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Electrochemical, invivo and invitro study of Acyclovir and Co(II) Complex

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ABSTRACT: The antibiotic drug 2-amino-1,9-dihydro-9-(2-hydroxyethoxy)methyl)-6H-purin-6-one has been quantitatively and qualitatively analysis by polarographic & amperometric process. Acyclovir give well identified wave in 1.0mkcl at pH5.0±0.2.Co (II)-Acyclovir complex studied in aqueous phase..The IR spectral data on the drug & its Co (II) complex indicate the co-ordination through nitrogen atom of azid group. The data showed a shift bands of azide group in complex from1634 cm^{-1}1651-cm^{-1}.Hence the tentative structure of the complex has been suggested. The antibiotic activity of the complex has been determine by using paper disc method against Streptococcus A ,K. Pneumonia, Salmonella. Typhi, and Aspergillus. A ,etc .Looking at this inhabitation power against the different test pathogens..It presumed that the complex may be more potent at compare to the parent drug .Pharmacological study shows the toxicological or non toxicological study of complex drugs

Keywords : Acyclovir, Electrochemical study, Spectroscopic, Metal complex, Microbial, Pharmacological studies

1 INTRODUCTION

A survey of relevant literature show that Co(II) is the major constituent of many enzyme involved in many metabolic activity of body. Some recent work reveles that some antibiotic, antidibetic, antiseptic antihistaminic drug metal complex have been synthesized according to their mode of biological importance & has been explained. Looking at the importance of role of transition metal ions in biological process.The bio-inorganic study of transition metal in Co(II)-Acyclovir complexation .The biological activities of the pure drug has been changed by the complexation with essential transition metal which has been evaluated the possible role of analgesic activity in present paper.(1,2)

2 PROCEDURE

Chemical and regents:- All the chemicals were used of analytical grade and used without of further purification. Sigma Laboratory, USA, supplied the anti-malarial drug Acyclovir,standard solution of Co(II) (0.01M),Acyclovir (0.01M) and KCl 2M were prepared in distilled water.

Polarographic study of Co(II)-Acyclovir complex-:

Polarographic measurements were made on a polarograh software connected metrohm 757VA computrance.The polarographic cell consisted of a three electrodes assembly and a stirrer having a dropping mercury electrode(DME) as a working electride,a platinum wire as an auxiliary electrode and Ag/AgCl electrode .The nitrogen gas was bubbled for five minutes. Elico digital PH meter model LI-108 was used to measure the PH of all test solutions.(3) Experimental sets were prepared by keeping overall CO(II) metal ion and KCl (supporting electrolyte) concentration fixed at 1.0M respectively.The ligand concentration was varied from 0.01 to 5mm. The PH of the solution was adjusted to 5.0± 0.2 using HCl/NaOH solution.

Amperometric study of (Co(II)-Acyclovir complex:-

The prepared complex have been characterized on the basis of IR spectroscopic and amperometric analysis.A systronic digited pH meter-335 was used for the pH measurements. The amperometric titration were performed on a manually operated set up , equipped with a polflex galvanometer and an AJCO varnier potentiometer(4) . IR spectrum of solid complex was recorded using KBr pelletes on an shimdzuy, japan, Model 470 IR spectrophotometer. For amperometric titration ,experiment; sets, each having different but known amount of Co(II) were prepared in appropriate quantity of supporting electrolyte KCl and pH was adjusted to 5.0±0.2.Titration separately against standard solution of Acyclovir at pH (5.0±0.2) using HCl/NaOH) at 1.02V for Co(II) V/s calomel electrode(SCE) the plateau potential of Co(II) respectively .The current volume plot resulted in L shaped curve obtained (5) Synthesis procedure of Co(II)-Acyclovir solid complex:- Acyclovir and cobalt nitrate solution were separately prepared and were mixed in 1:1 molar ratio. The mixture was then refluxed in a round bottom flask for 1-2h. The residue complex was filtered and washed thoroughtly to remove any unreacted materials. The complex was dried at low temperature ($36^{O}C$) and stored overP_4O_{10} [6] The IR spectrum of the solid complex was recorded using KBr pallets on a Perkin Elmer IR Spectrophotometer Model-379.

Antimicrobial screening

Paper disc method **(5,6)** was followed for the microbial screening of Co(II) Acyclovire complexes against various pathogenic bacteria's and i..e Streptococcus A ,K. Pneumonia, Salmonella. Typhi and Aspergillus A sterilized filter paper disc (6mm)were dipped into the complex solutions of 0.01M concentrations. Prior to this ,the bacteria and fungi were separately homogenized with nutrient agar and potato dextrose media (at 27-$30^{o}C$) plated on the sterilized Petri dishes. Dipped filter paper discs were placed on seeded medium. After 24 hour of incubation antimicrobial activities were The number of replicates in each case of three, percentage inhibition was calculated using the following formula

% inhabitation= a-b/a×100

Where a=diameter of inhibition zone for control Acyclovir and b=diameter of inhibition one for complex.

