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Physico- chemical and Pharmacological Characteristics of mixed ligand complex of Cu (II) with Famotidine and Methionine

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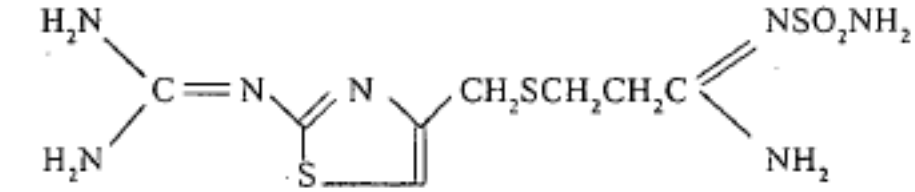
Abstracts:-
Mixed ligand complex of Cu (II) with Famotidine as one ligand and Methionine as second ligand was prepared. The complex was characterized on the basis of elemental analysis, electronic and I.R. Spectral and particle size measurements. Pharmacological effects of the complex on gastric secretion in pylorous ligated rats and gastric emptying rate in albino rates were also studies. It was found that the complex in dose range 200-500 mg/kg produced significant reduction in total and free acid and it had no effect on gastric emptying rate.

Introduction -:

Famotidine 3-[2-(diamino methylene amino) thiazole-4-yl methylthio]-N- Sulphamoyl propinoamidine is most useful drug in management of duodenal and pepticulcers having an excellent histamine (Imidazole-4-ethnamine) H2-receptor blocking effect (1).



Famotidine

It molecular formula is $C_8 H_{15} N_7 O_2 S_3$ with mol.wt.337.5 it is used in conditions where inhibition of gastric acid secretion may be beneficial such conditions includes duodenal and gastric ulcers, oesophageal reflux Zollinger- Ellison syndrome.

It is given 40 mg daily as tablet form at bedtime for-4-8weeks as well as intravenous route 20mg by slow injection over at least 2 minutes.

The drug in effective ligand and may be potentially interact with essential metal ions in blood plasma or other tissues(2). Famotidine have structures that suggest strong binding to Iron ions, which reduces it absorption in-vitro.

Therefore if the mixed ligand metal complex of famotidine as one ligand and methionine, which perform diverse biological function in the body, as second ligand were prepared and studied.

Material and method :-

A weighed quantity of famotidine (1 mole) was dissolved in minimum quantity of dimethyl formamide. The amino acid (methionine) (1mole) was dissolved in minimum quantity of liquor ammonia 'Metal salt solution (1 mole) was prepared separately in 50 ml distilled water. Drug and metal solution were gradually added to methionine with constant stirring at room temperature maintaining the PH near about 9 by adding liquor ammonia solution (1:3) The matrix was refluxed for 4 hour, over water bath using air condenser. On cooling the complex separates out which was filtered off through G-4 sintered crucible washed well with distill water and dried in desiccators over fused calcium chloride.

Carbon and hydrogen were estimated in micronalytical laboratory. Nitrogen was determined by Kjeldhl and sulphur by messenger method. Copper was estimated gravimetrically as Cuprous thio cynate. IR spectrum were taken on Perkin-Elmer64- spectrometer using KBr pellets.

The particle sizes of the famo, and the complex were detrmined by the microscope ERNST Leitz wetzlar Germany No. 538703 having eye pieces 10X objective 10/0.25 and fitted with Ocular micrometer (Erma Tokyo, Japan) and stage micrometer 0.01mm (Erma Tokyo, Japan). The eye piece was calibrated against stage micrometer, 1 division of the Ocular micrometer was found to be equal t o seven microns. The samples were suitably spread on the microscope slide and covered with cover glass. The diameters of 10 random particles of each sample were measured and the average of observations was recorded.

Gastric Secretion in Pylorous ligated rats [3]:
The albino rats weighing between 175-225g were used. They were divided into three groups. Each group was having three animals. The first group served as control which received normal saline, the second group received pure famotidine orally and the third group received complex of famotidine methionine in varying doses dissolved in water.

Gastric emptying rate [4]:
The albino rats weighing between 175-225g were used. They were divided into three groups. Each group was having three animals. The first group served as control which received normal saline, the second group received pure famotidine orally with phenol red, and the third group received complex of famo-cu-metho orally with phenol red.

