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CO ORDINATION OF SEPTRAN DRUG WITH TRACE METAL IONS IN THE BIOLOGICAL SYSTEM

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ABSTARCT

Sulphonamide inhibits both gram positive and gram-negative bacteria. Septran is a combination sulphonamide drug of sulphamethaoxazole and Trimethoprim. The aim of our study was to study of complexation of naturally occurring inorganic elements with this drug. The complex formation of sulphamethoxazole with trace metal ions such as Fe (III), Cu (II), Co (II), Ni (II), Mn (II), Zn (II), Al (III) and Ca (II) were studied by potentiometric method. It was found that Mg (II), Ca (II) and Zn (II), Cu (II) showed identical behavior. All metals form complex at acidic pH as well as at basic pH, the comparison of septran DS drug with single trimethoprim compound, it was observed that septran is a combination drug it formed complexes at lower pH as compare to trimethoprim, which is not a combination drug and formed complexes at higher pH.

Key-words: Septran, biological system, metal ions, drug

INTRODUCTION

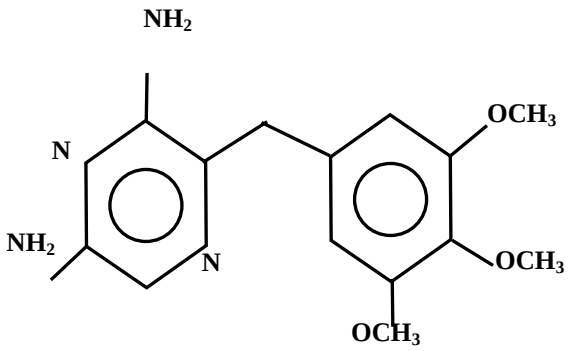
Septran is a sulphonamide combination drug containing trimethoprin and sulpha methaoxazole. The Sulphonamide drugs were the first effective chemotherapeutic agents to be employed systematically for prevention and cure of bacterial infections in man. In 1935 Domzak reported remarkable curative effects of this compound and named it Prontosil (Hussain and Naved, 1993). Over 3300 sulphonamides have been prepared, but only a few have been accepted for medicinal use. Most of these are insoluble in water but their sodium salts are relatively soluble. It is classified according to those employed for the treatment of bowel diseases. They are effective against gram-positive bacteria (e.g. hemolytic Streptococi and Pneumococi) and to lesser degree against gram-negative (meningcoci and gonococci), and virus (Dass., 1990). All sulphonamides in clinical use are structurally related to p-amino benzoic acid (PABA). The compound PABA now known as sulphonamidewas first synthesized in 1908 because of structural similarity, it competes with PABA for the synthesis of folic acid in microbes. Pteroate synthantase enzyme important for the synthesis of dihydroxy pteraic acid, which behaves as precursor of folic acid. The action of sulphonamide is bacteriostatic and reversible by the removal of drug in the prescence of excess of PABA. It acts indirectly on DNA synthesis. Since the active form of co-enzyme tetrahydrofolic acid, serves as an intermediate in the transfer of methyl, formyl and single carbon fragments, in the biosynthesis of purine nucleotide the thymidyl acid as well as some amino acids (Kuhse, 1995). Bacterial resistance to sulpha drugs can arise from plasmid transfers or random mutations. The resistance is generally irreversible and may be due to any three possibilities, altered enzyme, increased drug inactivation and increased PABA synthesis.

Sulpha drugs are metabolized in liver mainly by acetylation. Genetically the population is of two types, those is which acetylation is quick so duration is short and toxic effect is less and the other in which acetylation is slow so duration of action is long and toxic effects are present at neutral or acidic PH causing crystalluria and damages kidney (Zhou and Kunihiku, 2004]. In many infections they exert a more powerful effect in combination with penicillin given singly. The use of this drug without the direction of physician becomes some time serious and fatal toxic reactions which may result Hemolytic anemia, organulocytosis, hyperleukocytosis, various skin eruptions, hepatitis, kidney stone, complete suspension of kidney functions may occur during the course of therapy (Yahia *et al*., 2005). Sulpha drugs are distributed throughout the body water and penetrate well into cerebrospinal fluid even in the absence of inflammation. They can also pass the placental barrier. Drug is rapidly and adequately absorbed from the gastrointestinal tract and often is found in the urine. The small intestine is major site for absorption but some of the drug is also absorbed in the stomach (Hughes and Poole, 1989). The aim of our study was to be complex formation of sulpfamethoxazole and trimethoprim with trace metal ions such as Fe(III), Cu(II), Co(II), Ni(II), Zn(II), Al(III), Ca(II), and Mg(II) by potentiometric method.

MATERIALS AND METHODS

All reagents were of AR grade. Solutions were made in de-ionized water freed from CO_2. For all pH measurements Orion pH meter model SA 720 were used. A 0.05 M solution of potassium hydrogen pthalate, which has pH value 4.01 at 25°C, were used to calibrate the pH meter along with the standard buffer solution made from BDH standard chemicals (Martell and Motekaitis, 1988). For potentiometric titration a double walled glass cell was used. The temperature of the cell was kept constant throughout the experiment by circulating water. All the titration were done at room temperature. 20ml of 0.01 M metal ion solution mixed with 20ml of 0.01 M septran drug solution and titrated with 0.01M NaOH solution. The change in pH was noted with the small increment (0.1 ml) of base. The solution was stirred with magnetic stirrer constantly (Bassate, 1979). For each metal septran drug solution, these titrations were performed twice to minimize the probable error. The results obtained were given in the table.

