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Ibuprofen with Sodium Chloride at pH 7.2 and pH 2.4, an *In Vitro* Interaction Study

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Abstract*—Ibuprofen is a important drug which is a nonselective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis. Its pharmacological effects are believed to be due to inhibition of cyclooxygenase-2 which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Ibuprofen is administered as a racemic mixture and causes vasodilation and depresses myocardial contractility and liver toxicity and kidney dysfunction. Sodium Chloride aqueous is an sodium salt with immune adjuvant activity. Sodium chloride is the salt most responsible for the salinity of sea water and of the extracellular fluid of many multicellular organisms. In the form of edible or table salt it is commonly used as a condiment and food preservative. Large quantities of sodium chloride are used in many industrial processes, and it is a major source of sodium and chlorine compounds used as feed stocks for further chemical syntheses. A second major consumer of sodium chloride is de-icing of roadways in sub-freezing weather. My research study was to investigate the in vitro complexation nature and strength of complex which may be formed due to interaction between Ibuprofen and Sodium Chloride at different pH (7.2 and 2.4) by some physical methods. It was observed that Ibuprofen gives a sharp peak at 272nm when Sodium Chloride mixed with Ibuprofen in 1:1 ratio the intensity of the peak of Ibuprofen change remarkably due to interaction. The Job's plot was obtained by plotting absorbance differences against the mole fraction of the each drug at pH 7.2 and 2.4. Ibuprofen forms strong 1:1 complexes with Sodium Chloride and V shaped curves indicate the formation of 1:1 complexes of Ibuprofen with Sodium Chloride. These may indicate strong kinetics of complexation between Ibuprofen with Sodium Chloride .The value of stability constant for the complexation of Ibuprofen with Sodium Chloride at pH 7.2 and 2.4 were obtained from the spectral data using Ardon's plot. The values of stability constants for the drug-metal system at pH 7.2 and 2.4 are 0.0332 and 0.1018 respectively. It was found that the stability constant for complexation of Ibuprofen & Sodium Chloride system is higher at higher pH then that of Ibuprofen and Sodium Chloride system at lower pH. It can be noticed that a careful consideration is needed during concurrent administration of Ibuprofen with Sodium Chloride*.

***Keywords*—** *Ibuprofen, Sodium Chloride,Interaction, UV Spectroscopy*.

I. INTRODUCTION

The mission of pharmacy is to improve public health through ensuring safe, effective and proper use of medications. The pharmacists supervises any patient to take a right drug for right time and right diseases. This is very important for pharmacists to know about biopharmaceutics[1]. A biopharmaceutical or medical product, biological, or biologic, is any pharmaceutical drug product manufactured in, extracted from, or semisynthesized from biological sources[2]. Modern biopharmaceutics is the relationship of the physico-chemical properties and in vitro type of the drug and drug product delivering the body under normal and pathologic conditions. Drug interaction can be defined as the modification of the effect of drug by the prior concomitant administration of another drug[5]. This action can be synergistic (when the drug's effect is increased) or antagonistic (when the drug's effect is decreased) or a new effect can be produced that neither produces on its own. It is possible that an interaction will occur between a drug and another substance present in the organism (i.e. foods or alcohol). Or in certain specific situations a drug may even react with itself, such as occurs with dehydration. [6]Drug-food interaction occur when a precipitation or over-the counter medication interacts or interferes with something you eat or drink that includes drug-nutrient interactions and the effect of a medication on nutritional status. [7]A drug-metal interaction refers to a modification of the expected drug response in the patients due to the exposure of the patients to any percent in the body or administered stimultaneously[8]. Ibuprofen was discovered in 1961 by Stewart Adams and marketed as Brufen. Ibuprofen from isobutylphenyl propanoi acid, is a nonsteriodal antiinflammatory drug used for treating pain, fever and inflammation. It may also be used to close a patent ductus arteriosusn a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour [9-10].