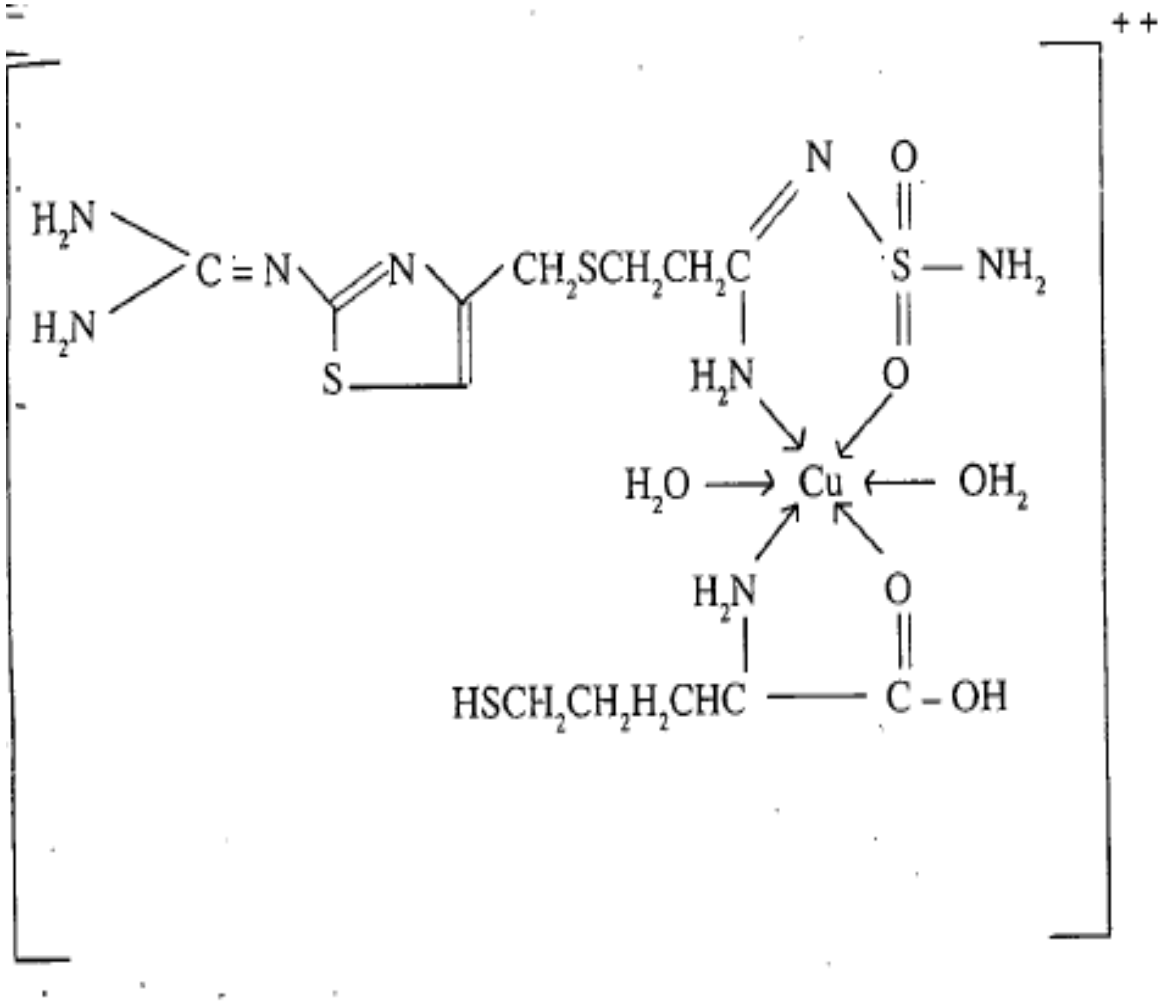
Result and discussion:-
A weighed quantity of dried metal complex was dissolved in 5 ml of analar concentrated nitric acid to decompose the organic matter. This solution was used for various estimations.
On the basis of elemental analysis, the complex has been assigned the composition as [cu (Famo) L.$(H_20)_2$] SO_4. Famotidine is a white to page yellow nonhygroscopic crystalline substance. It is slightly soluble in water and practically insoluble in ethanol, acetone, ethylacetate chloroform. It is freely soluble in glacial acetic acid and dimethyl famotidine. Methionine is a white crystalline power with a characteristic odour. The complex had grey colour and started decomposition at 200^0C.
The partical size of famotidine, methionine and the complex were 5-16, 4-17, 4-14 microns. The size of the complex is smaller than the parent drug. The small size of the complex may enhance the absorption of complex in comparison of the drug which may lead to increase in the potency of the drug if given in the complex form.

