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Research Article

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Stability Constant of Nadifloxacin with Trivalent Rare Earth Metal in Aqueous Media: A pH-Metric Study

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ABSTRACT

The interaction of lanthanide metal ions (such as Ce, Pr, Nd, Pm, Gd) with broad spectrum antibiotic Nadifloxacin has been investigated in aqueous medium at 25°C temperature and at an ionic strength of 0.2M $NaClO_4$ *by using a pH metric titration technique. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to calculate the values of proton-ligand (pK) and Metal-Ligand (logK) stability constants of data obtained for Nadifloxacin complexation with rare earth metal ions. The trend in the formation constants follows the order:* $Pr^{3+} > Ce^{3+} > Pm^{3+} > Nd^{3+} > Gd^{3+}$

Keywords: Nadifloxacin; Lanthanides; pH-metric titration technique; Stability constant

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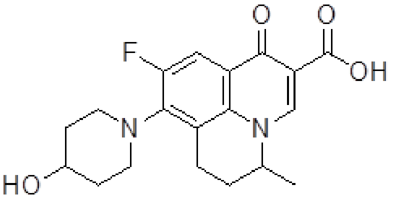
INTRODUCTION

The metal ligand equilibria plays important role in various fields. It is well known fact that the insertion of metal in medicinal drugs in the form of complexes exhibit remarkable difference in therapeutic values as compared to marginal drug, so various researchers reports stability constant of bioactive compounds with metal [1-3]. For the investigation of stability constant various technique are utilized such as potentiometry etc. pH-metric study is one of the best widely used technique because it has several superiority such as, it is easy to understand and work, cheap technique [4-6] etc. Now-days, various researchers have their interest in the investigation of complexation properties of the rare earth metals. Due to the outstanding functions of the lanthanide ions, It have often been efficaciously utilised as progressive calcium and magnesium cation substitutes in many metalloproteinase as chiral NMR shift reagents. In view of the importance of biologically active compounds and rare earth metal in medicine, in the present investigation complexation and determination of stability constant of Nadifloxacin with rare earth metal have been described. It was thought of interest to study the complexes of Nadifloxacin with five rare earth metal ions Ce^{3+}, Pr^{3+}, Nd^{3+}, Pm^{3+} and Gd^{3+} using pH metrically in aqueous medium. Nadifloxacin is a topical fluroquinolone antibiotic for the treatment of acne Vulgaris [7]. It is also used to treat bacterial infections. It showed broad-spectrum antibiotic activity against gram (+)ve, gram (-)ve and anaerobic bacteria. It played significant role against methicillin-resistant staphylococcus aureus in-vitro studies. It has functional group with donor atom N and O. Nadifloxacin is one of the approved drug for the treatment of acne Vulgaris in European countries [8].

From the literature survey it is revealed that no work is notified on the complexation of Nadifloxacin with rare earth metal. Hence we had carried out the study of complexation beheviour of Nadifloxacin with rare earth metal by employing pH-metric titration technique.

In the present investigation of proton-ligand and metal-ligand stability constant, we used metal ions from lanthanide series (Ce, Pr, Nd, Pm, Gd), complexing tendency of lanthanide series metal ions is lower than d-block elements but it represents significant binding properties with desirable ligands [9-10], Because d-orbitals are less diffused with respect to f-block elements [11-14].



Nadifloxacin

EXPERIMENTAL SECTION

Material and methodology

The double distilled water is prepared in the laboratory by using all glass quick fit assembly. The medicinal drug was procured from the local pharmacy college. Nitrates of lanthanides were purchase from local supplier and it was of British Drug House (BDH) India Ltd. Sodium perchlorate and perchloricacids were of A.R. grade and from S.D. fine chem. Ltd. The pure drug Nadifloxacin is soluble in double distilled water. The solutions used in the pH metric titration were prepared in double distilled CO_2 free water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of $HClO_4$. The rare earth metal salt solutions were also standardized using EDTA titration. All the measurements were made at temperature 25°C in aqueous medium at constant ionic strength of 0.2 M $NaClO_4$. The water thermostat model SL-131, scientific isotemperature refrigerated circulator accurate to ± 0.1 ºC is used to maintain the temperature constant. The solutions were equilibrated in the thermostat for about 15 minutes before titration. The pH measurement was made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ±0.01 pH units). The instrument was calibrated at pH 4.00, 7.00 and 9.18 using the standard buffer solutions.

