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Preparation, characterization and antiulcer activity of mixed ligand complex of Zn (II) with Famotidine and Glycine

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ABSTRACT

Mixed ligand complex of Zn(II) with famotidine and glycine has been prepared. The complex has molecular formula as [Zn(fam)(L)]NO_3; where fam = famotidine and HL = glycine. The complex has been characterized by elemental analysis, electronic and IR spectra and the particle size of the complex has been measured by microscopic method. Pharmacological activity of the complex on gastric secretion in pylorous ligated rates and gastric emptying rate in albino rats has been studied. The complex has significant reduction in total and free acid on gastric secretion. However, there is no significant change on gastric emptying rate.

Keywords : Zn, Famotidine, Glycine, Electronic, Infra-red, Particle size, Gastric secretion.

INTRODUCTION

Metal complexes of various drugs have been found highly effective in the treatment of gastric ulcer [1-3]. Famotidine (fam) ligand is a highly effective long acting histameric H_2-receptor antagonist [4,5] even in uncomplexed form. The compound has effective donor sites for formation of complexes with the metals. Therefore, prima facie, it seems worthwhile to prepare its complexes with metals and probe their pharmaceutical effects. Its activity may become more effective if its mixed ligand metal complex along with an amino acid as a second ligand is prepared as amino acids are fundamental structural units of proteins of the body. Keeping this in view, the present work was undertaken. The mixed ligand complex of zinc with famotidine and

glycine was prepared. The physical properties and antiulcer activity of the complex were studied to recommend it for pharmaceutical use.

EXPERIMENTAL SECTION

Preparation of the Complex :

Zinc nitrate, famotidine, and glycine were taken in the molar ratio 1:1:1 so that the total weight was about 1-1.5g. The metallic salt was dissolved in 50mL of distilled water. The famotidine and glycine were added slowly into the solution of the metallic salt with continuous stirring. The pH was maintained at 9.0 by adding ammonia solution. The matrix was refluxed for nearly two hours on a water bath. On concentrating and cooling the complex separated out which was filtered, washed and dried in desiccator.

Physical Measurements:

Zinc was determined gravimetrically as zinc ammonium phosphate. Carbon and hydrogen were estimated in microanalytical lab. Nitrogen and sulphur were estimated by Kjeldhl and Messenger methods respectively.

Electronic spectrum of the complex was run on Beckman Du-64 spectrophotometer in nujol mull and IR spectrum on Perkin-Elmer 621-Spectrometer using KBr pellets.

Particle sizes of the complex, famotidine and glycine were determined by the microscope ERNST Leitz Wetzlar Germany No.538703, having eye piece 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 to 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 :

The albino rats weighing between 175-225g were used. They were divided into 3 groups. Each group had 6 animals. The first group served as control which received normal saline subcutaneously. The second group received pure fam subcutaneously. The third group received complex of fam-Zinc-glycine subcutaneously in varying doses dissolved in distilled water.

Gastric emptying rate:

The albino rats weighing between 175-225g were used. They were divided into 3 groups. Each group was having 3 animals. The first group served as control which received normal saline, the second group received pure fam orally with phenol red, the third group received complex of fam-zinc-glycine orally with phenol red.

