

**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF FE-III AND CO-II  
COMPLEXES DERIVED FROM 4-CHLORO-2-[(2-FURANYLMETHYL)-AMINO]-5  
SULFAMOYL BENZOIC ACID**

Suman Malik<sup>1</sup> and \*Sonal Wankhede<sup>1</sup>

<sup>1</sup>Department of Chemistry, Sadhu Vaswani College, Bairagarh, Bhopal-462030. India

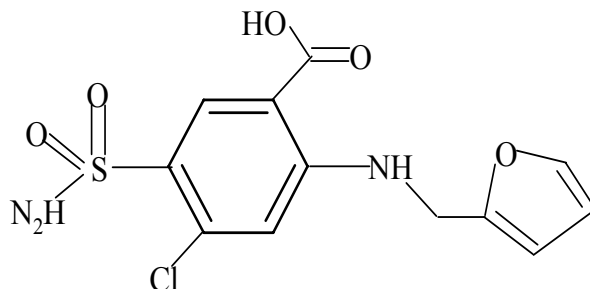
\*Corresponding author- sonal2107@gmail.com, Mobile-9893953427

**ABSTRACT:** The present investigation is an attempt to synthesize and characterize the ligand 4-chloro-2-[(2-furanylmethyl) - amino]-5-sulfamoylbenzoic acid, and its Fe-III and Co-II complexes. The nature of bonding and the geometry of the complexes have been deduced from elemental analysis, magnetic moment measurements and conductivity measurements. Conductometric titrations have suggested metal-ligand ratio of 1:2 for both Fe(III) and Co(II) complexes. The ligand behaves as a bidentate with N, O donor atoms. The electronic absorption spectra and magnetic susceptibility measurements of the complexes indicates octahedral geometry for both the complexes. IR, UV-Visible and SEM studies have been carried out to suggest the tentative structure for the complexes. The synthesized ligand as well as their metal complexes were screened for diuretic activity. The results revealed that the complexes are more potent diuretic than the ligand.

**Key Words:** Synthesis, Characterization, Spectral Studies, Antibacterial studies.

**INTRODUCTION**

The metal ions play a vital role during the biological process of drug utilization in the body (Efthimiadou et al., 2007; Sellappa & Jeyaraman, 2011; Magare & Ubale, 2011). The literature reveals that a large number of drugs have been used to synthesize the complexes with many metals with a view to enhance their therapeutic action. Based on the literature review, it appears that metal complexes are more potent as well as less toxic compared to the parent drug. The Diuretics are the most important bioactive and chemotherapeutic compounds made by microbiological synthesis. Furosemide (FSM) is loop diuretic (Das & Senapati, 2007) and is chemically known as 4-chloro-2-[(2-furanylmethyl)- amino]-5-sulfamoylbenzoic acid (Fig. 1) (Khade et al., 2011; Chaulang et al., 2008; Chaulang et al., 2009; Babu et al., 2010). It is extensively used for the treatment of edema, associated with pulmonary, hepatic, cardiac, and renal disease and hypertension accompanied by impaired renal failure or fluid retention (Basavaiah & Chandrasekar, 2005; Nair, 2012; Shetti et al., 2009; Hondrellis et al, 1988; Farcasa et al., 2006; Umarji et al., 2012). Considering the importance of diuretic drug and their complexes it has been desired to synthesize and characterize metal complexes of furosemide. In this paper we report the in- situ direct synthesis of Fe(III) and Co(II) complexes from 4-chloro-2-[(2-furanylmethyl)- amino]-5-sulfamoylbenzoic acid. The diuretic activity of FSM and its metal complexes was utilized on albino rats and results have been found to be encouraging as compared to the parent drug (Golcu, 2006).



**Fig-1. The Structure of FSM.**

**EXPERIMENTAL****Materials and methods:**

All the chemicals used in this work were of analytical reagent grades. Pure sample of furosemide (FSM) was received as a gift sample from Lupin, Mandideep. Metal salts ( $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ) were obtained from Sigma Aldrich in high purity.