Potentiometric determination of stability constant

Calvin-Bjerrum titration technique [14-15] has been used for the determination of stability constants. For evaluating the protonation constant of the ligand and the formation constant of the complexes in aqueous medium with different metal ions the following sets of solutions were prepared (total volume 50 ml) and titrated pH metrically against standard NaOH solution at temperature 25°C. The experimental procedure involved potentiometric titration of solutions of

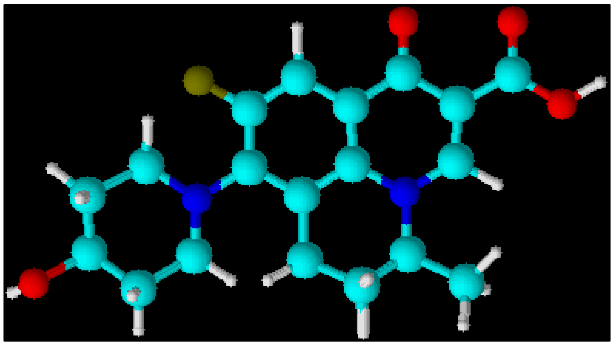
i) Free $HClO_4$, (A)
ii) Free $HClO_4$ + Ligand (A+L) and
iii) Free $HClO_4$ + Ligand + Metal ion (A+L+M)

The above mentioned sets prepared by keeping M: L ratio, the concentration of perchloric acid (0.2M) and sodium perchlorate (0.2M) were kept constant for all sets. The titrations were carried out in a 150ml corning glass beaker. Nitrogen gas slowly bubbled through the solution to remove dissolved oxygen and carbon dioxide. The gas was continuously bubbled after each addition of alkali from the burrate. pH meter reading were noted only after the gas bubbling was completely stopped. At the point where pH meter reading rise suddenly the rate of gas bubbling was increased so as to get quickly the steady readings. The titration curves are analysed using computer based program in Excel.

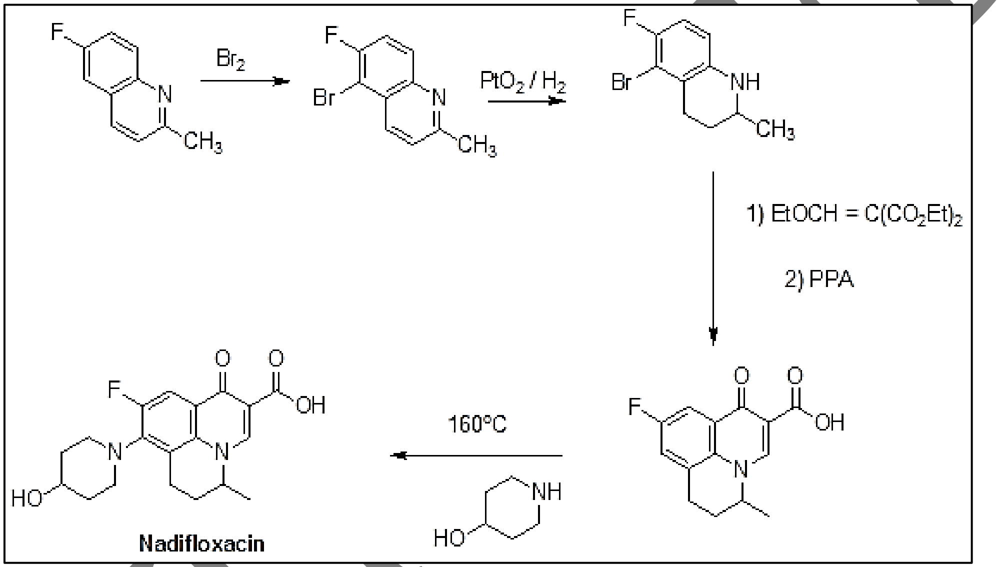
RESULT AND DISCUSSION

In the complexation study, we used aqueous solution of Nadifloxacin and metal nitrates.