Pharmacological studies:- For Pharmacological study the Swiss mice were infected by Virus Varicella zoster Virus. The albino mice were divided into 3groups and single mice in each group and kept in metal cage and feed with mice cube and water albitum.(7)

Group A-Control

Group B- Acyclovir

Group c-(Co (Acv)$No_3.H_2O)so_4.2H_2O$

The oral dose of the drug solution were prepared in distilled water.These prepared solution administrated orally to mice two time daily on 15,30,45,60 days.The mice in each group were marked for their identification. The mice were inoculated intravenously with 0.2ml of 1 x 106 parasitized erythrocytes suspended in buffered phys iological saline (pH 7). The mice were left for 6 days and their levels o f p a rasitaemias were monitored daily by counting parasites in blood sample, fixed with 70% methanol an d Giesnsa stain.(8) The co-ordination of metal and drug compex enhance the activity of the drug. This could be due to complex binding first without being decompose at recptor site and lso the deposition of free metal ion in the membrane of the parasite. The result show the comparison between the ligand(drug) and their complex showed that Co (Acv)$No_3.H_2O)so_4.2H_2O$ are more active than their respective free ligand.

Result and discussion:-
Polarographic behavior of Acyclovir with Co(II):- Polarographic behavior of Acyclovir with Co(II):- In 1.0 M KCl at pH 5.0±0.2 Co(II) and its complex with the ligand under study were found to be reversibly reduced involving three electrons which was evidenced by the plots of $i/(i_{d-i})$.The reduction was found to be diffusion controlled, which was evidenced by the plot of i_d Vs. *Corr.* When the concentration of Acyclovir ligand increase the half wave potential of Co(II) metal ion shifted to more electonegative value and the diffusion current also decreaded there by showing complex formation between Co(II) with Acyclovir. To study the composition and formation constant of the complex, plots of $\Delta E_{1/2}$ (shift in the $E_{1/2}$) i.e $\Delta E_{1/2}=(E_{1/2})_c-(E_{1/2})_s$ against log C_X (logarithm of the concentration of the ligand) were drawn. The plots were linear lines showing the formation of single complex species in solution Lingan's treatment[9] of the observed polarographic data reveals 1:1 metal Acyclovir complex with formation constant 1og β=4.0.

Amperometric determination of Acyclovir withCo(II)- Co(II) gives a well defined polarographic wave in 1.0M KCl at pH 5.0 ± 0.2.The diffusion current was found proportional to the concentration of Co(II). The plateau potential for the polarographic wave of Co(II) (-1.4V) vs Hg pool was applied for carrying out amperometric titration. On performing the amperometric titration of drug solution with standard solution of Co(II),the current volume plots resulted in L shaped curve (Fig 1).The end point as located by graphical method revealed metal to drug ratio of 1:1, which is in agreement with the author's observation on the metal:ligand equilibria using polarographic method.

Characterization of Co(II)-Acyclovir complex:- The IR spectra of the obtained complexes wrew compared with that of acyclovir. The more relevant featlure are : shift to lower frequencies of the strong band at 1718cm-1 which is assigned to the vibration v [C(6)=O(6)] in free ACV.This is consistent with the C=O group involved in hydrogen bonds.In some Co-ACV complex,it has been observed that short hydrogen bonds involving O(6) significantly diminish the carbonyl stretching frequency in the IR spectra Fig(1) . The 1634cm-1 band related to $\delta(NH_2)$ is not appreciably shifted for 1,2,4 and 5,although for 3 it is shifted to 1651cm-1, possibly due to the double interaction of the NH2 group present [N(3)···H2N,Cl···H2N]. (b) Splitting of the 1487cm-1band,for δ[C(8)-H]+v[C(8)-N(7)] and variation,related to the five membered ring,have been observed in the spectra of several structurally known N(7)-metallated complex. The far-IRspectra of the complex shown a new band at 312 and 313 cm-1 assigned as essential v(Co -N).The low frequency band at 332cm-1,found for compound 3,may be attributed to the Co-Cl stretching mode of the terminal chlorides. Table(2) (10),

Antibacterial study of Acyclovir cobalt(II) complex:- Antibacterial activity of the complexes/ligands was investigated by a previously reported method against different bacterial strains such as Streptococcus A ,K. Pneumonia, Salmonella. Typhi, and Aspergillus. A .The nutrient agar medium (piptone,Beef extract,NaCl and Agar-Agar) and 5mm diameter paper disks (whatman No.1) were used.The investigated compounds,i.e ligands and their complexes, were dissolved (30µg) in DMF (0.01ml).The filter paper disks were soaked in solutions of ligands as well as complexes,dried ad then placed in petri plates previously seeded with the test organisms. The plates were incubated for 24h at 37oC and the inhibition zone around each disk was measured.The result obtained are tabulated in table Table (1) (11)

In-Vivo Study :- Albnio mice for experiment was injected as describe by Sanchey-Selgado et al. The mice were divided into 3 groups and keep 1 mice I each group.