Aim of the Present Work

The purpose of the present study was to investigate the in vitro complexation and strength of complexes, which may be formed due to interaction of Ibuprofen with Sodium Chloride. The specific purpose was to observe and determine the atability of the complexes, which coulde be formed between Ibuprofen and Sodium Chloride at pH 2.4 and pH 7.2. To see the potentiation and activity of Ibuprofen by observation of absorption spectral, Job's spectrophotometric method of continuous variation and the Ardon's spectrophotometric method. To evaluate the influences of interaction of Ibuprofen can possibly open up a new avenue to formulate new dosage form of the drug chosen, as well as developing better combination systen of therapy.

II. MATERIALS AND METHODS

Preparation of Phosphate Buffer at pH 2.4:

To prepare this buffer 1000 ml of 0.01 M potassium dihtdrogen phosphate (Mol. Wt. 136.09) solution was

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prepared in a volumetric flask (solution A) and then 1000 ml of 0.05 M sodium chloride was prepared in another volumetric flask (solution B). In order to phosphate buffer of pH 2.4, approximately 500 ml of solution A was properly mixed with approximately 500ml of solution B. Finally the solution was adjusted at pH 2.4 by a pH meter.

Preparation of Ibuprofen:

10 ml. of 0.01x 10^{-3} M solution of Ibuprofen was prepared as the stock solution by dissolving 0.0206 gm of Ibuprofen in 10 ml of de-ionized water in a 10ml volumetric flask. to prepare 0.01x 10^{-3} M solution of Ibuprofen, 1 ml of 0.01x 10^{-3} M solution was taken in another 100 ml volumetric flask and the volume was adjusted by de-ionized water upto mark.

Preparation of Sodium Chloride:

10 ml. of 0.001x 10^{-3} M solution of Ibuprofen was prepared as the stock solution by dissolving 0.05844 gm of Sodium chloride in 10 ml of de-ionized water in a 10ml volumetric flask. to prepare 0.01x 10^{-3} M solution of Ibuprofen, 1 ml of 0.01x 10^{-3} M solution was taken in another 100 ml volumetric flask and the volume was adjusted by de-ionized water upto mark.

Preparation of Standard Curve of Ibuprofen:

Ibuprofen stock solution at pH 7.2 and concentration of 0.01x 10^{-3}M was added in different concentration to the nine tubes, to have the following concentrations: 0.09x 10^{-3}M, 0.08x 10^{-3}M, 0.07x 10^{-3}M, 0.06x 10^{-3}M, 0.05x 10^{-3}M, 0.04x 10^{-3}M, 0.03x 10^{-3}M, 0.02x 10^{-3}M and 0.01x 10^{-3}M. The solutions were then properly mixed. The absorbance values of the solutions were determined at £ max 272 nm by a UV spectrophotometer. As a control or reference sample, phosphate buffer solution of pH 7.2 was used. The standard curve was obtained by plotting the absorbance values against the corresponding concentrations.

Concentration Mx10^{-3}	Absorbance
0.01	0.053
0.02	0.100
0.03	0.14
0.04	0.141
0.05	0.158
0.06	0.206
0.07	0.193
0.08	0.21
0.09	0.206

Job's Spectrophotometric Method of Continuous Variation: [11]

In this method, absorbance of series of Ibupeofen and Sodium Chloride mixtures with ratios 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 at pH 2.4 and pH 7.2 were measured by keeping the total moles constant. The absorbance of Ibuprofen and Sodium chloride solutions was measured at 272 nm which is the absorption maxima of Ibuprofen. The observed absorbance of the mixtures at various mole fractions was subtracted fron the sum of the values for free Ibuprofen and free Sodium Chloride. The absorbance difference (D) were then plotted against the mole fractions of drugs in the mixtures. A curve, thus, obtained showed a maximum at a point which indicated the molar ratios of Ibuprofen to Sodium Chloride in the complex.

III. Results and Discussion

In the present investigation, the interaction of Ibuprofen and Sodium Chloride have been studied by different methods of analysis under different pH (2.4 & 7.4) at different concentrations at the temperature (37±0.5) °C .The spectral characteristics and spectrophotometric analysis of the complexation process as well as the effects of this interaction on the protein binding of the drugs have been evaluated. The effect of Sodium Chloride on the protein binding characteristics of Ibuprofen has been explained. The results obtained from various methods are discussed below.

