Spectral and diuretic study of Cu(II) complex of Sulfonamides

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ABSTRACT

The synthesis and characterization of Cu (II) complexes of three diuretic drugs acetazolamide, furosemide and hydrochlorothiazide are reported here. On the basis of elemental analyses, electrical conductivity and molecular weight data the adducts are assigned to the general composition [M(L)₂]. All the adducts are paramagnetic in nature. The IR studies indicate that ligand is coordinated to metal through azomethine nitrogen atom. The electronic spectral data and magnetic moment values suggest square planar geometry and coordination number 4 for these complexes. We assessed diuretic activity of the ligand FSM-SA and complex FSM-SA-Cu in vivo following the protocol of Institutional Animal Ethical Committee norms. While studying the results of the experiment it was concluded the diuretic activity of the FSM-SA and FSM-SA-Cu was found to be more than the parent drug.
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INTRODUCTION

Schiff bases and their metal complexes have been found to posses important biological and industrial applications. There is enormous interest presently in the field of coordination chemistry of '3d'transition metal ion with Schiff bases[1-7]. Metal complexes of Schiff bases have occupied a major role in the development of coordination chemistry[8]. Study of metal complexes has been of great importance, metal ions play a vital role in the biological activity and certain metal complexes of the drug are more potent than their parent drug[9]. Survey of literature reveals that very few studies have been done on metal complexes of Schiff bases of diuretic drugs. We report herein the synthesis and characterization of some bipositive 3d metal ion chelates of diuretic drugs along with the assessment of diuretic activity. In continuation of our previous work on metal complexes of established drugs [10-12] the synthesis and structural studies of (AZM-SA)₂Cu, (FSM-SA)₂Cu, (HCT-SA)₂Cu complexes are described below.

MATERIALS AND METHODS

Synthesis of Schiff base- Pure sample of acetazolamide (AZM) molecular formula $C_4H_6N_4O_3S_2$, molecular weight 222.24 was obtained from Shalaks Pharmaceuticals Pvt. Ltd., New Delhi. Pure sample of furosemide (FSM) molecular formula $C_{12}H_{11}N_2O_5S$, molecular weight 330.75 was obtained from Geno Pharmaceuticals Pvt. Ltd., Goa. Pure sample of Hydrochlorothiazide (HCT) molecular formula $C_7H_8Cl\ N_3O_4S_2$, molecular weight 297.74 was obtained from Novartis India Pvt. Ltd., Mumbai. These drugs were used as such for the synthesis of ligands.Metal salts were Qualigen chemicals. Solvents used were methyl alcohol and acetone. All the chemicals used were of analytical grade.

1204

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Equimolar solutions of pure drugs (0.01M) and salicyldehyde (0.01M) were taken in methanol-water mixture (1:1 ratio). Both the solutions were mixed and refluxed for three hours. The reaction mixture was kept overnight.

Light yellow crystals of acetazolamide-Schiff base (AZM-SA) were formed in the reaction mixture, which are washed with 50:50 methanol : water mixture, filtered, dried and weighed. Melting point was recorded. Similar procedure was adopted for the preparation of Schiff bases of furosemide and hydrochlorothiazide.

Ligand-Metal ratio and Stoichiometry- To confirm the ligand metal ratio, conductometric titrations using monovariation method were carried out on Systronics conductivity meter and dip type electrode. Titrations were carried out at room temperature. 0.01M solution of drug-Schiff base was prepared in 60:40 acetone: water mixture and diluted to 200ml with same solvent. This Schiff base solution was titrated against 0.02M metal solutions using monovariation method. After making volume corrections the results were plotted that suggests the ligand metal ratio as 2:1. Formation of 2:1 complex was further confirmed by Job's method of continuous Variation, modified by Turner and Anderson. The stability constants and free energy change were also calculated.

Synthesis of complexes-For the synthesis of complexes, 0.01 M ligand solution was prepared in 60:40 acetone : water mixtures and refluxed for four hours with 0.005M solution of $CuCl_2$. The refluxed solutions were kept for two days. Fine crystalline compounds appeared in the solutions. Complexes were washed with acetone, filtered, dried and weighed. Melting points were recorded.