In the I.R. Spectrum frequencies of complexes of famotidine were compared with that of pure drug famotidine the results indicated that frequencies found near 3940-3700 cm^1 are due to NH_2 stretching, these frequencies are found in complexes but absent in pure drug, indicates that may be methionine has coordinated through nitrogen atom [5]. While bands near 3663-3500 indicate NH_2 stretching found both in complex as well in the drug indicate that drug has also coordinated through nitrogen atom [6].
Frequencies found near 2940-2800 are due to C-H stretch of methy1 group directly attached to benzene nucleus may also be due to SO_2- NH group present in ligand as well as in complexes, Bonds near 1850-1800 cm^{-1} indicate carbony1 stretching of the acid group [7] in methionine present in complexes, while absent in pure drug, This is further confirmed by bands near 1790 cm^{-1} -1600 cm^{-1} and bands found near 1600-1500 $cm^{-1.}$ -Bands near 1500-1350 are may be due to C=N stretching ; also due to six membered chelate ring frequencies of the type H-C=N, Bond near 1360-1310 cm^{-1} indicate ionic sulphates $(SO_4)^{--}$; and also due to thiazole ring.
Bonds near 660-410 cm-1 indicate metal-oxygen bonding found in complexes while absent in pure drug [8].

The thermal studies indicates that complexes of famotidine with methionine and various metal ions decompose in two step ; the first step decomposition starts from 100^0C to 155^0C without any break upto 200^0C. The observed weight loss corresponds to loss of methionine molecule; and moisture, or water molecule coordinated. The second step decomposition corresponds to loss of famotidine, of Cu(II). The Briodo method was applied to TG data to determine the energy of activation and order of reaction.

DTA curves of the complex are of similar nature, in each case two peaks were obtained, as DTA curves presents the rate of weight change as a function of temperature, two peaks endothermic and exothermic peaks are obtained. The first peak corresponds to the weight loss of amino acid and moisture present and coordinated water, if present in the complex; liberation of drug molecule and formation of metal oxide.
The result of magnetic moment indicate that complex of Cu(II) is high spin octahedral complex with one and three unpaired electrons. [9]
The following structures may be assigned on the basis of elemental analysis infrared analysis, thermogravimetric analysis, differential thermal analysis, magnetic susceptibility measurement of Cu(II) complex.

Complex of Famotidine with Copper and methionine :-



Where Proposed Molecular Formulae is [Fam Cu(Meth)(H_2O)$_2$] SO_4 Molecular weight=682.20
Copper is in bivalent state and shows octacedral geometry

Gastric Secretion in Pylorous ligated rats :

The effects of famotidine and its complex on gastric secretion are given in Table 1. The complex in dose range of 200-500mg/kg produced significant reduction in the total acid and free acid.

Table-1

Dose mg/kg (sc)	Total acid mEq/l			Free acid mEq/l			Mean volume		
	Control	Fam	Fam+Cu+ Cys	Control	Fam	Fam+Cu+ Cys	Control	Fam	Fam+Cu+ Cys
-	10.00 ± 0.10	-	-	9.20 ± 0.09	-	-	7.9 ± 0.20	-	-
100		8.30 ± 0.08	6.16 ± 0.06		5.00 ± 0.08	4.10 ± 0.10*	7.9 ± 0.20	6.0 ± 0.16*	5.6 ± 0.10*
200		6.60 ± 0.08	4.10 ± 0.09*		4.60 ± 0.08	3.30 ± 0.09**	7.9 ± 0.20	5.6 ± 0.14*	5.0 ± 0.10**
500		3.30 ± 0.09*	2.50 ± 0.09**		3.30 ± 0.10	2.00 ± 0.09**	8.0 ± 0.18	2.8 ± 0.18**	2.0 ± 0.16*

Each value represents the mean ± SEM of 6 observations.

P Values * < 0.05 ** < 0.001

Total and free acidity expressed as the volume of 0.01N NaOH required to neutralize 1 ml of gastric juice in miliequivalent/litre.

Although, no attempt had been made to test the H_2- receptor blocking activity of complex, it is possible that the antisecretary activity of the complex may also be due to the blockade of the H_2- receptor in the stomach. The prevention of the gastric lesions by the complex would be attributed to the reduction of the volume and acidity of the gastric secretion which will lead to healing of ulcer [10].

Gastric emptying rate :-

Famotidine had no effect on gastric emptying rate. On complexation also there was no significant change observed as evident from Table 2.

Table 2.

Dose mg/kg	Control	Fam	Fam+Cu+Meth
_	95	_	-
100	-	93.8	95.5
200	-	94.4	96

Each value represents the mean ± SEM of 3 observations

Conclusion:-

Mixed ligand complex of cu (II) with famotidine as one ligand and methionine as second ligand was synthesized. The complex was found to have octahedral geometry. Pharmacological effects of the complex was studied and it was found that the complex in dose range of 200-500 mg/kg produced significant reduction in total and free acid and it had no effect on gastric emptying rate.

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