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ORGINAL RESEARCH

The Determination of the Stability Constant of Finasteride Complexes with Various Metals by Potentiometric and Spectrophotometric Methods

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ABSTRACT

In this study, the stability constants of the cobalt(II), zinc(II), cadmium(II) and copper(II) complexes of finasteride were determined potentiometrically by using Irving-Rossotti and Calvin-Bjerrum methods and supported by spectrophotometric way [1-3]. The evaluated protonation constant of finasteride was found as logK=2,21. Potentiometrically the logarithms of the stability constants of the finasteride-metal complexes were found by Calvin-Bjerrum and Irving-Rossotti methods: for cobalt(II) complex logK=3,01; for zinc(II) complex logK=2,82; for cadmium(II) complex logK=3,04 and for copper complex logK=2,85 at 25^{o}C (I=0,10). Conditional formation constants of the complexes were calculated and pH ranges of the complexation were found.

Spectrometric measurements were recorded for cobalt(II)-finasteride, zinc(II)-finasteride, cadmium(II)-finasteride and copper(II)-finasteride solutions and the results of the measurement supported the formation of complexes.

In this study, the stability constant of finasteride complexes with metals were determined using the potentiometric and spectrophotometric methods. These metals can be received directly or indirectly to the human body. Therefore, the stability constants that we found, can shed light on the analysis of blood samples of patients.

Keywords: Finasteride, Stability Constant, Potentiometry, Spectrophotometry

INTRODUCTION

Finasteride, chemically known as *N*-(1,1-dimethylethyl)-3-oxo-(5α,17β)-4-azaandrost-1-ene-17-carboxamide (Figure 1), is a synthetic 4-azasteroid compound which acts by inhibiting the type II 5-alpha reductase enzyme that converts testesterone to dihydrotestesterone (DHT) in prostatic epithelial cells. Blocking of DHT production, finasteride reduces androgenic activity in the scalp, treating hair loss at its hormonal source. In the prostate, inhibition of 5-alpha reductase leads to a reduction of prostate volume, which improves the symptoms of benign prostatic hyperplasia (BPH) and reduces the risk of prostate cancer [4,5]. Finasteride is being accepted as the most efficient cure in the whole World, to the hair loss related with DHT.

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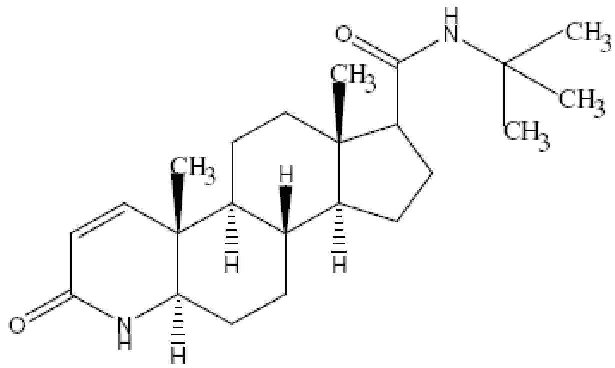


Figure 1: Structure of finasteride

The literature research showed that several methods for determination of finasteride in the pharmaceutical preparations and biological fluids including high-performance liquid chromatography (HPLC) [5-7], liquid chromatography tandem-mass spectrometry (LC-MS) [8-11], gas chromatography (GC) [12], ultra-performance liquid chromatography (UPLC-MS) [13], spectrophotometry [14], voltametry [15] and polarography [16] have been developed. Because most drugs are weak acids or bases, information about their ionization at physiological pH values carry important information related to the behavior of drugs in penetrating different parts of the body. But no reports have been published for stability constants of finasteride complexes in the literature.

In the present study, the stability constants of finasteride complexes with cobalt(II), cadmium(II), zinc(II) and copper(II) were determined potentiometrically by using Irving-Rossotti and Calvin-Bjerrum procedures [17-20]. Also, spectrometric measurements were recorded for cobalt(II)-finasteride, zinc(II)-finasteride, cadmium(II)-finasteride and copper(II)-finasteride solutions.

