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Synthesis, characterization and antimicrobial activity of alkaline earth metal complexes

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ABSTRACT

The more versatile Mg^{+2}, Ca^{+2}, Sr^{+2} and Ba^{+2} complexes in their biological activity, were synthesized by using biologically important ligand. Synthesized complexes were characterized by IR, Mass spectra, TGA analysis and Elemental analysis. All the complexes and ligand have been screened for antibacterial and antifungal activities.

Key words: Acyclovir, antibacterial, antifungal.

INTRODUCTION

In recent years, research into new pharmaceuticals, both organic and inorganic, has seen a change in trend away from cytotoxic compounds to molecular targeting agents [1]. This is particularly true for the treatment of cancer as well as antiviral as there is a constant strive to overcome drug resistance by opening up new mechanism of action [2]. One approach which has shown rapid growth in recent years and a number of notable successes is the design of metal chelate incorporating biologically active ligands. Such compounds offer the possibility for design of metal based drugs with enhanced, targeted activity by combining the specificity of the ligand to interact with a particular molecular site with the properties inherent to the metal centre.[3]

Acyclovir (ACV), 9-[(2-hydroxyethoxy)methyl]guanine, an analogue of 29-deoxyguanosine is an efficient topically active acyclic nucleoside with inhibitory activity towards several herpes viruses, especially HSV-1 and HSV-2.[4] Acyclovir (ACV) is both the ancestor of and the paradigm for development of many of the purine nucleoside inhibitors. Acyclovir is well known antiviral – a broad spectrum antibiotic – a chemical acyclic analogue of the natural nucleoside 2'-deoxyguanine with antiviral activity " in vitro", against herpes simplex viruses (HSV), varicella zoster virus (VZV), Epstein barr virus (EBV), cytomegalovirus (CMV) and human herpes virus 6 (HHV-6) [5], which is effective against gram positive and gram negative bacteria [6].

Metal chelates have a broad range of medicinal applications. A number of metallic elements play crucial roles in biology and it is clear that many organic compounds used in medicine require metal ions for activation or biotransformation in order to achieve their mode of action.[7] Metal ions are often classed as 'toxic' and 'non-toxic', however their biological activity depends very much on speciation and it is now widely accepted that, with carefully controlled co-ordination chemistry, even 'toxic' metals can exhibit therapeutic properties.[8] It is therefore very important to investigate and understand the effects of varying the oxidation state, numbers and geometries of coordinated ligands on the biological properties of metal chelates to design metal – based drugs.

MATERIALS AND METHODS

The ligand used was of A.R. grade. It was obtained as a gift from different pharmaceuticals companies and their purities were checked by noting their melting point as well as TLC. All metal carbonates used were also A.R. grade. Stock solutions of Mg (II), Ca (II), Sr (II), and Ba (II) perchlorates were prepared and analyzed by complexometric methods. Conductivity water was used through out the work. The pH of this water was found to be ~ 6.9.

Preparation of Chelates

1:1 molar ratio of metal perchlorate {$Ca(ClO_4)_2$, $Mg(ClO_4)_2$, $Sr(ClO_4)_2$, $Ba(ClO_4)_2$} and ACV were taken in the form of DMSO solutions, after mixing, this mixture with constant stirring and it was refluxed for 2 hours at 150°C temperature, until the mixture remains ¼ part. After doing this process the solutions were cooled and the binary chelate isolated from the mixture, it was cooled, filtered and washed with pure water and alcohol to remove impurities soluble in those solvents, then they were characterized by different methods.

The analytical data of the chelates showed 1:3 stoichiometry. The general equation for the formation of the chelate with acyclovir is as shown below.

$M^{2+} + L + H_2O \longrightarrow [M\ L_3]\ H_2O$

$Mg^{2+} + L + H_2O \longrightarrow [Mg\ L]\ H_2O$

Where, L = Conjugated base of acyclovir,

$M^{2+} = Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}$

The Mg (II), Ca (II), Sr (II), and Ba (II) chelates are colourless; all are crystalline or amorphous and stable in air. The chelates are soluble in DMSO and partly soluble in water and other common organic solvents. The melting points of the chelates are higher, which suggest their greater thermal stability. To check the presence of single or more than one chelates, TLC of the solid was carried out using silica gel as the stationary phase and N-amyl alcohol, glacial acetic acid and water (6:1:2) as the solvent system. For all the four chelates only one clear spot was obtained indicating the formation of only a single product.