Table I- Synthesis and physicochemical characteristics of ligand and complexes

Ligand\Complex	Ligand/metal Ratio	Colour	% Yield	Stabilty Constant logK (L/mole)	Free energy change -Δ F(Kcal/mole)
AZM-SA	-	Pale yellow	70	-	-
(AZM-SA)$_2$Cu	2:1	Green	42	12.088	17.038
FSM-SA	-	Pale yellow	65	-	-
(FSM-SA)$_2$ Cu	2:1	Green	42	11.352	15.996
HCT-SA	-	Yellow	72	-	-
(HCT-SA)$_2$ Cu	2:1	Green	57	11.222	15.457

Table II-Analytical data of complexes

Ligand \Complex	Elemental analysis Found (Calculated)%						m.p ^{0}C
	C	H	Cl	N	S	metal	
$C_{11}H_{10}N_4O_3S_2$	40.66 (40.49)	3.33 (3.06)	-	17.57 (17.17)	9.29 (9.81)	-	212
$(C_{11}H_9N_4O_3S_2)_2Cu$	36.98 (36.00)	2.5 (2.91)	-	15.69 (16.67)	17.93 (17.50)	8.86 (8.91)	199
$C_{19}H_{14}ClN_2O_6S$	52.63 (52.46)	3.66 (3.45)	8.29 (8.16)	6.87 (6.24)	7.33 (7.38)	-	212
$(C_{19}H_{13}ClN_2O_6S)_2Cu$	49.25 (49.00)	3.09 (3.00)	7.25 (7.12)	5.33 (5.61)	6.25 (6.42)	6.52 (6.32)	199
$C_{14}H_{11}ClN_3O_5S_2$	41.22 (41.89)	2.44 (2.74)	8.12 (8.72)	10.55 (10.47)	15.33 (15.96)	-	255
$(C_{14}H_{10}ClN_3O_5S_2)_2Cu$	38.15 (38.85)	2.59 (2.54)	8.77 (8.21)	9.70 (9.71)	14.14 (14.80)	7.86 (7.28)	240

RESULTS AND DISCUSSION

Ligand-Metal ratio and stoichiometery-
Conductometric studies, monovariation method and Job's method of continuous variation modified by Turner and Anderson [13-14] indicate the formation of 2:1 (L: M) complexes of Schiff base of ligands with Cu ion. . Analytical data of these complexes are in agreement with the composition

IR Spectra-
Proposed structure of (AZM-SA)$_2$Cu, (FSM-SA)$_2$Cu, (HCT-SA)$_2$Cu complexes were further confirmed by IR spectra1 data [15-19]. In the present work the IR spectra of ligands and their metal complexes were recorded on Perkin Elmer Spectrophotometer in KBr pallets.

1205

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Bands observed at 1173 cm^{-1} 1157 cm^{-1} and 1152 cm^{-1} characteristic of SO_2-N group. Absorption bands at 1413cm^{-1}, 1410cm^{-1} and 1429cm^{-1} shows presence of chelate ring. Frequencies at 653 cm^{-1}, 680 cm^{-1} and 676 cm^{-1} are characteristics of M-O linkage. Bands at 550 cm^{-1}, 586 cm^{-1} and 608 cm^{-1} are characteristic of M-N linkage. Frequencies at 892 cm^{-1}, 805 cm^{-1} and 859 cm^{-1} indicate the S-N linkage. Lowering of azomethine frequencies in the metal complexes indicate its involvement in coordination[20]. The disappearance of frequencies of phenolic -OH in complexes supports its involvement in complexation.

Infra Red Spectral Bands (Cm^{-1}) of (AZM-SA)$_2$Cu, (FSD-SA)$_2$ Cu and (HCT-SA)$_2$Cu complexes-

Ligand/Complex	ν (HC=N)	ν (Phenolic OH)	ν (M-O)	ν (M-N)	Chelate Ring
AZM-SA	1680 vs	3303 vw	-	-	
(AZM-SA) $_2$ Cu	1590 s	-	653 s	550 s	1413 vs
FSM-SA	1672 vs	1620 vs	-	-	-
(FSM-SA) $_2$ Cu	1620 vs	-	680 w	586 m	1410 m
HCT-SA	1602 m	3271 m	-	-	-
(HCT-SA) $_2$ Cu	1580 w	-	676 w	608 m	1429 w

Electronic Spectra and Magnetic Moment-
In this study the room temperature magnetic susceptibility measurements were carried out on a Vibrating Sample Magnetometer (VSM) at Center for Advance Technology, Indore (M.P.) and the electronic spectra were recorded in the range of 260-800 nm at Central Drug Research Institute, Lucknow.