**Techniques**

The analysis of carbon, hydrogen, nitrogen and sulphur were performed in Elementar, Vario analyzer at CSMRI, Bhavnagar, Gujrat. IR spectra were recorded as KBr disc in the  $400 - 4000 \text{ cm}^{-1}$  region using a Bruker spectrometer. Electronic spectra of ligand and the complexes were taken in DMF solution in quartz cells. The spectra were recorded on a Perkin- Elmer UV Win Lab spectrophotometer in the range 200-800 nm at room temperature at SAIF, Punjab University, Chandigarh. The mass spectra were carried out on the Waters Quadrupole Time of Flight (Q-TOF) Micromass (LC-MS) spectrometer at SAIF, Punjab University, Chandigarh. SEM images were recorded in a Hitachi SEM analyzer at MANIT, Bhopal.

**Synthesis of complexes:**

For the synthesis of the complexes, 0.02 mol ligand solution was prepared in 80% methanol-water solvent and thereafter the required metal salt (0.01mol) was added. The pH of the solution was adjusted in the range of 8 to 9 by adding sodium hydroxide. The resulting solution was refluxed for 4–5 h. The refluxed solutions were kept for some days whereby solid crystalline compounds appeared in the solution, which were filtered, washed with 80% methanol-water mixture, dried and weighed. Melting points of the complexes were also recorded.

**Diuretic activity:**

The diuretic activity of  $\text{Fe}^{\text{III}}$  complex was checked on Wistar Albino rats of 4 months of both sexes, weighing between 140 to 180 g. The animals were acclimatized to the standard laboratory conditions in cross ventilated animal house at temperature  $25 \pm 2 \text{ }^\circ\text{C}$ , relative humidity 44–56% and light and dark cycles of 12–12 h, fed with standard pallet diet and water *ad libitum* during experiment.

**RESULTS AND DISCUSSION**

The ligand and its metal complexes are coloured and made stable at room temperature. The ligand is soluble in common organic solvents, but the complexes are found to be soluble in DMSO and DMF. The elemental analyses data concur well with the planned formulae for the ligand and also recognized the  $\text{ML}_2$  composition of the metal complexes. Based on elemental analysis and Mass, the analytical data obtained for the new complexes agree well with the proposed molecular formula and presented in Table 1. It has been found that complexes are insoluble in water but fairly soluble in DMSO. It has also been found that complexes are non-hygroscopic which are stable at room temperature.

**Table 1. Analytical data of FSM and its metal complexes**

S.No.	Empirical formula	Molecular weight (g/mol)	Colour	M. P. ( $^\circ\text{C}$ )	Elemental analysis (%): Found (Calculated)				
					C	H	N	S	Metal
1.	$[(\text{L})_2]$	330.745	White to light yellow	223.64	42.28 (43.63)	3.32 (3.35)	8.15 (8.48)	9.44 (9.70)	-
2.	$[\text{Fe}(\text{L})_2(\text{H}_2\text{O})_2]$	752.42	Dark brown	365.00	37.79 (38.30)	1.99 (2.94)	7.66 (7.44)	8.35 (8.52)	6.88 (7.42)
3.	$[\text{Co}(\text{L})_2(\text{H}_2\text{O})_2]$	755.51	Pale pink	330.35	37.27 (38.15)	2.49 (2.93)	6.73 (7.41)	7.33 (8.48)	6.87 (7.80)