Table: 1 Analytical Data and Some Physical Properties of the Metal Chelates

Compound Molecular Formula	Colour	Yield %	Molar conductance	Formula Weight	Analysis (%) Calculated / (Found)				M.P. °C
					C	H	N	M	
$C_8H_{11}N_5O_3$ (ACV)	White	-	-	225.21	42.67 (42.77)	4.92 (4.99)	31.10 (31.89)	-	256.5 °C
[Mg- (ACV)].H_2O	White	49.04	44.714	267	35.95 (36.27)	4.86 (4.90)	26.21 (26.84)	2.97 (2.73)	>240°C
[Ca- $(ACV)_3$] ·3H_2O.2ACV	White	44.80	0.158	1219	39.37 (40.32)	4.10 (4.79)	28.71 (29.23)	4.99 (4.40)	>256°C
[Sr$(ACV)_3$ ·$(H_2O)_4$] ·3ACV	White	40.29	0.399	1509	38.17 (40.28)	4.90 (4.86)	27.83 (28.72)	9.76 (8.98)	>248°C
[Ba$(ACV)_3$] ·4ACV	White	30.85	1.587	1762	38.13 (39.89)	4.37 (4.55)	27.80 (28.01)	15.01 (14.41)	>253°C

Table-2 Infrared Spectroscopy of the Metal Chelates of Acyclovir (Cm^{-1})

Compound & Chelates	-NH_2	>NH	-OH	>C=O	C–O–C	C–O Ether	C–O Alcohol	-CH_2	-C–N	M–N
ACV	3471, 3440 1573	3302 1541	3522	1715	1106	1183	1048	3183 2927-2854	1346 1308	-
[Mg- (ACV)].H_2O	- 1584	3386	3512	1720	1109	1183	1048	3121 2952	1346	412
[Ca- $(ACV)_3$] ·3H_2O.2ACV	3442 1575	3312	3521	1720	1106	1183	1049	3187 2928-2855	1347	410
[Sr$(ACV)_3$ ·$(H_2O)_4$] ·3ACV	3442 1576	3311	3521	1721	1106	1183	1049	3187 29928-2855	1347	418
[Ba$(ACV)_3$] ·4ACV	3441 1575	3375	3512	1720	1106	1183	1049	3187 2927-2855	1347	412

Table:-3 Antibacterial activity

Sr. No	Code no.	minimal inhibition concentration			
		E.coli	***P.aeruginosa***	***S.aureus***	***S.pyogenus***
	Compound & Chelates	**MTCC 443**	**MTCC 1688**	**MTCC 96**	**MTCC 442**
1	AMPICILLIN (STD. DRUG)	100	100	250	100
2	ACV	250	250	500	500
3	[Mg- (ACV)].H_2O	100	100	150	150
4	[Ca- $(ACV)_3$] ·$3H_2O$.2ACV	250	150	500	500
5	[Sr$(ACV)_3$ ·$(H_2O)_4$] ·3ACV	500	500	250	500
6	[Ba$(ACV)_3$] ·4ACV	25	100	150	200

Table:-4 Antifungal activity

Sr. No	Code no.	minimal fungicidal concentration		
		C.albicans	***A.niger***	***A.clavatus***
	Compound & Chelates	**MTCC 227**	**MTCC 282**	**MTCC 1323**
1	GRESEOFULVIN (STD. DRUG)	500	100	100
2	ACV	500	1000	1000
3	[Mg- (ACV)].H_2O	150	250	250
4	[Ca- $(ACV)_3$] ·$3H_2O$.2ACV	250	500	>1000
5	[Sr$(ACV)_3$ ·$(H_2O)_4$] ·3ACV	500	>1000	>1000
6	[Ba$(ACV)_3$] ·4ACV	500	>1000	>1000

RESULTS AND DISCUSSION

Elemental analysis:

Elemental analysis of the binary chelates isolated in the present study indicates 1:3 compositions. This is also confirmed by observing their non-conducting nature.

Magnetic Susceptibility Study:

In the present study, chelates of Mg (II), Ca (II), Sr (II), and Ba (II) are found to be diamagnetic in their character from the values of magnetic moments.

Conductance Measurements:

The conductivities of all the chelates are measured in DMSO at 25°C at a concentration 10^{-3} M using Systronics conductivity meter. All chelates were found to be non conducting in nature.

Infrared spectra

The IR spectra of the obtained chelates were compared with that of acyclovir.[9,10] The more relevant features are: (a) shift to lower frequencies of the strong band at 1715 cm^{-1} (1720, 1694 for 1; 1720, 1695 for 2; 1721, 1695 for 3 and 1720, 1694 cm^{-1} for 4) which is assigned to the vibration *n*[C (6) = O (6)] in free ACV. This is consistent with the C=O group involved in coordination. The 1610 cm^{-1} band related to *d*(NH_2) is not appreciably shifted for 1, 2, 3 and 4, possibly due to the double interaction of the NH_2 group present [N(3) ----H_2N, OH----H_2N]. (b) Splitting of the 1484 cm^{-1} band [9] (for1, 2, 3, and 4)assigned to *d*[C(8)– H] 1 *n*[C(8)–N(7)] and these variations, related to the five membered ring, have been observed in the spectra of several structurally known N(7)-metallated chelates.[9,11]. (c) The weak intensity non-ligand bands observed in chelates in the regions 470-410 cm^{-1} are assigned to v(M-N) stretching vibrations [12]. The presence of free -NH_2 band in acyclovir appears at 3471 cm^{-1} in metal chelates it appears at 3440-3442 cm^{-1}. It shifts to lower side by 30-35 cm^{-1}. This effect is convincing proof of coordination of the metal with ligand in all the chelates [13]. M – O stretching frequencies generally formed at lower values than 400cm^{-1} therefore could not be reported.