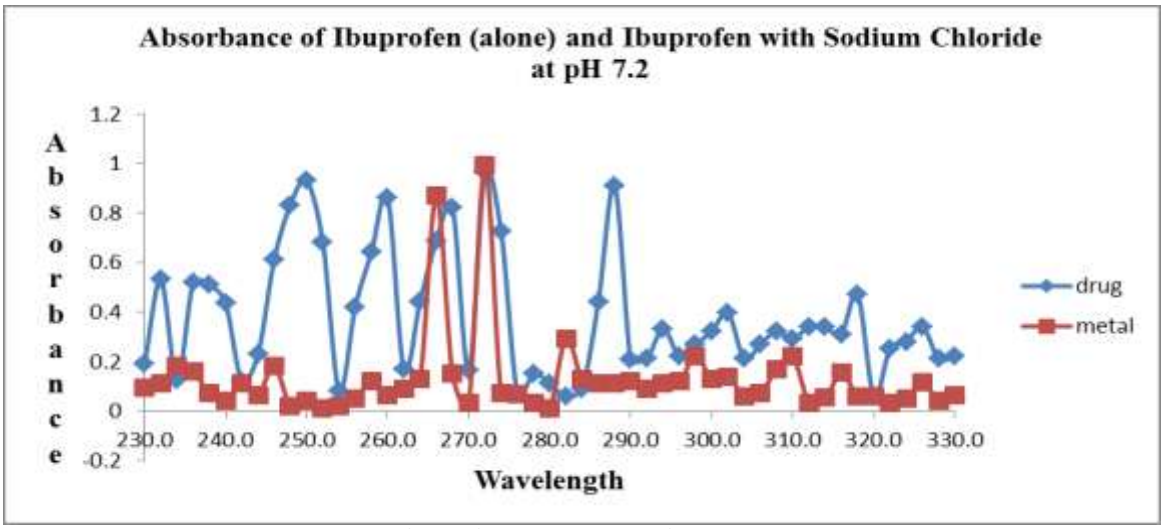

Fig. 1. Spectral studies of Ibuprofen (alone) and Ibuprofen with Sodium Chloride at pH 7.2

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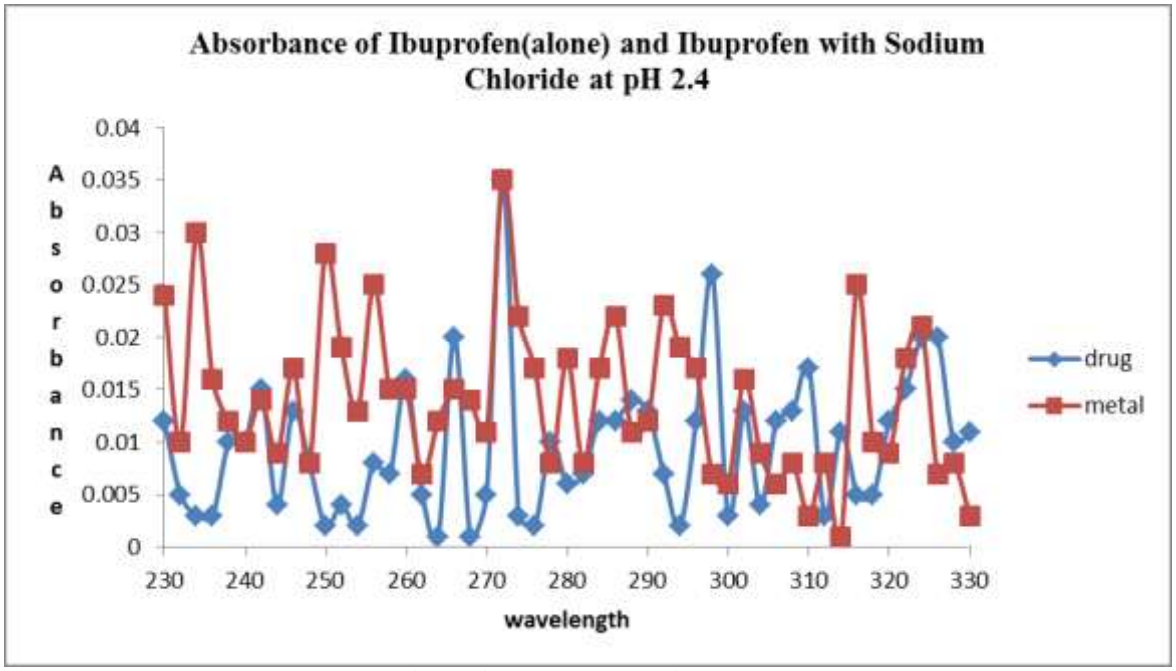