EXPERIMENTAL

Material and Methods

Potentiometric method

The stock solutions of metal ions were prepared from nitrate salts. Sodium hydroxide, sodium perchlorate and perchloric acid were other chemicals that were used. All chemicals were analytical reagent grade from Merck. A Radiometer TIM800 Titration Manager, ABU 901 Autoburette, HI 1131B Combination pH electrode were used for potentiometric measurements and Shimadzu UV-2550 UV-VIS double beam spectrophotometer was used for spectrophotometric measurements. Computer calculations were performed on the pH-metric data.

Procedure

Finasteride was dissolved in acetonitrile-water (1:1, v/v). The ionic strength of the reaction media was kept constant at I=0,10 (25° C) using $NaClO_4$ solution during the experiment. Stock solution of ligand (0,01M) was prepared prior to use. The exact calibration was done daily by using commercial buffer solutions (Merck) of pH 4 and 7.

In order to determine the protonation constants and stability constants, solutions including (0,10M $HClO_4$ + 1,00M $NaClO_4$), (0,10M $HClO_4$ + 1,00M $NaClO_4$ + 0,01M ligand) and (0,10M $HClO_4$ + 1,00M $NaClO_4$ + 0,01M ligand + 0,01M metal ion) were titrated potentiometrically using 0,10M NaOH at 25°C as shown in Figures 2,3,4 and 5.

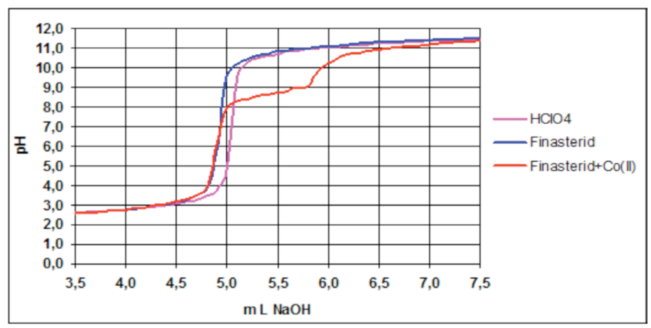


Figure 2: Potentiometric titration curve of finasteride-cobalt(II) complex

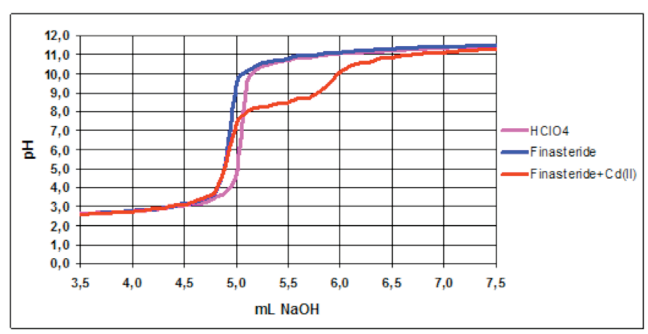


Figure 3: Potentiometric titration curve of finasteride-cadmium(II) complex

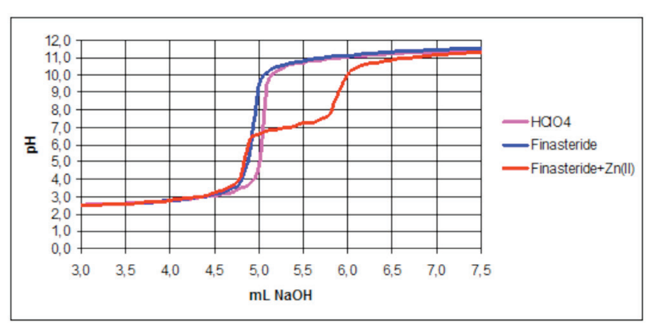


Figure 4: Potentiometric titration curve of finasteride-zinc(II) complex

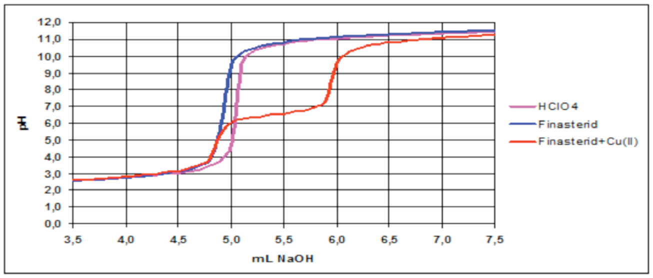


Figure 5: Potentiometric titration curve of finasteride-copper(II) complex

The calculations were performed according to Irving-Rossotti method [19]. The following equations were used in the present study:

$$\bar{n}_A = y + [(V_2 - V_1)(N + E^o)] / [(V^o + V_1)\, T^o_L] \quad (1)$$

$$\bar{n}_L = [(V_3 - V_2)(N + E^o + T^o_L (y - \bar{n}_A))] / (V^o + V_2).\ \bar{n}_A \,.\, T^o_M \quad (2)$$

$$pL = \log(1+\beta_1[H^+] + \beta_2[H^+]^2) / (T^o_L - \bar{n}_L \,.\, T^o_M) \quad (3)$$

V^o	= Starting volume	: 50,00 mL
N	= NaOH normality	: 0,1000N
T^o_L	= Ligand concentration	: 0,0020M
E^o	= $HClO_4$ concentration	: 0,0102M
y	= Number of protons in the molecule	: 0
T^o_M	= Metal concentration	: 0,0010M

According to formula (1) of titration curve of $HClO_4$ + $NaClO_4$ with $HClO_4$ + $NaClO_4$ + Ligand mixture, the $\bar{n}_A$ = f (pH) graphic was drawn (Figure 6). The protonation constant was found for finasteride as logK = 2,21.

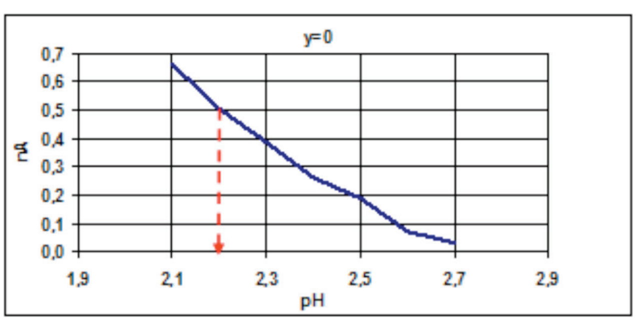
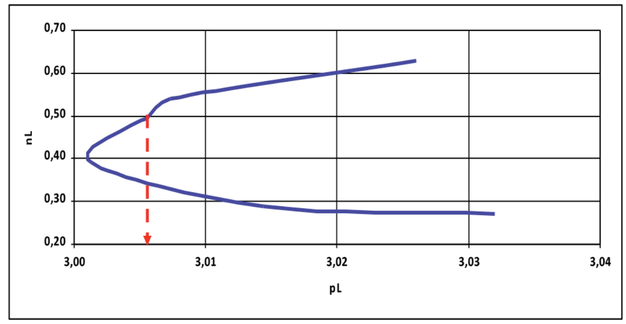
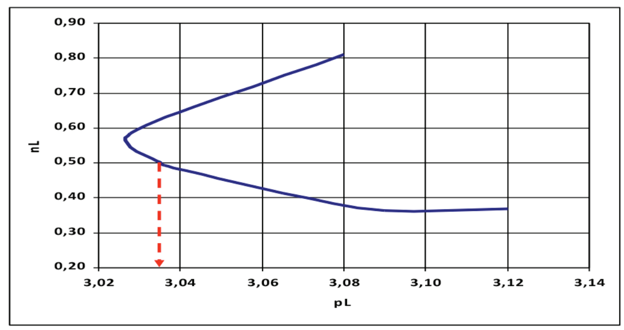


Figure 6: pH-$\bar{n}_A$ curve for finasteride

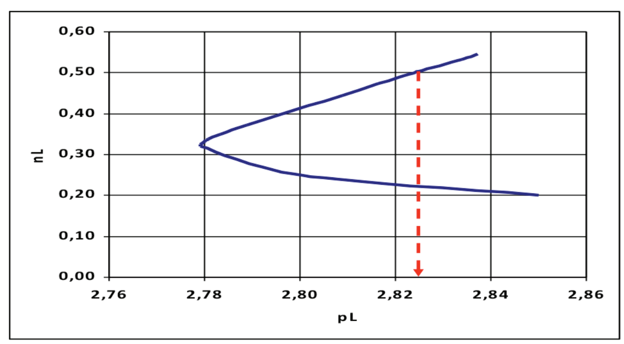
$\bar{n}_L$ values were calculated using $\bar{n}_A$ values. pL values were calculated using $\bar{n}_L$ and β values to calculate the stability constants. $\bar{n}_L$ = f (pL) graphs (Figure 7) were plotted using $\bar{n}_L$ and pL values which were calculated for each metal-ligand complex. The formation constans of complexes were found from pL values which corresponded to $\bar{n}_L$ = 0,5 value.