**Spectroscopic Studies****Fourier Transform Infrared (FTIR) analysis:**

The IR spectra of the ligands were compared with those of the  $\text{Fe}^{\text{III}}$  and  $\text{Co}^{\text{II}}$  metal complexes in order to confirm the binding mode of the ligands to the metal complexes (Table 2). Pure FSM spectra showed sharp characteristic peaks which demonstrates that the characteristic absorption bands for stretching vibrations of asymmetric amine N-H stretching appeared at  $3397 \text{ cm}^{-1}$  (Chaulang et al., 2009; Babu et al., 2010; Umarji et al., 2012; Singh et al., 2011). Symmetric N-H stretching appeared at  $3283 \text{ cm}^{-1}$ , and the peak at  $3116 \text{ cm}^{-1}$  was due to the C-H stretching. The peaks at  $1671 \text{ cm}^{-1}$  and  $1564 \text{ cm}^{-1}$  were assigned for C=O asymmetric and symmetric stretching vibrations of carbonyl group  $\nu_{\text{as}}(\text{COO})$  and  $\nu_{\text{s}}(\text{COO})$ .

The peak which appears at 1323-1243  $\text{cm}^{-1}$  for asymmetric stretching vibration of the sulfonamide group (Umarji et al., 2012) and the C-Cl stretching vibration appeared at 582  $\text{cm}^{-1}$  respectively (Das & Senapati, 2007; Shetti et al., 2009; Golcu, 2006; Patel et al., 2008). The IR spectra of the  $\text{Fe}^{\text{III}}$  (Fig. 2) and  $\text{Co}^{\text{II}}$  metal complexes demonstrate sharp bands in the range 3379 and 3405  $\text{cm}^{-1}$ , which were not found in the ligand recognized in presence of coordinated water molecules (Golcu, 2006). The spectra of Co (II) show, in addition to the sharp band of coordinated water, a weaker broad continuous absorption is due to the consequential presence of coordinated and crystal water.

The spectrum of FSM- Co (II) complexes showed important bands at 2926  $\text{cm}^{-1}$  for C-H stretching. The metal complexes show strong and complex band at 1000-1273  $\text{cm}^{-1}$  due to C-O bond stretching (Patel et al., 2008). The sharp signal assigned at 1501-1562  $\text{cm}^{-1}$  due to sulphonamide group which reduces its intensity and sharpness in the complexes (Shetti et al., 2009; Farcasa et al., 2006).

The coordination of the ligand was reflected in the spectra by the disappearance of the band at 1671  $\text{cm}^{-1}$  due to COOH group which is engaged in intra or intermolecular hydrogen bonds and the observation of  $\nu_{\text{as}}(\text{COO})$  and  $\nu_{\text{s}}(\text{COO})$  for Fe(III) and Co(II) complexes assigned at region 1607, 1608 respectively (Golcu, 2006; Bhattacharya et al., 2012).

The new bands in the region of 625-689 and 536-587  $\text{cm}^{-1}$  in the spectra of the complexes are assigned in stretching frequencies of (M-O) and (M-N) bonds respectively. The absence of large systematic shift bands in the spectra of the metal complexes implies that the  $-\text{SO}_2\text{NH}_2$  group is not coordinated to metal ions (Hondrellis et al, 1988). This indicates that the carboxylate group of FROSEM is coordinated to the metal ions as a monodentate ligand (Golcu, 2006).