Mass Spectra

The base peak obtained in the case of chelates of Mg, Ca, Sr, and Ba is at M\Z = 248 amu. This mass is most probably due to Ligand + Na because the mass spectra obtained is Fast Atomic Bombardment method. A very feeble molecular peak 267 m/z is seen in mass spectra of chelate of Mg^{2+}. However m + 23 is not observed at all. The 178 m/z peak is base peak for Mg^{2+}, Ca^{2+}, and Sr^{2+} chelates and 43% of base peak in case of Ba^{2+} chelate the most probable explanation for this peak is due to ACV-1-C_2H_5OH = 178 amu. In case of mass spectra of Ba^{2+} chelate ACV + 1 is the molecular peak which also supports the presence of ACV molecules in crystal formation. Like spectra of other chelates, it also shows the presence of 178 m/z peak.

Thermo gravimetric Study

Examination of the TGA curves of all the chelates and data showed that degradation of most of the chelates occurred in two steps. The first stage of decomposition of complexes in range 50-150^{0}C with a mass loss of about 10% indicate the pressure of associated water molecules. Examination of TGA curves of all the chelates reveals that,

(1) Chelate degradation occurred in two steps.
(2) The degradation of all the chelates starts in the temperature range of depending upon the nature of chelates.
(3) The weight loss amount in the first stage is in between to 50-150^{0}C.

In general, the water of hydration may be considered as either the crystallization water or coordinated water. According to Nikolaev et al [14] water eliminating below 100^{0}C can be considered as the water of crystallization and water eliminated above 150^{0}C may be due to its coordination in the metal.

(4) The second stage of decomposition of most chelates is rapid with the loss of mass about 30%. This is due to loss of molecular fragments of ligand.

The thermo grams were analyzed to obtain information about the percentage weight loss at different temperatures. It has been observed that M(II) chelates show loss in weight corresponding to water molecules in range 50-150^{0}C. Decomposition of Mg (II), Ca (II), Sr (II) and Ba (II) chelates starts above 200^{0}C, so the chelates are the more thermally stable.

Antibacterial Activity:

All synthesized chelates were screened for their antimicrobial activity in vitro against both Gram-positive and Gram-negative bacteria. Staphylococus Aureus, Streptococcus Pyogenes, Escherichia coli and Pseudomonas aeruginosa were the microorganism employed. All the synthesized chelates gave incisive activity against different antimicrobial genus in comparison with the ligand as well as the standard drug which indicates that due to chelation the antimicrobial activity of organic counterpart increases.

In comparison with the standard drug Ampicillin, chelate of Ba^{2+} gives enhanced activity against Escherichia coli, while chelate of Mg^{2+} gives equal activity against the same.

Similarly in comparison with the same standard drug Ampicillin, the chelates of Ba^{2+} and Mg^{2+} illustrates excellent activity against Staphylococus Aureus, while chelate of Sr^{2+} gives equal activity aligned with the same standard drug.

In this progression, when the synthesized chelates were screened in conjunction with Pseudomonas aeruginosa, the chelates of Ba^{2+} and Mg^{2+} bestows identical activity as the standard drug, while the chelate as well as the ligand did not give even equal activity abutting Streptococcus Pyogenes.

But the study revealed interesting changes in antimicrobial activity on chelation including significant activity by some chelates as they compared with the ligand's activity.

The ligand was not sowing even equal activity in comparison with the standard drug, while on chelation it not only give better activity than the standard drug Ampicillin but also donates equal activity as another standard drug Ciprofloxacin (e.g. chelate of Ba^{2+}).

Antifungal Activity:

Three fungii selected viz. C.albicans, A.Niger and A.Clavatus. The synthesized chelates showed antifungal activity against only one organism C.albicans compared to the standard drug Nystatin and Greseofulvin. The chelates exerted less activity against A.Niger and A.Clavatus. The chelates of Mg^{2+} and Ca^{2+} exhibited better activity than Greseofulvin against C.albicans.

Out of all the complexes, the Ba^{2+} chelate exhibited promising antimicrobial activity as a whole.

CONCLUSION

The confirmation and characterization of the compounds prepared in the present studies are interesting. The formation of metal chelates from various considerations is tentatively assigned on the basis of above studies. It is suggested that all metal chelates are dimagnetic, six coordinated, two of them crystalline, having birnary; metal: ligand (1:3) composition.

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