Fig. 2. Spectral studies of Ibuprofen (alone) and Ibuprofen with Sodium Chloride at pH 2.4

TABLE 1. Values of job's plot for complexation of Ibuprofen with Sodium Chloride at pH 7.2:

Conc. of Ibuprofen $M\times10^{-3}$	Absorb. of Ibuprofen at 272 nm $M\times10^{-3}$ A	Conc. Of Sodium Chloride $M\times10^{-3}$	Absorb. of Sodium Chloride $M\times10^{-3}$ B	Absorb. Of mixture C	Absorb. Difference D=(A+B)-C
0.1	0.12	0.9	0.12	0.12	0.12
0.2	0.060	0.8	0.222	0.015	0.267
0.3	0.38	0.7	0.241	0.101	0.38
0.4	0.183	0.6	0.369	0.069	0.483
0.5	0.297	0.5	0.484	0.184	0.597
0.6	0.275	0.4	0.376	0.176	0.475
0.7	0.362	0.3	0.223	0.223	0.362
0.8	0.236	0.2	0.101	0.101	0.236
0.9	0.1	0.1	0.006	0.1	0.1

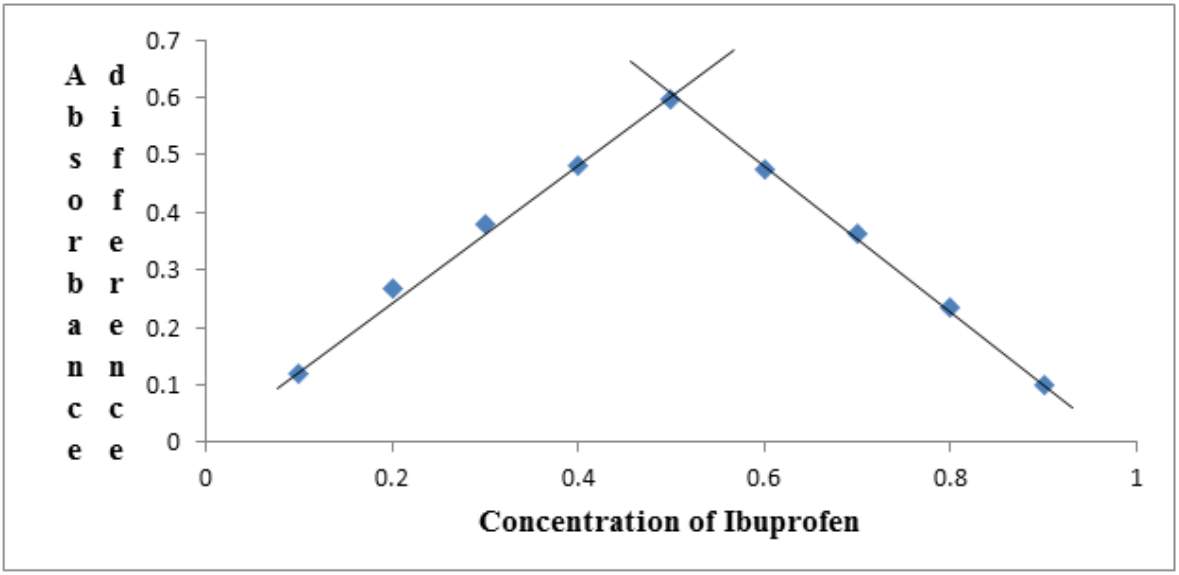

Fig. 3. Job's plot for complexation of Ibuprofen and Sodium Chloride at pH 7.2

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TABLE 2. Values of job's plot for complexation of Ibuprofen and Sodium Chloride at pH 2.4