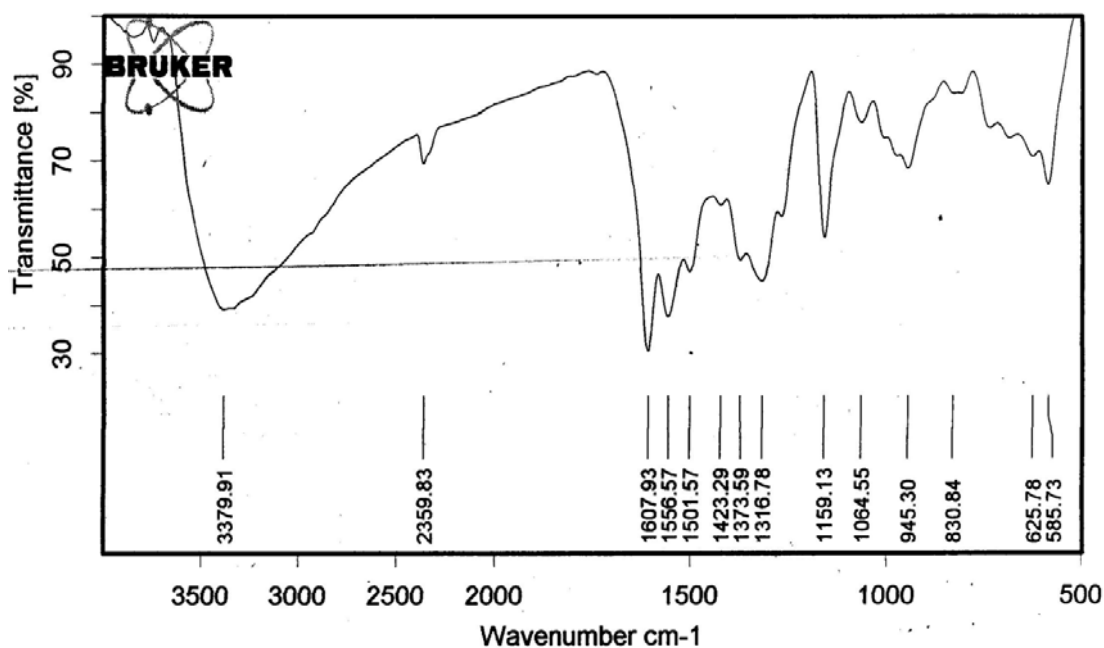


Fig. 2 FSM-Fe (III)

Table 2. Infrared Stretching Frequencies ( $\text{cm}^{-1}$ ) of the Various Functional Groups of FSM and its Metal Complexes

Ligand /complexes	$\nu(\text{OH})$	$\nu(\text{N-H})$	$\nu_{\text{as}}(\text{SO}_2)$	$\nu_{\text{s}}(\text{SO}_2)$	$\nu_{\text{as}}(\text{COO}^-)$	$\nu_{\text{s}}(\text{COO}^-)$	$\nu(\text{M-O})$	$\nu(\text{M-N})$
$\text{C}_{12}\text{H}_{11}\text{ClN}_2\text{O}_5\text{S}$ (FSM)	-	3283 m	1323 s	1143 vs	1671 vs	1564 s	-	-
$[\text{Fe}(\text{L})_2(\text{H}_2\text{O})_2]$	3379 b	3275 m	1316 mb	1159 vs	1607 s	1556 mb	625 w	585 m
$[\text{Co}(\text{L})_2(\text{H}_2\text{O})_2]$	3405 b	3280 m	1307 m	1157 vs	1608 vs	1554 m	689 w	585 s

vs very sharp;  $\nu_{\text{as}}$  asymmetric stretching;  $\nu_{\text{s}}$  symmetric stretching; s strong; m medium; w weak; b broad

### Electronic spectral analysis

In the UV spectra of ligand FSM absorption peaks are found at 226 and 317 nm. However, the relative absorption peak is slightly shifted to 230 and 329 nm after complexation. The chelation of ligand might have led to excitation of  $\pi-\pi^*$  transitions due to the formation of C=N bond (Shetti et al., 2009).

Magnetic moment of  $\text{Fe}^{\text{III}}$  complex as obtained is 5.23 B.M. The electronic spectra of the  $\text{Fe}^{\text{III}}$  complexes shows a weak intensity band between  $17,535-21,240 \text{ cm}^{-1}$  which correspond to spin allowed transitions assigned to  $^5\text{T}_{2g} \rightarrow ^5\text{E}_g$ ,  $^4\text{A}_{1g} \rightarrow ^4\text{T}_{2g}$  within the range of values corresponding to a high spin octahedral arrangement. The absorbance spectra of this complex have transitions confirming an octahedral arrangement (Mohamed et al., 2001).