Group A-Control Group A

Group B-Acyclovir complex

Group C- -(Co (Acv) $No_3.H_2O)so_4.2H_2O$

The drug solution prepared with DMSO Were administered orally to the mice , two times daily for 15 days,30 days,45 days ,60 days at a dosage level 0.65 mg/150 g of drug. The mice in each group were marked for easy identification. The mice in each group were marked for easy identification. The albino mice were injected intravenously with 0.2m of 1×10^6 bacterial parasitized erythrocytes suspended in buffered saline solution (pH 7.4).The mice were left under observation 10 to 15 days interval of each dosing and their level of bacterial ppm of solution of each of the ligand and complex was prepared 0.4ml each of the solution was injected daily into the each mice of group and their effect of bacteria was determine on 15 days of intervals. Only physiological Saline solution was given to the control animal.(12) The protocol study of histropathalogical effect of oral administration of the ligand and the complex on rat liver cell and intestinal cell-wall by xyline-alcoholic test showed mentioned in slide. These slide of liver cell and intestine cell-wall showed the toxicological and non-toxicological behavior of the drug and its metal complex in liver cell and intestineal cell-wall Fig (2)

6 TABLE AND FIGURE

Table 1-In-Vitro study of Acyclovir Cobalt(II) Complex

Acetetaminophen	Assignments	Complex
~3640 ~178 ~1017 ~2960 ~2880 ~3030	O-H streaching M-N streatching C=O C-H stretching (aromatic methyl group) C-H stretching (aromatic methyl group)	3640 ~178.8 1726 2960 2880 3030
~1580 ~1460 ~1495 ~1606	C-H stretching - - -	1580 - 1495 1606
~1634	-N-H	~1635