Conc. of Ibuprofen $M\times10^{-3}$	Absorb. of Ibuprofen at 272 nm $M\times10^{-3}$ A	Conc. of Sodium Chloride $M\times10^{-3}$	Absorb. of Sodium Chloride $M\times10^{-3}$ B	Absorb. of mixture C	Absorb. Difference D=(A+B)-C
0.1	0.285	0.9	0.045	0.317	0.013
0.2	0.399	0.8	0.023	0.300	0.122
0.3	0.287	0.7	0.014	0.060	0.241
0.4	0.388	0.6	0.031	0.050	0.369
0.5	0.543	0.5	0.021	0.080	0.484
0.6	0.289	0.4	0.027	0.060	0.376
0.7	0.275	0.3	0.008	0.060	0.223
0.8	0.688	0.2	0.013	0.600	0.101
0.9	0.245	0.1	0.028	0.267	0.006

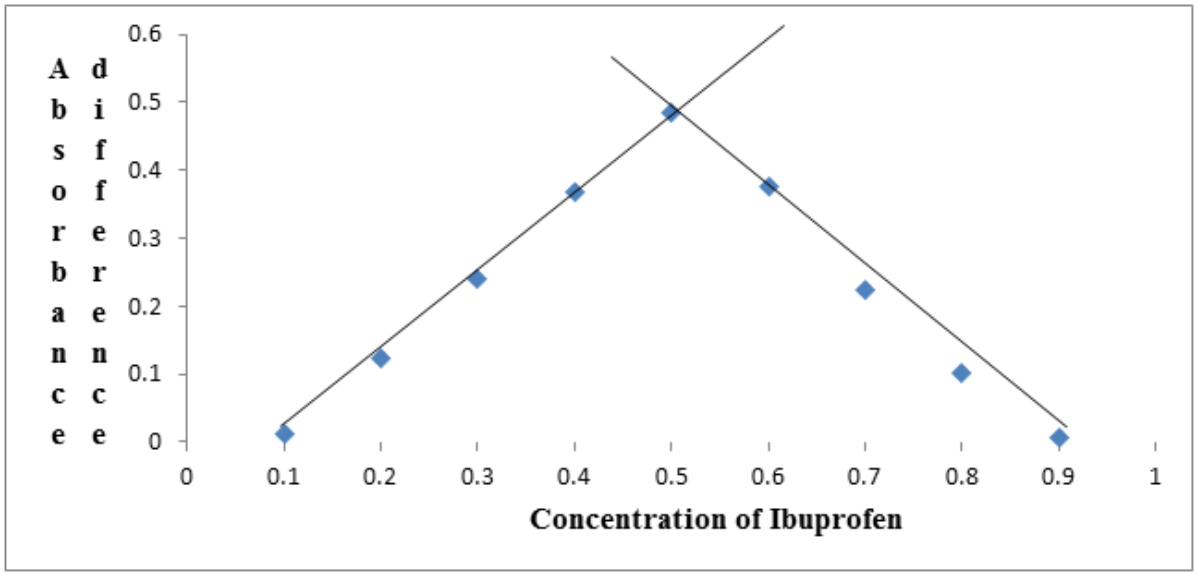

Fig. 4. Job's plot for complexation of Ibuprofen and Sodium Chloride at pH 2.4