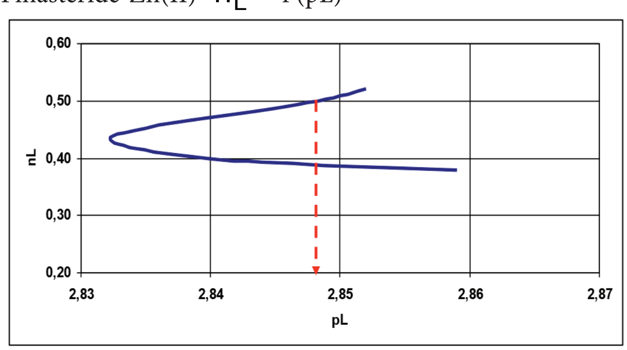
Finasteride-Co(II) $\bar{n}_L$ = f (pL)



Finasteride-Cd(II) $\bar{n}_L$ = f (pL)



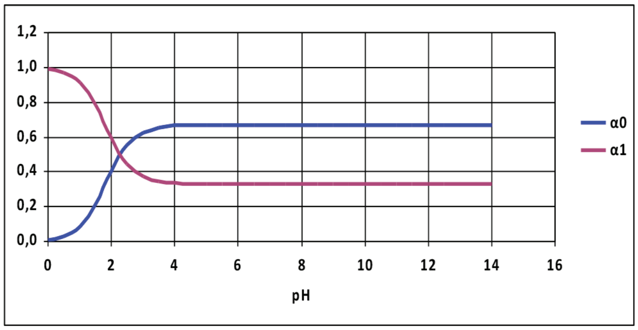
Finasteride-Zn(II) $\bar{n}_L$ = f (pL)



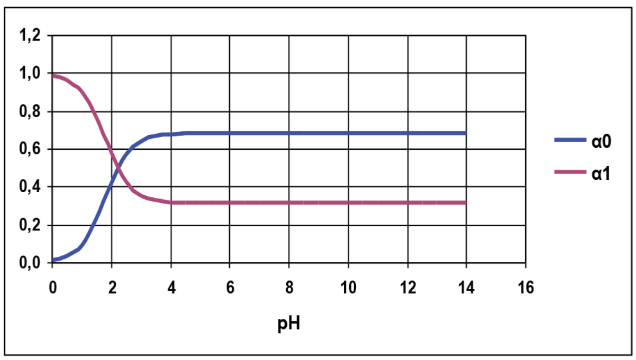
Finasteride-Cu(II) $\bar{n}_L$ = f (pL)

Figure 7: $\bar{n}_L$ = f (pL) curves for metal-finasteride complexes

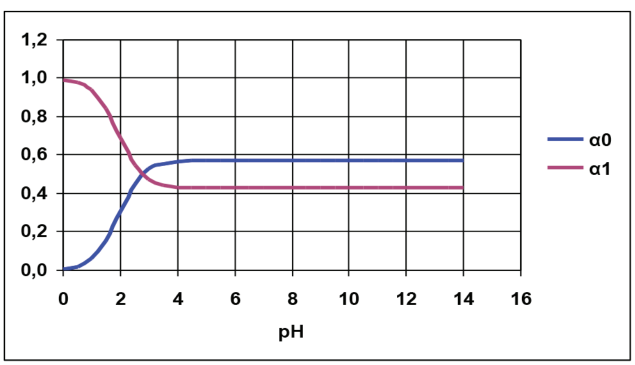
In addition, the changes, in mole fractions of the molecular and ionic species derived from complexes by calculating the pH of solutions (Figure 8).



