH 1.2 at the molar ratio of 1:1. The alteration in spectral pattern was considered as an interaction of ciprofloxacin with paracetamol.

References

1. B. Laurence, B. Donald, B. Iain and P. Keith, Goodman & Gilman's manual of pharmacology and therapeutics (McGraw-Hill Inc., New York, 2008) pp. 24-50.
2. M. R. Ahsan, M. Z. Sultan, M. A. Baki, M. A. Rahman1, M. A. Hossain, M. A. Hossain and M. S. Amran, Dhaka Univ. J. Pharm. Sci. **10** (2), 137 (2011).
3. F. Siraji, A. T. M. Z. Azam, M. S. Amran, J. N. Islam, F. M. Amjad, and M. A. Hossain, J. Sci. Res. **4** (1), 173 (2012). http://dx.doi.org/10.3329/jsr.v4i1.7599
4. D. E. Cadwallader, Biopharmaceutics and drug interactions, 3rd edn. (Raven press, New York, 1985) pp. 107-143.
5. United States Pharmacopoeia 30 - National Formulary 25 (USP 30 - NF 25), United States Pharmacopeial Convention, Rockville, MD, 2007.
6. British Pharmacopoeia (BP)-2009 (the Stationery Office, London, 2002).
7. S. C. Sweetman, Martindale: The complete drug reference, 34th edn. (Pharmaceutical Press, London, 2005).
8. N. M. Kassab, A. K. Singh, E. R. M. K. Hackmam and M. I. R. M. Santoro, Braz. J. Pharm. Sci. **41** (4), 507 (2005).
9. P. Beringer, Remington: The science and practice of pharmacy, Vol. II, 19th edn. (Mack Publishing Co., Easton, Pennsylvania, USA, 1995).
10. J. S. Wolfson and D.C. Hooper, Clin. Microbiol. Rev. **2**, 378 (1989). PMid:2680058 PMCid:358131
11. D. D. Perrin and D. Boyd, Buffers for pH and metal ion control (Science papers back, New York, 1974) pp. 44-64.
12. B. Bates, Determination of pH – Theory and Practice (Wily, New York, 1964) pp. 50-67.
13. A. I. Vogel, A Textbook of Quantitative Inorganic Analysis. 3rd edn. (Longmans, London, 1961) p. 93.
14. M. Ardon, J. Chem. Soc. 1811 (1957). http://dx.doi.org/10.1039/jr9570001811