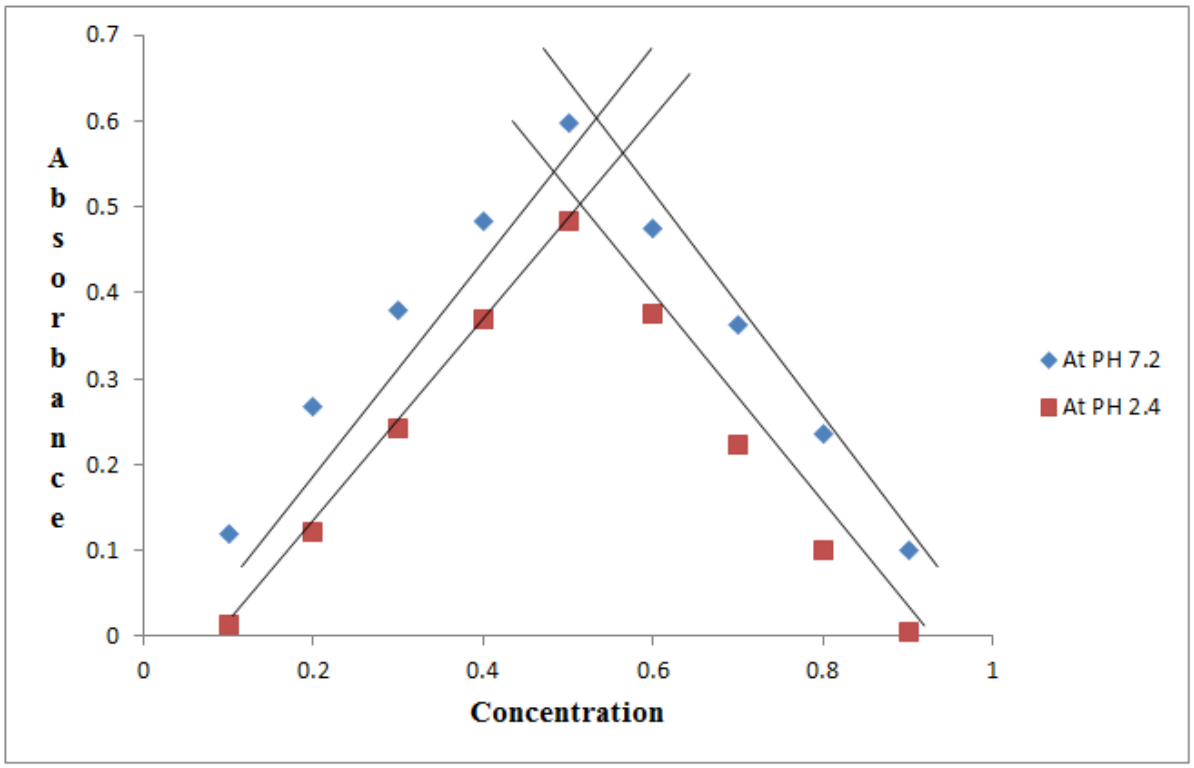

Fig. 5. Job's plot for complexation of Ibuprofen and Sodium Chloride at pH 2.4 and 7.2

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TABLE 3. Observed absorbance values for Ardon's plot for Ibuprofen and Sodium Chloride system at pH 7.2:
Absorbance of 0.2×10-3 M NaCl = 0.0011688

Conc. of Ibuprofen M×10^{-3}	Absorb. of Mixture (D)	1/(D -ϵ_AC)×10^{-3}	1/Ibuprofen ×10^{-3}
0.1	0.405	2.4698	10
0.2	0.492	2.02334	5
0.3	0.2862	3.4983	3.33
0.4	0.2033	4.9301	2.5
0.5	0.2142	4.6813	2
0.6	0.1502	6.6890	1.67
0.7	0.1110	9.0759	1.42
0.8	0.0970	11.4096	1.25
0.9	0.080	12.6665	1.11