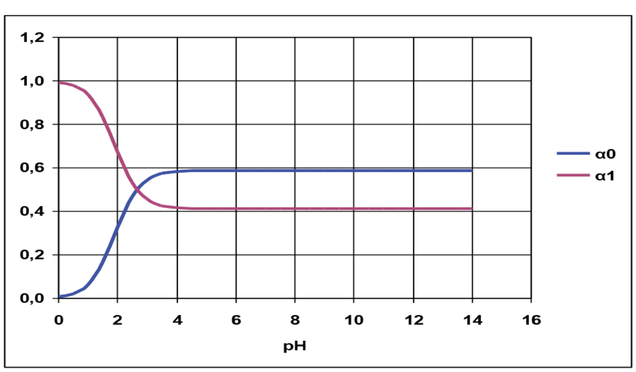
Finasteride-Co(II) complex



Finasteride-Cd(II) complex



Finasteride-Zn(II) complex



Finasteride-Cu(II) complex

Figure 8: The relative abundance curve of metal-finasteride complexes depending on the pH

Spectrophotometric method

1,00.10^{-2}M Co(II), Cd(II), Zn(II) and Cu(II) solutions and freshly prepared 1,00.10^{-2}M finasteride solution were diluted to 1,00.10^{-4}M and a spectrophotometric measurement of each solution were performed separately with Shimadzu UV-2550 spectrophotometer. Then, finasteride-metal mixtures (1:1, v/v) was prepared by mixing finasteride with each metal solutions and spectrophotometric measurement of each mixtures were performed. The spectrums supported the formation of complexes (Figure 9,10,11,12).