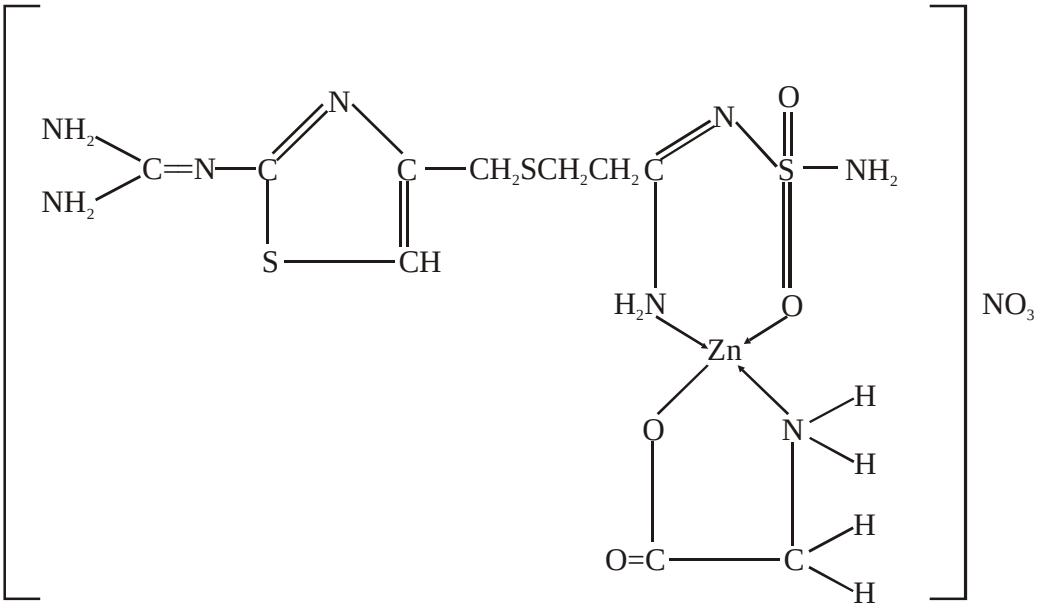
RESULTS AND DISCUSSION

On the basis of elemental analysis, the complex has been assigned the composition as $[Zn(fam)(L)]NO_3$; where L = glycine.

The particles of famotidine, glycine and the complex had white shining spindle shape, white shining irregular and cream yellow irregular appearance respectively. The complex starts decomposing at 200°C.
The electronic spectrum of the complex shows no d-d transition bands which in the present case corresponds to $3d^{10}4s^0$ configuration of Zn(II). Therefore, it can be inferred that the complex has tetrahedral geometry [6].

In the IR spectra of famotidine, bands appearing at 1350 and 1180 cm^{-1} assigned due to $^{\nu}S=O$ (asym) and $^{\nu}S=O$ (sym) respectively are shifted to 1320 and 1150 cm^{-1}, showing the coordination of oxygen of S=O bond with the metal[6]. Also two bands appearing at 3250 cm^{-1} and 3150 cm^{-1} in famotidine and 3260 cm^{-1} and 3100 cm^{-1} in glycine due to $^{\nu}N–H$ (asym) and $^{\nu}N–H$ (sym) respectively are observed in the complex at 3220 (asym) and 3060 (sym) cm^{-1} as broad bands which may be resulting from the shifting (due to complex formation) of $^{\nu}N–H$ bands of famotidine and glycine.

Bathochromic shift of the bands at 1620 cm^{-1} and 1400 cm^{-1} due to $^{\nu}COO$ (asym) and $^{\nu}COO$ (sym) of carboxylic group of glycine, observed at 1615 and 1412 cm^{-1} respectively in the complex shows the coordination of oxygen with the metal. The absence of $^{\nu}OH$ of the carboxylic group in the complex which appears at 2600 cm^{-1} in free glycine, confirms, the deprotonation of OH group on coordination [7] Complex formation is further confirmed by the bands [8,9] found in the complex at 525 and 420 cm^{-1} due to M—O and M—N bonds respectively. On the basis of elemental analysis, electronic and IR spectra, the following structure can be assigned to the complex.



The particle sizes of famotidine, glycine and the complex have 5–16, 4–17 and 4–12 microns respectively. This shows that the complex has smaller size than the parent drug which is of prime importance in suspension drug formulation [10].

The famotidine is absorbed in the stomach. The smaller particle size of the complex of the drug may enhance the absorption of complex in comparison to the parent compound which may lead to increase in potency of the drug if given in the complex form.

Table 1. Effect of Famotidine and Famotidine-Zinc-Glycine Complex on Gastric Secretion in Pylorous Ligated Rats

Dose in mg/Kg	TOTAL ACID meq/L			FREE ACID meq/L			MEAN VOLUME		
	Control	fam	fam-Zn-Gly	Control	fam	fam-Zn-Gly	Control	fam	fam-Zn-Gly
-	10.0±0.10	-	-	9.20±0.09	-	-	7.9±0.20	-	-
100	-	8.30±0.08	5.42+0.06	-	5.00±0.08	3.30±0.10*	7.9±0.20	6.0±0.16*	5.60±0.10*
200	-	6.60±0.08	3.50±0.09*	-	4.60±0.08	2.70±0.09**	7.9±0.20	5.6±0.14*	5.0±0.10**
500	-	3.30±0.09*	2.00±0.09**	-	3.00±0.10	1.60±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 1mL of gastric juice in milliequivalent/litre.

Gastric Secretion in Pylorous ligated rats:

The effects of famotidine and complex of Famotidine on gastric secretion are given in Table 1. It is clear from the Table that the compound in dose range of 200–500mg/kg produced significant reduction in total acid and free acid.

Although no attempt has 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 [11].

Gastric emptying rate:

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

Table 2. Effect of Famotidine and Famotidine-Zinc-Glycine Complex on Percent Gastric Emptying Rate in Albino Rats

Dose in mg/kg	Percent Gastric Emptying Rate		
	Control	Ram	Fam-Zn-Gly
-	96	-	-
100	-	94.5	96.2
200	-	95.2	96.8
500	-	96.5	97.0

Each value represents the mean±SEM of 3 observations

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