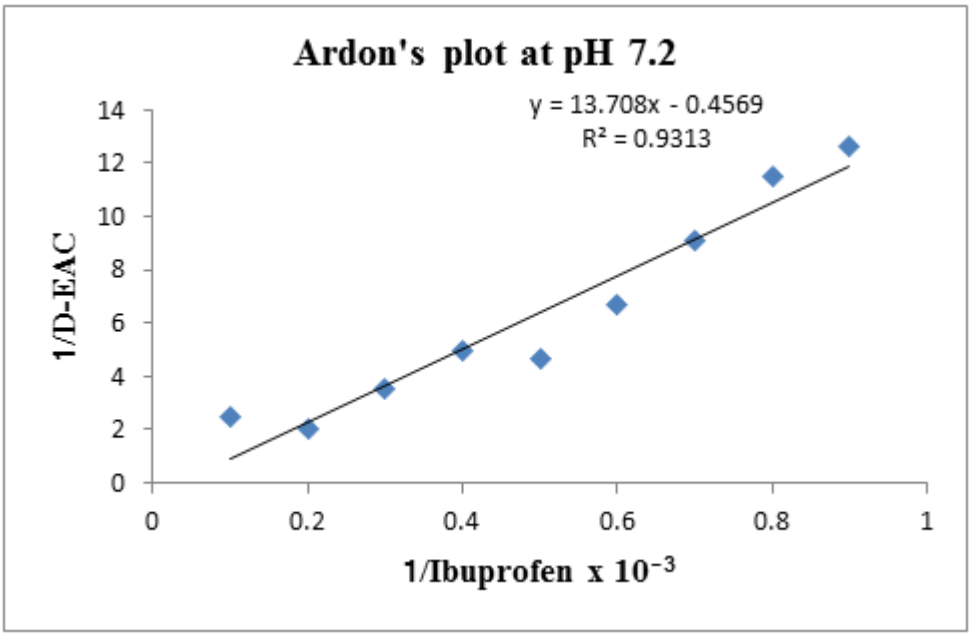

Fig. 6. Ardon's plot for Ibuprofen and Sodium Chloride at pH 7.2

TABLE 4. Observed absorbance values for Ardon's plot for Ibuprofen and Sodium Chloride system at pH 2.4:
Absorbance of 0.2×10-3 M NaCl = 0.0011688

Conc. Of Ibuprofen M×10^{-3}	Absorb. of Mixture (D)	1/(D-ϵ_AC)×10^{-3}	1/Ibuprofen ×10^{-3}
0.1	0.32	3.1261	10
0.2	0.241	3.8945	5
0.3	0.166	6.0368	3.33
0.4	0.144	6.9670	2.5
0.5	0.120	8.3741	2
0.6	0.104	9.6806	1.67
0.7	0.091	11.0887	1.42
0.8	0.087	11.6191	1.25
0.9	0.067	15.1634	1.11

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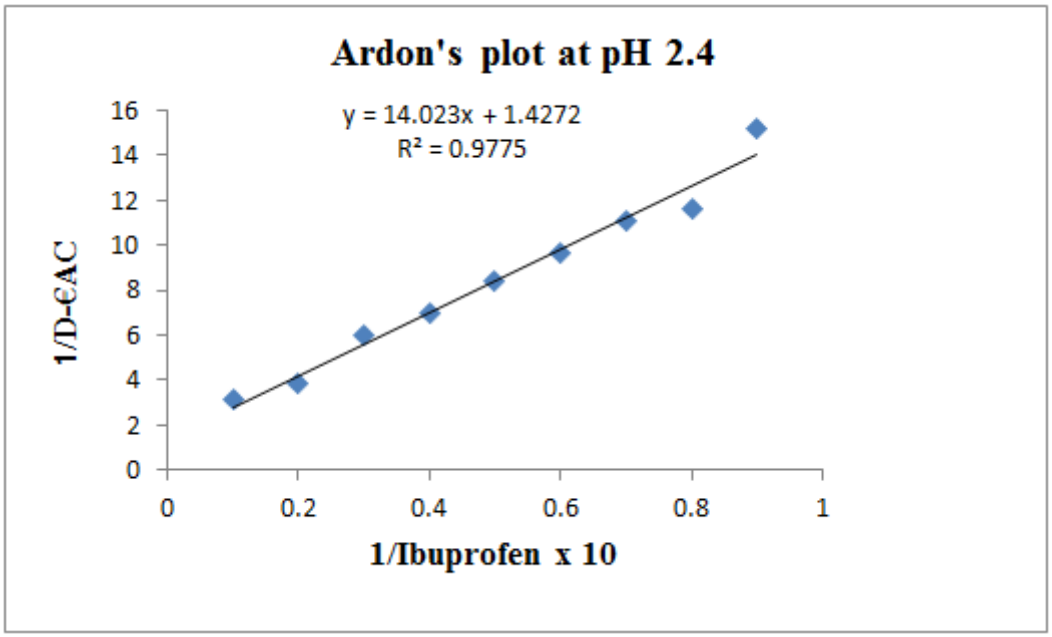