The electronic spectra of Cu (II) complex of the ligand AZM-SA is characterized by three absorption bands at 26650cm^{-1}, 18880cm^{-1} and 14030 cm^{-1} which can be assigned to charge transfer, $^2A_{1g} \leftarrow {}^2B_{1g}$ and $^2E_g(G) \leftarrow {}^2B_{1g}$ transitions respectively. The magnetic moment value was observed to be 1.75 B.M. The electronic spectral data and μ_{eff} value suggest a square planar environment around Cu(II) ion.

For the Cu(II) complex of FSM-SA three bands are observed at 27650cm^{-1} ,18960 cm^{-1} and 15030 cm^{-1}.The first band is assigned to charge transfer and the second band would be due to $^2A_{1g} \leftarrow {}^2B_{1g}$ transition and the third band may be $^2E_g(G) \leftarrow {}^2B_{1g}$, suggesting an square planner geometry around Cu(II) ion. The μ_{eff} value 1.55 B.M. agrees with a square planar configuration. The Cu (II) complex of HCT-SA showed three bands at 27650 cm^{-1}, 18980 cm^{-1} and14930 cm^{-1}, are assigned to charge transfer,$^2A_{1g} \leftarrow {}^2B_{1g}$ and $^2E_g(G) \leftarrow {}^2B_{1g}$ The μ_{eff} value has been found to be 1.65 B.M. .The spectral data and magnetic moment value indicate a square planar geometry around Cu (II) ion [21-22].

Electronic Spectra and Magnetic Moment values of (AZM-SA)$_2$Cu, (FSD-SA)$_2$Cu and (HCT-SA)$_2$Cu complexes-

Complexes	Magnetic Moment (B.M.)	Electronic Bands (cm^{-1})	Possible Assignments	Proposed Geometry
(AZM-SA)$_2$Cu	1.75	26 650 18 880 14 030	Charge transfer $^2A_{1g} \leftarrow {}^2B_{1g}$ $^2E_g \leftarrow {}^2B_{1g}$	Square plannar
(FSM-SA)$_2$Cu	1.55	27 650 18 960 15 030	Charge transfer $^2A_{1g} \leftarrow {}^2B_{1g}$ $^2E_{1g} \leftarrow {}^2B_{1g}$	Square planar
(HCT-SA)$_2$Cu	1.65	27 650 18 980 14 930	Charge transfer $^2A_{1g} \leftarrow {}^2B_{1g}$ $^2E_{1g} \leftarrow {}^2B_{1g}$	Square planar

Thermogravimetric analysis (TGA) of furosemide its schiff base and Cu complex.
Thermal analysis play an important in studying structural properties of metal complexes.[23,24]

The thermogravimetric analyses were carried out for the furosemide, its Schiff base and its Cu complex.

Pure drug furosemide(FSM):
On observing the TGA graphs in case of the pure drug furosemide we find falls in various temperature ranges, which may be assignable to the loss of different moieties.On observing the graph the first fall is found in the temperature

1206

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range 190-249^{0}C which corresponds to the loss of –NH$_2$ group. In the TGA graph of furosemide fall is observed in the temperature range 249-276^{0}C which can be attributable to the loss of – COOH group.

At the temperature range 276-356^{0}C fall is observed which is assignable to the loss of -SO$_2$ group.Weight loss of 14.29% was observed at the temperature range 356-456^{0}C which indicates the loss of   -NH and CH$_2$ group along with   one carbon atom of furan ring.

Rest of the molecule decomposes at the temperature range 456-459^{0}C

Furosemide salicylaldimine Schiff base (FSM-SA):
In the case of furosemide Schiff base at the temperature range 25-211^{0}C falls are observed which are assignable to the loss of -NH group.

Weight loss of 5.67% was observed at the temperature range 211-254 ^{0}C which indicates the loss of -CH=N group.