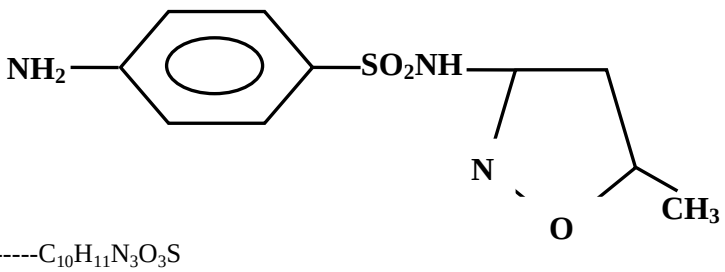
TRIMETHOPRIM



Mol. Formula----------$C_{14}H_{18}N_4O_3$
Mol. Weight----------290.3

DESCRIPTION
A white or yellowish white powder.
SOLUBILITY
Very slightly soluble in water and also slightly soluble in alcohol. It shows polymorphism.
PREPARATION
Co-trimoxazole intravenous infusion.
Co-trimoxazole oral suspension.
Paediatric co-trimoxazole oral suspension.
MELTING POINT
The melting point of trimethoprim is 199 C to 203 C.
STORAGE
Should be protected from light and air.

SULPHAMETHOXAZOLE



Mol.Formula----------$C_{10}H_{11}N_3O_3S$
Mol.Weight----------253.3

DESCRIPTION
A white or yellowish white crystalline powder & odorless.
SOLUBILITY
Very slightly soluble in water, soluble in acidic or alkaline medium on heating.
PREPARATION
In this preparations using 30-amino-5-methylisoxazole as the coupling amine.
MELTING POINT
The melting point of sulphamethoxazole is 169 °C to 172 °C.
STORAGE
Store in a well close container and should be protected from light.

RESULTS AND DISSCUSION

The potentiometric titration (pH and volume of base added) for septran (sulphaoxazole , trimethoprim) and metal complexes i.e Fe(III), Cr(III), Cu(II), Co(II), Ni(II), Zn(II), Ca(II), Mg(II) were shown in Table 1. It was concluded that septran is a combination drug of two types of sulpha drugs that is sulphamethaoxazole and trimethoprim therefore two types of complexation occur with metal ions one with sulphamethaoxazole and another with trimethoprim. Mg(II) from first complex at 2.6 pH and other at 6.4, Ca(II) formed first complex at 2 pH and other at 6.2 ,Mn(II) formed first complex at 2 pH and other at 5.6 , Co(II) formed three types of complexes one at 2.2 pH and other at pH 6.2 and third at 8.6, Ni (II) formed first complex at 2.2 pH and other at pH 9, Cu(II) formed first complex at 2.0 pH and other at pH 7 and Zn(II) formed complexes at pH 2 and other at pH 7.6 .Among tripositive metal ions Al(III) formed complexes at pH 2.0 and other is at pH 4.4. In Cr (III) first complexation started at pH 2 and other at pH 6.2, Fe(III) showed very different behavior first complex formed at 0.8 – 1.4 pH and other the complex was formed at pH 3. This shows that septran drug have high affinity for spherically symmetric tripositive ions. Therefore these septran drugs have interactions for Fe (III) in the biological available metal ions that is the reason prolong therapy of these septran drugs may result in anemia of iron deficiency (Bodo and Maksay, 2002) .This type of chelation studies of septran drug are very important in drug metabolism. If changing the concentration of metal ions, abolishes activity against the microorganism. Septran drugs also become unaffected, when they are used in metal free system. They can kill the bacteria very effectively when only traces of metal are present (Linder and Hazegh-Azam, 1996).

Table 1. Formation of Septran DS metal Complexes at different pH (SULPHA METHAOXAZOLE AND TRIMETHOPRIM).

Metals	Formation of complex at different pH.
Mg(II)	2.6-5.2 and 6.4-10.4
Al(III)	2.0-3.2 and 4.4-10.2
Ca(II)	2.2-5.4 and 6.4-10.8
Cr(III)	2.0-4.8 and 6.2-11.0
Mn(II)	2.0-3.8 and 5.6-10.4
Fe(II)	0.8-1.4 and 3.0-10.6
Co(II)	2.2-5.6,6.2-7.4 and 8.6-10.6
Ni(II)	2.2-6.6 and 9.0-10.8
Cu(II)	2.0-5.4 and 7.0-11.0
Zn(II)	2.0-6..4 and 7.6-11.2

Table2. Formation of metal Complexes with Trimethoprim at different pH.

Metals	Formation of complex at different pH
Al(III)	4.80-5.84
Ca(II)	4.06-5.05
Cu(II)	4.06-4.09
Co(II)	4.05-5.05
Mn(II)	4.44-5.30
Zn(II)	4.74-5.24
Fe(II)	5.36-5.68
Ni(II)	4.86-5.36 and 5.30-6.12

Table 3. Jobs plot of iron septran complexes.

M : L	Absorbance L_{max} 500
1 : 1	0.214
1 : 2	0.15
1 : 3	0.12
1 : 4	0.10
1 : 5	0.90
1 : 6	0.80

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