Fig. 7. Ardon's plot for Ibuprofen and Sodium Chloride at pH 2.4

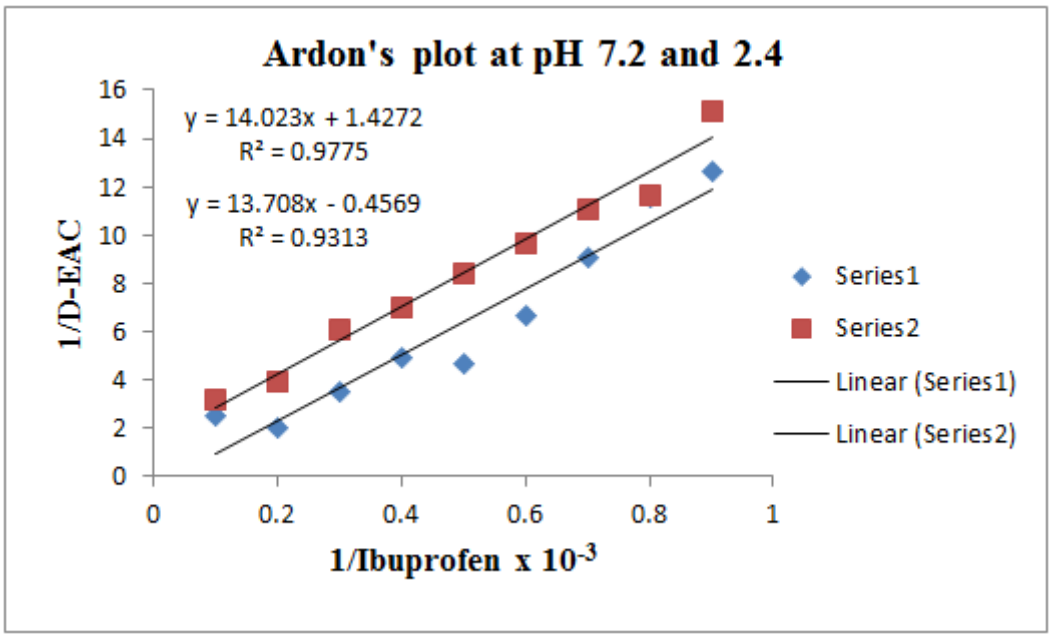

Fig. 8. Ardon's plot for Ibuprofen and Sodium Chloride at pH 7.2 and 2.4

The values stability constants at different p^H are given in the following table:

System	p^H	Stability constant
Ibuprofen	pH -2.4	0.1018
Sodium Chloride	PH -7.2	0.0332

It is found form the numerical values of stability constants for Ibuprofen-Sodium Chloride at lower pH is higher than that of higher pH

On the other hand, at pH 7.2the stability constants value is relatively low than that of pH 2.4. That means Ibuprofen from relatively stable complexes with Sodium chloride at lower pH 2.4 than at higher pH

IV. Conclusion

The study of complexation between drug and metal is a subject of a number of experimentations with a large number of physical and chemical parameters, which have been investigated. Still there is no single method perfectly satisfactory to study the stability of the complex. In the present

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work, the interaction of an anti-inflammatory drug Ibuprofen with Sodium Chloride has been studied in the aqueous system at pH 7.2 and pH 2.4 by a variety of physical methods, to detect confirm the nature of complications of this drug with Sodium Chloride. The methods include inspection of spectral behaviour, Job's method of continuous variation and Ardon's straight line plots by spectrophotometry. Spectral studies showed that complexes are formed between Ibuprofen and Sodium Chloride. The changes in UV-absorbance of Ibuprofen and its mixture with Sodium Chloride indicated formation of complexation. Job's plot has given the molar ratios of complexes of Ibupeofen and Sodium Chloride. The Ardon's spectrophotometric plots confirmed the phenomenon of 1:1 complexation. as is indicated by straight lines so obtained.The stability constant of the complex was estimated from this line plots using Ardon's equation. The stability was calculated from the values (intercept)/(slope) of the straight line so obtained, indicated a complexation between Ibuprofen and Sodium Chloride at pH 7.2 and pH 2.4. It can be therefore be inferred that a careful consideration is needed during concurrent administration of Ibuprofen with Sodium Chloride. The study is of limited scale and a beginning matter in such interaction. This study has some limitation e.g. the study is not involved with animal and human. At this moment, it is possible to arrive at a conclusive idea on the changes of pharmacokinetic and pharmacodynamic properties of Ibuprofen when this may be administered in combination with Sodium Chloride.

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