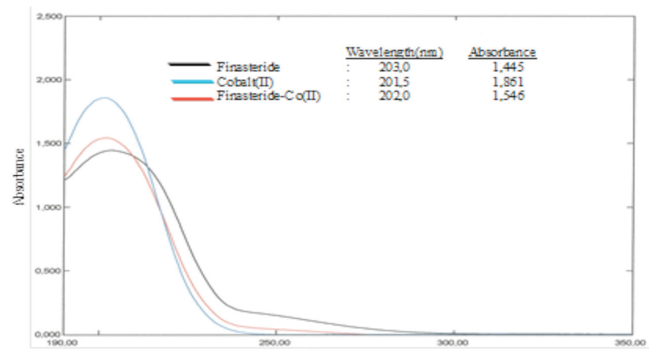


Figure 9: The spectrum of finasteride-cobalt(II) complex

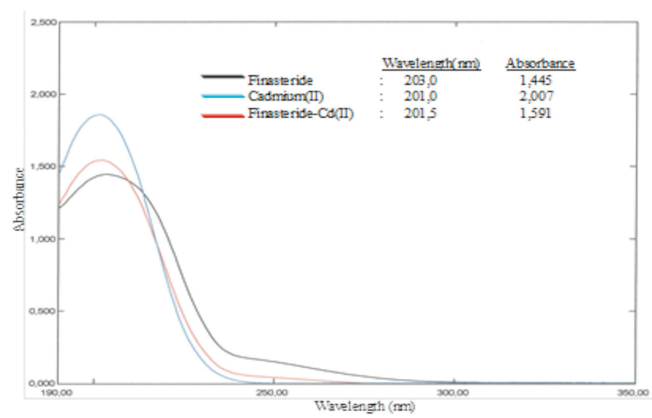


Figure 10: The spectrum of finasteride-cadmium(II) complex

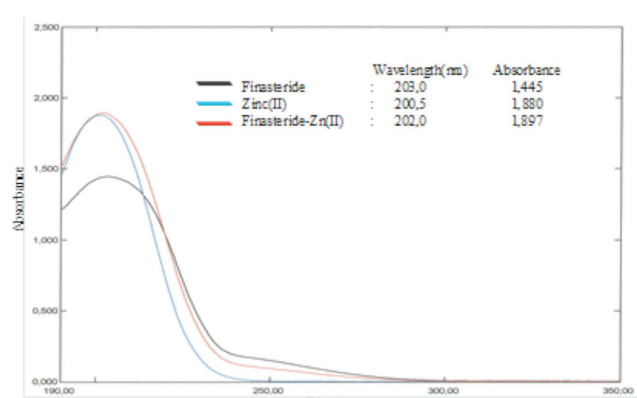


Figure 11: The spectrum of finasteride-zinc(II) complex

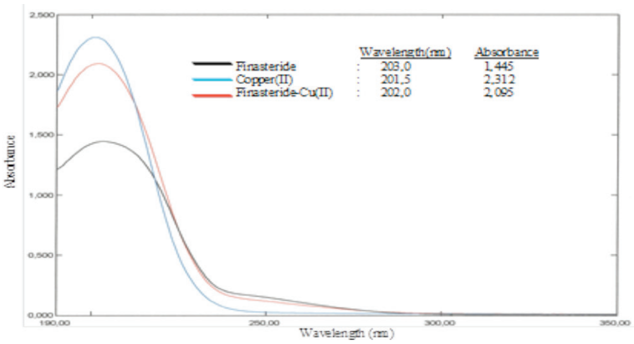
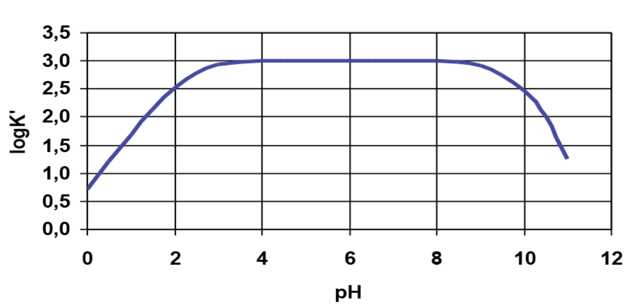


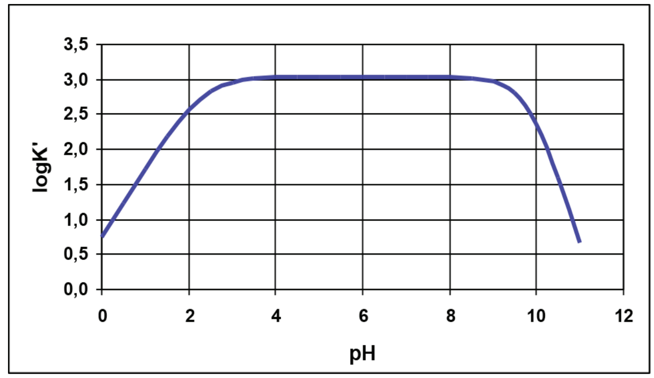
Figure 12: The spectrum of finasteride-copper(II) complex

RESULTS AND DISCUSSION

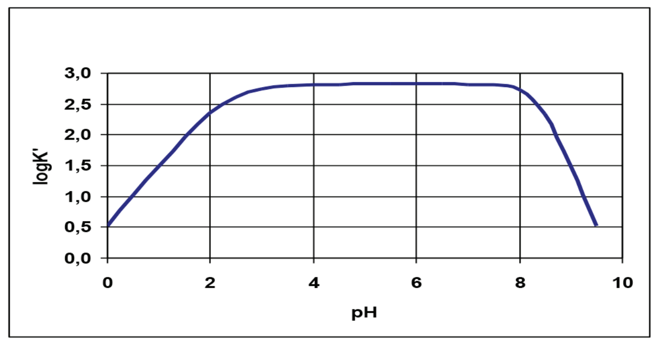
In this study the protonation constant of ligand was found graphically by using the Irving-Rosotti method. The result is shown in Figure 5. For finding the stability constans of complexes, the solutions which contain Co(II), Cd(II), Zn(II), Cu(II) salts in certain concentrations were titrated with NaOH solution potentiometricaly at 25 ºC. Titration curves were obtained by plotting the pH changes versus the 0,10M NaOH volumes. The titration curves belonging to metals are shown in Figures 2,3,4 and 5. The $\overline{n}_L$ = f(pL) figures were plotted by using $\overline{n}_L$ values which were calculated by the potentiometric titraiton curves. The formation constant of the complexes have been read, and they correspond to the n=0,5 value from $\overline{n}_L$ = f(pL) figures. In the evaluation of the relative abundance (mole fractions) of the species in the system are plotted aganist the pH (Figure 7). The analytical applications are showed that the different ligands in the system have an influence in the formation of complexes. In addition, the pH range where the conditional formation constant was at the maximum, was overlapped wiht the pH range where the relative abundance of complexes is at the maximum. The conditional formation constants of the complexes were calculated and they were plotted versus the corresponding pH ranges (Figure 13).



