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Research Article

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Formation of rare earth metal complexes with Zonisamide in aqueous medium

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ABSTRACT

The stability constant of Zonisamide with trivalent rare earth metal ions Ce^{3+}, Pr^{3+}, Nd^{3+}, Pm^{3+} and Gd^{3+} using a pH metric titration technique in aqueous medium at 25°C temperature and at an ionic strength of 0.2M NaClO4 were studied. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant (logK) values. The trend in the formation constants follows the order: $\boldsymbol{Pr^{3+} < Ce^{3+} < Nd^{3+} < Pm^{3+} < Gd^{3+}}$

Keywords: Zonisamide drug, Stability constant, rare earth metal ions, pH meter etc

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INTRODUCTION

The coordination chemistry of metal ion in aqueous solution is the vast field of investigation. The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Metal complexes of medicinal drugs have played a central role in the development of coordination chemistry. Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. It is well known that proton transfer plays an important role in the reactions such as complexation, acid–base catalyzing and enzymatic reaction in aqueous solution. The stability constants can be of significance in order to predict different chemical processes such as isolation, extraction or preconcentration methods. Thus, the accurate determination of acidity and stability constants values are fundamental to understanding the behavior of ligands and their interaction with metal ions in aqueous solution. pH metric titration is accepted as a powerful and simple electro analytical technique for determination of stability constants. Most of the f-block elements form complexes. There are different kinds of ligands used for complexation. For the present investigation, we have selected Zonisamide drug, having molecular formula $_{C8H8N2O3S.}$ The IUPAC name of Zonisamide is Benzo[d]isoxazol-3-yl methane sulfonamide. *Zonisamide* is a sulfonamide anticonvulsant use as an adjunctive therapy in adults with partial-onset seizures, infantile spasm, mixed seizure types of lennox– gastaut syndrome, myoclonic and generalized tonic clonic seizure. Zonisamide is approved in the United States, United Kingdom and Australia for adjunctive treatment of partial seizures in adults and in Japan for both adjunctive and monotherapy for partial seizures (simple, complex, secondarily generalized), generalized (tonic, tonic-clonic (grand mal) and a typical absence) and combined seizures. For epilepsy, most studies have used oral zonisamide in daily doses ranging from

200 to 600 milligrams/day, divided in 2 daily doses, adjusted to maintain serum levels of 15 to 40 micrograms/milliliter.

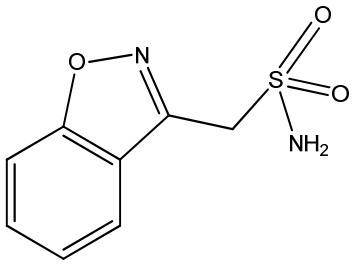

Figure: Zonisamide

In recent years, there has been an increased interest in the study of the rare earth metal complexes. Owing to the unique properties of the lanthanide ions, lanthanides have often been effectively employed as active Ca^{2+} and Mg^{2+} substitutes in many metalloproteins as chiral NMR shift reagents. MRI contrast agents and also luminescent probes of metal binding in biological systems. Thus after a review of literature survey and in continuation of our earlier work with complexation of medicinal drugs[1-13]and Schiff bases[14-15], we have carried out a solution study on the complexation of drugs. It was thought of interest to study the complexes of Zonisamide with five rare earth metal ions Ce^{3+}, Pr^{3+}, Nd^{3+}, Pm^{3+} and Gd^{3+} using pH metrically in aqueous medium.

EXPERIMENTAL SECTION

***I. Materials and Solution*:**

The pure drug **Zonisamide** is soluble in double distilled water. All rare earth metal salts, NaOH, NaClO4 and HClO4 are of AR grade. The solutions used in the pH metric titration were prepared in double distilled CO2 free water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of HClO4. 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 NaClO4. 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.

***II. pH metric procedures*:**

The Calvin–Bjerrum titration technique has been used in the present study. 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.

i. Free Acid HClO4 (A)

ii. Free Acid HClO4 + Ligand (drug) (A+L)

iii. Free Acid HClO4 + Ligand (drug) + Metal solution (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.

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

Metal ion	*Proton- ligand* **pK1**	*Stability constant* **pK2**	*Metal-ligand* **logK1**	*Stability* **logK2**	*Constant* **logβ**
Ce (III)	9.0284	9.9823	1.8165	- -	1.8165
Pr (III)	9.0284	9.9594	1.8054	- -	1.8054
Nd (III)	9.0284	9.9594	3.4580	- -	3.4580
Pm (III)	9.0284	9.9594	3.4548	- -	3.4548
Gd (III)	9.0284	9.9594	3.4952	- -	3.4952

RESULTS AND DISCUSSION

The results obtained are analyzed by the computer programme and the stability constant values are calculated. The proton-ligand stability constant (pK_a) of Zonisamide drug is determined by point wise calculation method as suggested by Irving and Rossoti. The result reveals that the complexation curve bifurcate at lower pH, which indicate the formation of complexes. Further since there was no precipitation of hydrides at higher pH indicating strong tendency of ligand towards metal ions for complexation.

The overall stability constant can be given as
M + A + L_____MAL

Metal ligand stability constant (logK) of rare earth metal ions with Zonisamide are calculated by point wise and half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed. Since we got values of proton-ligand formation number ($\boldsymbol{n_A}$) between 0.2 to 0.8 indicating 1:1 complex formations.

The shielding of the 4f electrons is exhibited in the stability constants of the present rare earth metal complexes with Zonisamide reported in Table 1. Zonisamide follows order of stability constants of their trivalent metal complexes as $Pr^{3+} < Ce^{3+} < Nd^{3+} < Pm^{3+} < Gd^{3+}$ The trivalent Gd is stable, it has half field f-orbital even then it forms a more stable complex. This may be due to involvement of probably vacant d-orbital for complexation without disturbing the stability of half field f-orbital. Since the atomic size of lanthanide ion is almost identical therefore the stability does not depend on ionic size. Also in our investigation stability cannot be correlated with atomic number. The graphs of logk vs atomic number, atomic radii, were plotted & found in good agreement with earlier studies.

CONCLUSION

In the present investigation Zonisamide plays the role of ligand in the complex formation with trivalent rare earth metals ions. pH metric study on stability constants of Zonisamide complexes with rare earth metals ions follows the order of stability constants as:

$Pr < Ce^{3+} < Nd^{3+} < Pm^{3+} < Gd3+$

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