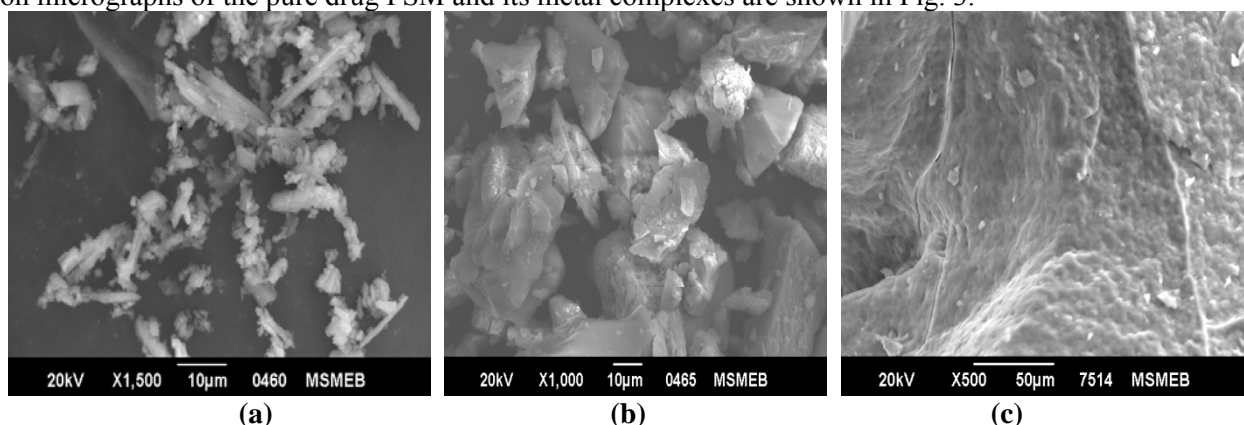
The electronic spectra of  $\text{FSM-Co}^{\text{II}}$  complex show two bands at  $18,228-19,607 \text{ cm}^{-1}$  and  $22,507-25,724 \text{ cm}^{-1}$  assigned to  $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{A}_{2g}(\text{F})$  and  $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{1g}(\text{P})$  transitions respectively. The magnetic moment of the  $\text{FSM-Co}^{\text{II}}$  complex was found to be 4.79 B.M. suggesting an octahedral environment around  $\text{Co}^{\text{II}}$  (Hondrellis et al, 1988). The absorption data for the complexes are given in Table 3.

**Table 3. Electronic spectral data and magnetic moments values of the ligand and its complexes**

S. No.	Complex	Magnetic Moment $\mu_{\text{eff}}$ (B.M.)	Band Position ( $\text{cm}^{-1}$ )	Possible Assignments
1	$[\text{Fe}(\text{L})_2(\text{H}_2\text{O})_2]$	5.23	17,535-21, 240 29,850-33003	$^5\text{T}_{2g} \rightarrow ^5\text{E}_g$ $^4\text{A}_{1g} \rightarrow ^4\text{T}_{2g}$
2	$[\text{Co}(\text{L})_2(\text{H}_2\text{O})_2]$	4.79	18,228- 19,607 22,507 – 25,724	$^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{A}_{2g}(\text{F})$ $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{1g}(\text{P})$

### Scanning Electron Microscopy (SEM):

The scanning electron micrographs confirmed that the crystalline character of ligand have been mixed with all complexes and was seen adhering to their surfaces. Morphology of both the metal complexes of drug was found to be discrete and spherical in shape (Das & Senapati, 2007). The photomicrograph of  $\text{Fe}^{\text{III}}$  and  $\text{Ni}^{\text{II}}$  metal complexes show small size particles with the tendency of aggregation. Which suggest the existence of an amorphous product with the presence of a single component in the complexes. This indicated a complete complex formation and the drug was also found uniformly dispersed at the molecular level in the microspheres as observed by SEM analysis. The scanning electron micrographs of the pure drug FSM and its metal complexes are shown in Fig. 3.