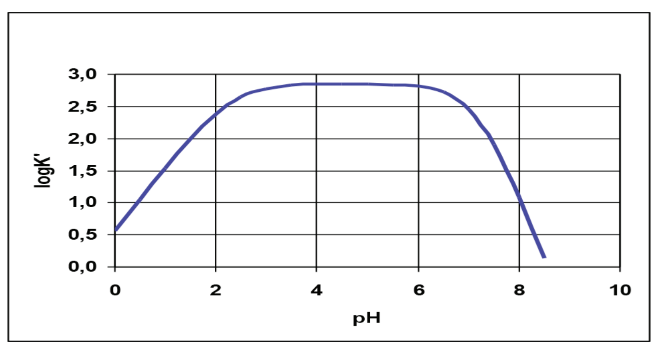
Finasteride-Co(II) complex



Finasteride-Cd(II) complex



Finasteride-Zn(II) complex



Finasteride-Cu(II) complex

Figure 13: The conditional formation constants of the finasteride-metal complexes

On calculation of conditional formation constans, it is accepted that the only competitive ligand is the hydronium ion in the reaction medium. The pH ranges in which the complexation occurs, the maximum values of conditional formation constants and the pH values corresponding to these conditional formation constants for 25 ºC are shown in Table 1. The formation constants of metal-ligand complexes are given in the Table 2.

Table 1: The conditional formation constants for the metal-ligand complexes(I=0,10; t=25 °C)

Metal	pH range of the metal complexes	pH (log K'is max)	log K'_{max}
Cobalt(II)	0-11,0	6,0	3,01
Cadmium(II)	0-11,0	6,0	3,04
Zinc(II)	0-9,5	6,0	2,82
Copper(II)	0-8,5	4,5	2,85

Table 2: The formation constants of the metal-ligand complexes(I=0,10; t=25 °C)

Metal	logK
Cobalt(II)	3,01
Cadmium(II)	3,04
Zinc(II)	2,82
Copper(II)	2,85

In this study, the stability constant of finasteride complexes with metals which can show a direct impact on living organisms or be toxic at high concentrations were determined using the potentiometric and spectrophotometric methods. These metals can be received directly or indirectly to the human body. Therefore, the stability constants that we found can shed light on the analysis of blood samples taken from patients which are using finasteride.

Finasteridin Çeşitli Metallerle Oluşturduğu Komplekslerin Kararlılık Sabitlerinin Potansiyometrik ve Spektrofotometrik Yöntemlerle Tayini

ÖZ

Bu çalışmada, finasteridin kobalt(II), çinko(II), kadmiyum(II) ve bakır(II) metalleri ile oluşturduğu komplekslerin kararlılık sabitleri Irving-Rossotti ve Calvin-Bjerrum yöntemleri kullanılarak potansiyometrik ve spektrofotometrik yoldan tayin edildi [1-3]. Finasteridin protonlanma sabiti potansiyometrik yöntemle $logK_1$ = 2,21 olarak bulundu. Potansiyometrik olarak Calvin-Bjerrum ve Irwing-Rossotti metodlarıyla oluşum sabitleri: kobalt(II) için $logK_1$ = 3,01; çinko(II) için $logK_1$ = 2,82; kadmiyum(II) için $logK_1$ = 3,04 ve bakır(II) için $logK_1$ = 2,85 olarak 25°C (I=0,10) için bulundu. Oluşan komplekslerin koşullu oluşum sabitleri hesaplandı ve buradan kompleksleşmenin ortaya çıktığı pH aralıkları bulundu.

Kobalt(II)-finasterid, kadmiyum(II)-finasterid, çinko(II) finasterid ve bakır(II)-finasterid çözeltilerinin ayrı ayrı spektrofotometrik ölçümleri alındı ve ölçüm sonuçları kompleksleşmenin gerçekleştiğini gösterdi.

Bu çalışmada, finasteridin metaller ile oluşturduğu komplekslerinin kararlılık sabitleri potansiyometrik ve spektrofotometrik yöntemler ile tayin edilmiştir. Bu metaller, insan vücuduna doğrudan ya da dolaylı olarak alınabilir. Bu nedenle, bizim bulduğumuz kararlılık sabitleri, hastaların kan örneklerinin analizine de ışık tutabilir.

Anahtar kelimeler: Finasterid, Kararlılık Sabiti, Potansiyometri, Spektrofotometri.

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