Fall is observed in the temperature range 254-275^{0}C which can be attributable to the loss of – COOH group. In the temperature range 275-350^{0}C fall is observed which is assignable to the 14.53 % loss, corresponds to the loss of SO$_2$ group.On observing the graph the fall is found in the temperature range 350-459^{0}C which corresponds to the loss of – C$_6$H$_4$OH group.
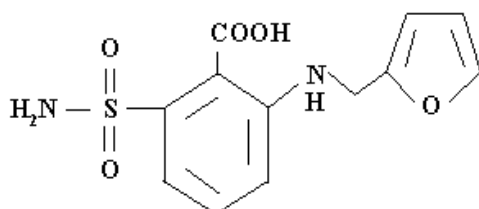
Structure of Furosemide
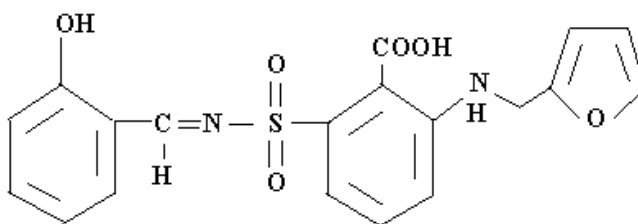
Structure of Furosemide schiff base

Furosemide salicylaldimine -Cu complex (FSM-SA-Cu):
On observing the TGA graphs in case of the Furosemide-Cu complex we find falls in various temperature ranges, which may be assignable to the loss of different moieties.

On observing the graph the first major fall is found in the temperature range 227-293^{0}C which may be corresponds to the loss of furan ring along with–NH-CH$_2$ group.

Fall is observed in the temperature range 293-365^{0}C which can be attributable to the loss of benzene ring with –Cl and -COOH groups.

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At the temperature range 365-442^{0}C fall is observed which corresponds to 16.05% weight loss , is assignable to the loss of SO$_2$ group.
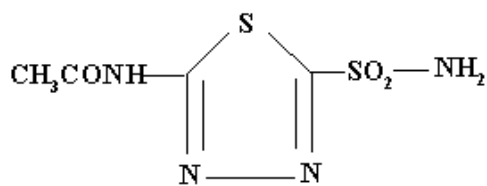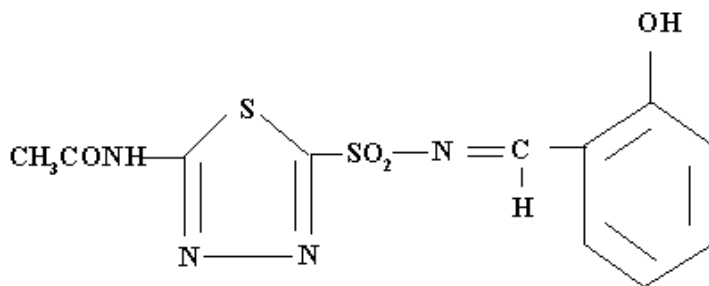
Weight loss of 27.51% was observed at the temperature range 442-507^{0}C which indicates the loss of chelate ring and molecule collapses at this temperature.
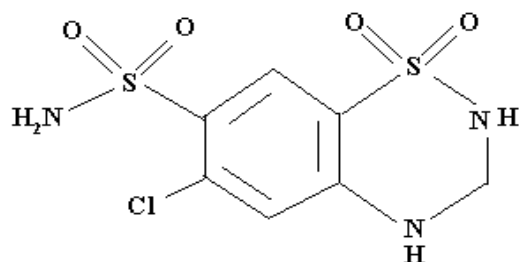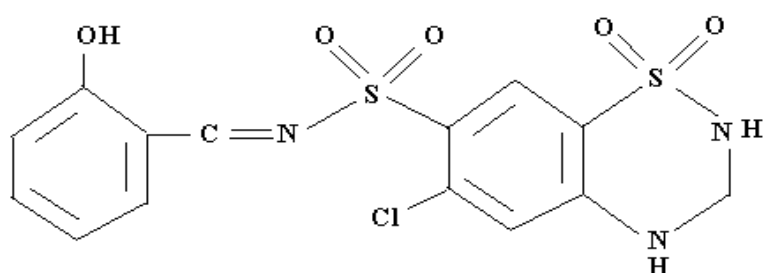
Rest of the molecule decomposes at the temperature rang 507-804^{0}C.