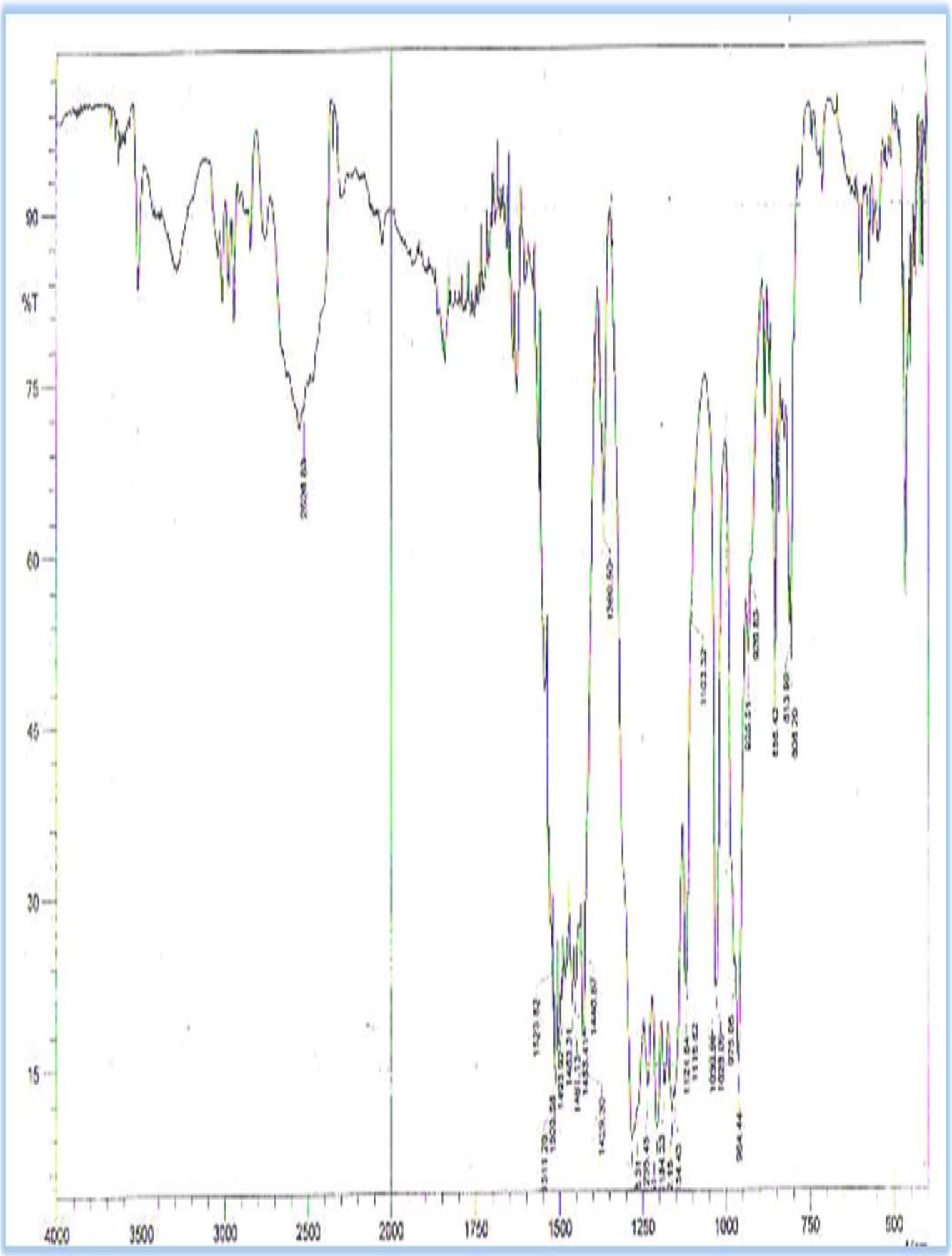

Fig:-1 FT-IR spectrum of Acyclovir-Co(II) complex

Table 1-In-Vitro study of Acyclovir Cobalt(II) Complex

	Organism	In-habitation zone (mm) conc. Of compound 1.0mM [B]	Con-trol of met-al [A] 1.0mM	% change over con-trol met-al (A-B)/A ×100	Con-trol drug (Y) 1.0mM	% change over con-trol drug (Y-B)/Y ×100
1	Strepto-coccus.A	14	25	44	25	44
2	K.pneumonia	–	–	–	17	–
3	Salmo-nella.Typhi	–	–	–	21	–
4	Aspergillus.niger	–	–	–	11	–

7. Acknowledment and Reference

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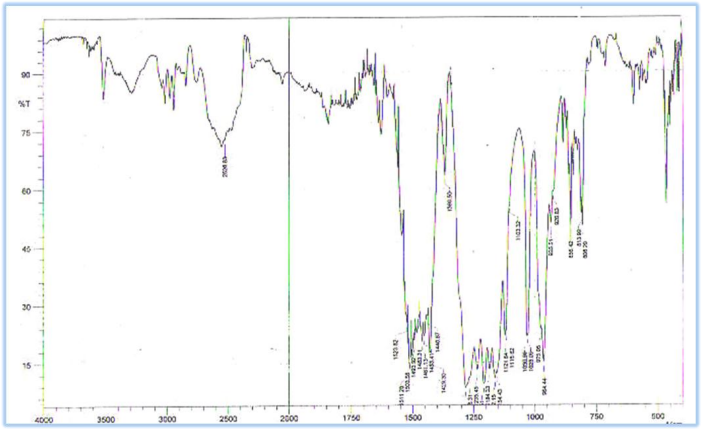

Fig:-1 FT-IR spectrum of Acyclovir-Co(II) complex

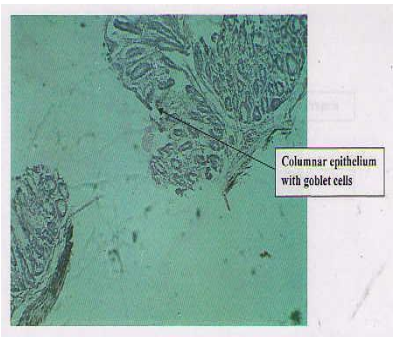

Fig No(2) Shows Columnar epithelium with goblet cells of Jejunum part of mice Intestine due to oral dose of Acyclovir+Cobalt(II) Nitrate as observed in 10X

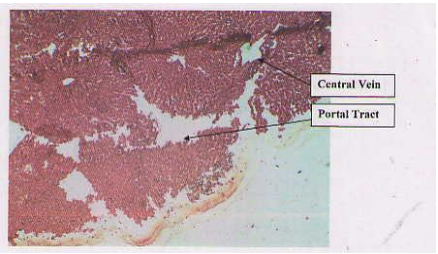

Fig No(3) Shows Portal Tract of mice Liver due to oral dose of Acyclovir+Cobalt(II) Nitrate as observed in 10X.