Nadifloxacin: Drug information
Mol. Formula: $C_{19}H_{21}FN_2O_4$
Mol. Weight: 360.379
Chirality: Racemic Mixture



IUPAC name: 9 –fluoro–8 - (4–hydroxypiperidin - 1- yl)–5–methyl–1–oxo 6,7– dihydro- 1*H*, 5*H*–pyrido [3,2,1 -*ij*] quinoline – 2 - carboxylic acid.
As per literature synthetic route of Nadifloxacin [16] as given below:



Calvin-Bjerrum theory was used for the estimation of stability constant [13]. The equillibria concerned in the preparation of binary complexes may be represented as

$$M \quad + \quad L \rightleftharpoons ML \qquad \text{(i)}$$

Where M: metal and L: Ligand.
Applying the law mass action

$$K = \frac{[ML]}{[M]\,[L]} \qquad \text{(ii)}$$

Where k: equilibrium constant.
The stepwise formation of a complex MLcan be described by the following set of equilibrium constants.

$$K1 = \frac{[ML]}{[M]\,[L]} \qquad \text{(iii)}$$

$$K2 = \frac{[ML]}{[M]\,[L]} \qquad \text{(iv)}$$

Calvin - Bjerrum was firstly discuss the broad technique to eastimate the stepwise stability constant of metal ligand complexes [11-12].

$$\bar{n} = \frac{\sum_{i=0}^{N} i[ML_i]}{\sum_{i=0}^{N} [ML_i]} \qquad \text{(v)}$$

Where,

$\bar{n}$: Degree of formation or ligand number

A similar function for the proton - ligand complexes is given by

$$\bar{n}_A = \frac{\sum_{i=0}^{j} i\beta_i^H [H]^i}{\sum_{i=0}^{j} \beta_i^H [H]^i}, \ (\beta_0^H = 1) \qquad \text{(vi)}$$

Where, $\bar{n}_A$: mean number of protons bound per non-complex bound ligand molecule.

Stability constant of observed Nadifloxacin complexes were calculated with help of computer programme. Irving and Rossoti's point-wise calculation methods are employed for the determination of pK_a values of Nadifloxacin drug whereas half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti was used for the calculation of logK of lanthnide ions with Nadifloxacin. We observed values of ($\overline{n_A}$) in between 0.2 to 0.8 indicating 1:1 complex formations.

Table 1: **Proton-ligand and metal-ligand stability constant of Nadifloxacin with rare earth metal ions in aqueous medium at 25 °C**

Metal ion	***Proton- ligand* pK1**	***Stability constant* pK2**	***Metal-ligand* logK1**	***Stability* logK$_2$**	***Constant* logβ**
Ce (III)	3.909	8.9502	3.4444	- -	3.4444
Pr (III)	3.909	8.9501	3.7438	- -	3.7438
Nd (III)	3.909	8.9502	2.9087	- -	2.9087
Pm (III)	3.909	8.9501	3.4242	- -	3.4242
Gd (III)	3.909	8.9501	2.865	- -	2.865

The result of Proton – ligand stability constant and metal ligand stability constant of the present lanthanide ion complexes with Nadifloxacin are shown in Table 1.

From above observation we found the order of stability constants for lanthanide ion complexes with Nadifloxacin is: $Pr^{3+} > Ce^{3+} > Pm^{3+} > Nd^{3+} > Gd^{3+}$.

The trivalent Gd has half field f-orbital and it forms a less stable complex, may be related to discontinuity in crystal radii at gadolinium. As we proceed through the lanthanide series, the nuclear charge and the number of 4f electrons increase by one at each step. The shielding of the 4f electrons by another is quite imperfect owing to the shifts of orbitals, so that at each increase the effective nuclear charge experience by each 4f electron increases, Thus causing a reduction in the size of the entire 4f shell. The lowering in the logK values in the Gd(III) chelates in relation to the other may be due to the fact that progressively smaller radii of Gd(III) impose increasingly greater steric hindrance on the ligands on account of metal–ligand interaction. The graphs of logK vs atomic number, atomic radii were plotted & found in good agreement with earlier studies.

CONCLUSION

In the present investigation antibiotic drug (Nadifloxacin) plays the role of ligand in the complex formation with trivalent metals ions of lanthanide series. From the pH metric study of Nadifloxacin complexes with rare earth metals we observed and conclude the order of stability constants is $Pr^{3+} > Ce^{3+} > Pm^{3+} > Nd^{3+} > Gd^{3+}$.

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