(Some of the results are subjected to ± 2% variation.)
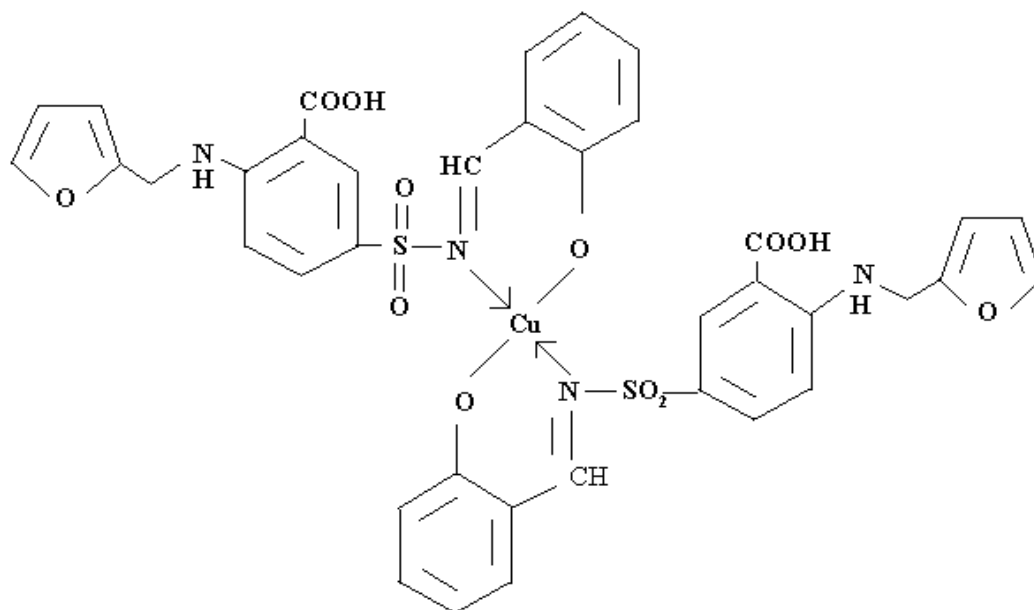
Structure of Furosemide schiff base copper complex

Structure of Acetazolamide

Structure of Acetazolamide Schiff base
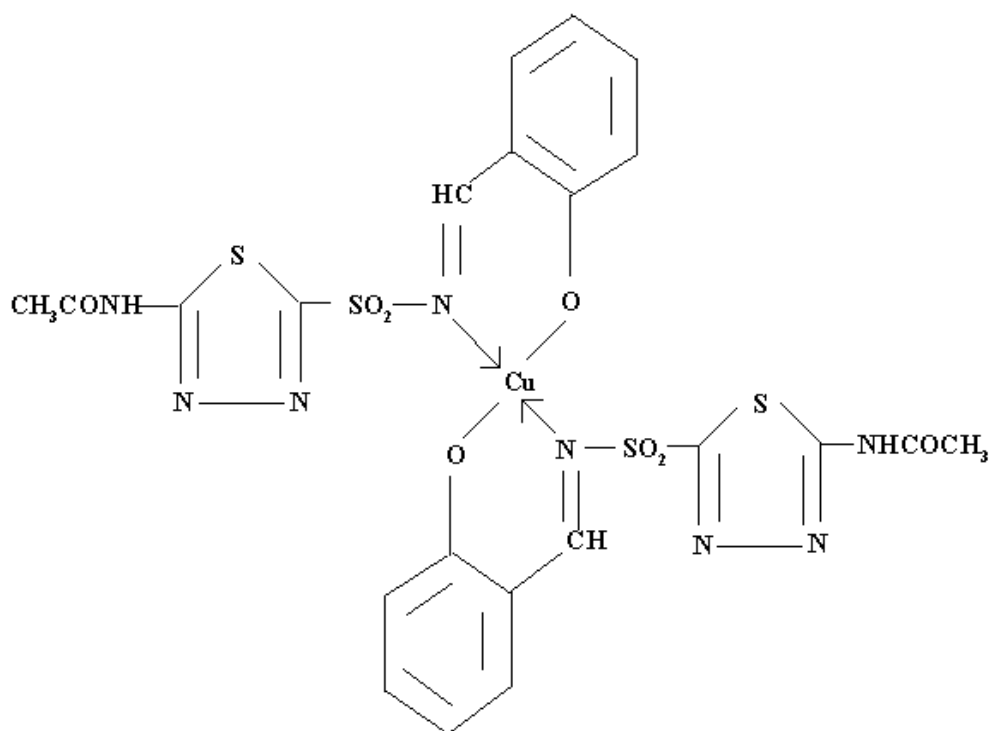
Structure of Acetazolamide Schiff base copper complex

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Structure of Hydrochlorothiazide

