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# Physico-chemical and pharmacological characteristics of mixed ligand complex of Zn(II) with Ranitidine and Glycine

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**ABSTRACT**

*Mixed ligand complex of Zn(II) with ranitidine as one ligand and glycine as second ligand was prepared. The complex was characterized on the basis of elemental analysis, electronic and IR spectral and particle size measurements. Pharmacological effects of the complex on gastric secretion in pylorous ligated rats and gastric emptying rate in albino rats were also studied. 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.*

**Key words :** Zn, Ranitidine, Glycine, Particle size, Gastric secretion.

## INTRODUCATION

Ranitidine (ran) is a histamine $H_2$-receptor antagonist. The drug has been used in the treatment of duodenal and gastric ulceration [1,2] and is given orally as a tablet as well as in the form of injection. It has been reported by some workers [3,6] that complexation of antiulcer drugs has profound effect on their potency. Therefore, if the mixed ligand metal complexes of ranitidine as one ligand and amino acids which perform diverse biological functions in the body as second ligand, are prepared and probed for their pharmacological effect, the study can be of great use in the treatment of ulcer. Keeping this in view, the complex of Zn(II) with ranitidine as one ligand

and glycine (gly) as second ligand was prepared and its physico-chemical and pharmacological studies were carried out.

## MATERIALS AND METHODS

Zinc nitrate, ranitidine (ran) and glycine (gly) were taken in the molar ratio 1:1:1 so that the total weight was about 1-1.5g. Zinc nitrate was dissolved in 50mL distilled water. The ran and gly were added slowly into the solution of the 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.

Carbon and hydrogen were estimated in micronalytical laboratory. Nitrogen was determined by Kjeldhl and sulphur by messenger method. Zinc was estimated gravimetrically as Zinc ammonium phosphate. Electronic spectrum of the complex was run on beckman Du-64 spectrophotometer in nujol mull and IR spectrum on Perkin- Elmer 64- spectrometer using KBr pellets.

The particle sizes of the ran, and the complex 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 [7] :**
The albino rats weighing between 175-225g were used. They were divided into three groups. Each group had six animals. The first group served as control which received normal saline subcutaneously. The second group received ranitidine subcutaneously. The third group received complex of ran-Zn-gly subcutaneously in varying doses, dissolved in water.

**Gastric emptying rate[8] :**
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 ranitidine orally with phenol red, and the third group received complex of ran-zn-gly orally with phenol red.

## RESULTS AND DISCUSSION

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

The appearance of ranitidine was pale yellow powder and irregular in shape while glycine powder was white, shining and irregular in shape and the complex had buff colour and oval shape. The complex started decomposing at 180°C.

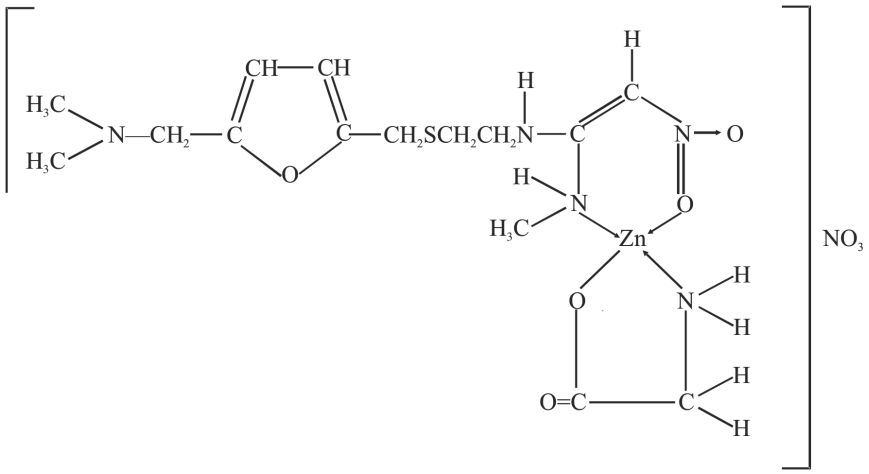
The particle sizes of ranitidine, glycine and the complex were 3-14, 4-17 and 3-9 microns. From this, it is clear that the size of the complex is smaller than the parent drug and glycine. The smaller size of the drug is of great importance in the formulation of the suspension drug [9]. The ranitidine drug is absorbed in the stomach. The smaller particle size of its complex may enhance the absorption of complex in comparison to the drug which may lead to increase in the potency of the drug if given in the complex form.

The electronic spectrum of the complex showed 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.

In the IR spectrum of ranitidine two bands appearing at 1455 $cm^{-1}$ and 1318 $cm^{-1}$ assigned due to $\nu_{N=O}$ (asym) and $\nu_{N=O}$ (sym) respectively [10] shifted to lower side; 1425 (asym), 1290 (sym), showing the bonding of oxygen of N=O group with metal.

Also, two bands appeared at 3250 $cm^{-1}$ and 3100 $cm^{-1}$ in ranitidine and 3260 $cm^{-1}$ (asym) and 3100 $cm^{-1}$ (sym) in glycine due to $^{\nu}$N–H (asym) and $^{\nu}$N–H (sym) vibrations respectively. In the mixed ligand complex, these bands appeared as broad bands at 3240 $cm^{-1}$ (asym) 3070 $cm^{-1}$ (sym) due to shifting of $^{\nu}$N-H bands of ranitidine as well as 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 $cm^{-1}$ and 1410 $cm^{-1}$ respectively in the complex, showed the coordination of oxygen with the metal. The absence of $^{\nu}$OH of the carboxylic group in the complex which appeared at 2600 $cm^{-1}$ in free glycine, confirms the deprotonation of –OH group on coordination [11]. Complex formation is further confirmed by the bands [12,13] found in the complex at 525 $cm^{-1}$ and 380 $cm^{-1}$ due to M—O and M—N bonds respectively.

On the basis of elemental analysis and electronic and IR spectral studies, the complex is assigned the following structure.




**Gastric Secretion in Pylorous ligated rats:**

The effects of ranitidine 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. Effect of Ranitidine and Ranitidine-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 | Ran | Ran-Zn-Gly | Control | Ran | Ran-Zn-Gly | Control | Ran | Ran-Zn-Gly |
| - | 10.0±0.20 | - | - | 9.0±0.20 | - | - | 8.01±0.38 | - | - |
| 100 | - | 9.0±0.10 | 6.54±0.12 | - | 6.10±0.12 | 3.20±0.10 | 8.0±0.38 | 6.50±0.50* | 6.0±0.20* |
| 200 | - | 7.20±0.08* | 4.62±0.10* | - | 5.30±0.08* | 2.61±0.06* | 7.9±0.35 | 6.10±0.38** | 5.8±0.10* |
| 500 | - | 4.21±0.12* | 2.53±0.11** | - | 4.11±0.07 | 2.41±0.06** | 7.9±0.35 | 3.0±0.30** | 2.6±0.20* |

*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.*

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 [14].

### Gastric emptying rate:

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

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

| Dose in mg/kg | Percent Gastric Emptying Rate | | |
|---|---|---|---|
| | Control | Ran | Ran-Zn-Gly |
| - | 95 | - | - |
| 100 | - | 95.5 | 95 |
| 200 | - | 95.8 | 96.2 |
| 500 | - | 96.8 | 96.2 |

*Each value represents the mean±SEM of 3 observations*

## CONCLUSION

Mixed ligand complex of Zn(II) with ranitidine as one ligand and glycine as second ligand was synthesized. The complex was found to have tetrahedral 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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