**Fig. 3. Scanning Electronic Micrograph of (a) FSM, (b) and (c)  $\text{FSM-Fe}^{\text{III}}$  and  $\text{Co}^{\text{II}}$  metal complexes.**

### Diuretic activity

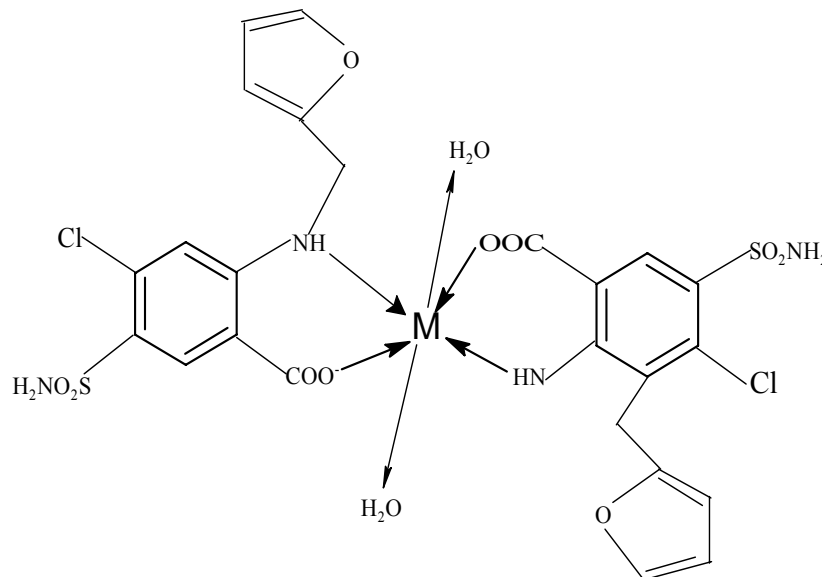
The diuretic activities of  $\text{Fe}^{\text{III}}$  complex of FROSM were significant ( $p < 0.01$ ) when as compared to control [19]. The values are expressed as mean  $\pm$  SEM ( $n = 6$ ), compared with control (ANOVA followed by Dunnett's *t* test),  $**p < 0.01$ . Statistical significance on comparison with standard drug and control groups  $p$  values less than 0.05 were considered as significant. The results confirm that  $\text{Fe}^{\text{III}}$  complex of FSM show better activity than the parent drug. The results of diuretic activity of FSM and  $\text{Fe}^{\text{III}}$  complex obtained from the urine samples of the rats are shown in Table 4.

**Table 4. Effect of metal complexes on urine volume and electrolyte contents of urine after 24 hrs.**

S. No	Treatment	Dose (mg/kg)	Urine volume (ml/kg)	Electrolyte Concentration in ppm		
				Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>
1	Control (vehicle)	1ml/ 100g	2.0 ± 0.35	86 ± 4	64.4 ± 3	1105
2	Furosemide (FSM)	10	6.1 ± 0.14**	134 ± 3**	119.4 ± 3**	152.7 ± 4**
3	FSM-Fe(III)	10	5.7 ± 0.36a**	129.7 ± 4**	119 ± 4**	149.4 ± 8**

## CONCLUSION

Based on the physico-chemical and spectral aspects as discussed above it is implicit that the complexes suggested as octa coordinated may probably having octahedral geometry. The diuretic study results have been found to be encouraging with metal complexes as compared to the parent drug. The results obtained by different characterization techniques clearly indicate that the complexation of FROSM with Fe<sup>III</sup> and Co<sup>II</sup> ions will lead to a better therapeutic efficacy. Based on the above studies, An octahedral structure (Fig. 4) has been tentatively proposed for the Fe<sup>III</sup> and Co<sup>II</sup> complexes of FSM.



**Fig-4: Proposed structure for the metal complexes of FSM: M=Fe<sup>III</sup> and Co<sup>II</sup>**

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