Structure of Hydrochlorothiazide Schiff base
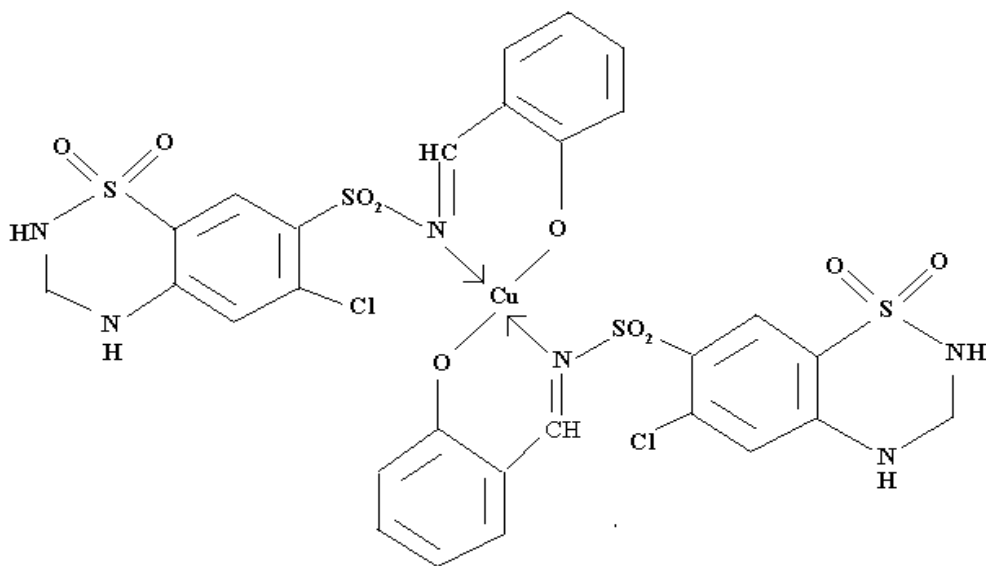
Structure of Hydrochlorothiazide Schiff base copper complex
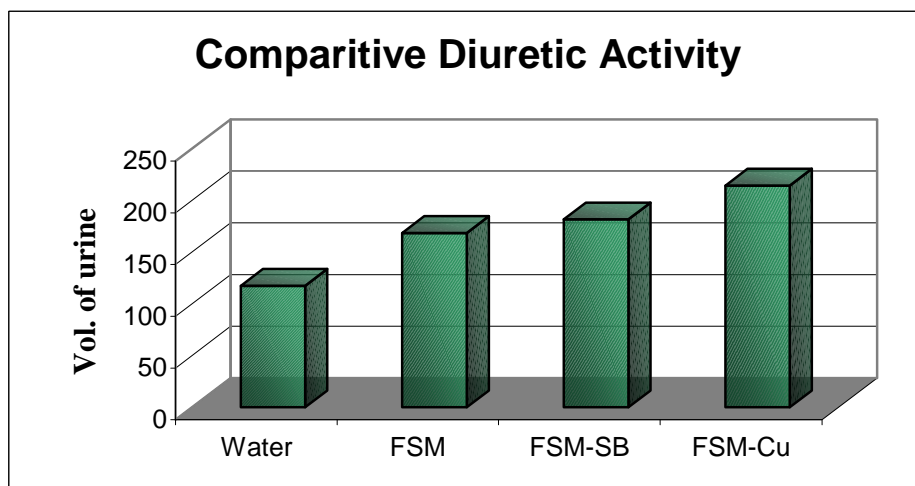
Diuretic activity-
Diuretic activity of FSM-SA and (FSM-SA)$_2$Cu complex was assessed at Jawahar Lal Nehru Cancer Hospital and Research Center, Bhopal, following the protocol and Institutional Animal Ethical Committee norms.

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The experiment was carried out on mice. Detailed survey of literature indicated that dose prescribed for human being is also safe in mice [25-26].

The average volume of urine output for various sets of experiments explains clearly the order of diuretic activities of the drug its Schiff base and metal complexes as follows-

(FSM-SA)$_2$Cu(Complex)>FSM-SA(Schiff base) > FSM(Pure drug)>Water

The order is indicating that a metal complex of the drug is more potent diuretic than its Schiff base and pure drug itself.

Comparitive Diuretic Activity

Vol. of urine (y-axis: 0, 50, 100, 150, 200, 250)

Water — FSM — FSM-SB — FSM-Cu

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1212