

A novel synthesis of Mn(II)-metoclopramide complex and its characterization.

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Abstract: As a part of ongoing research for more effective drugs, Mn(II) complex of metoclopramide (MCP) has been successfully synthesized for the first time and shown to be a good antimicrobial agent. Metoclopramide (MCP) has been characterized well on the basis of analytical data like conductance, magnetic measurement, electronic and infrared spectrometry and thermogravimetric-differential thermal analysis, etc. From analytical data, the stoichiometry of the complex has been found to be 2:1(L:M). The antimicrobial activity of this complex tested against *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis*) and *Bacillus megaterium* (*B. megaterium*).

Keywords: Mn (II) complex, metoclopramide, synthesis, antiemetic drug, characterization, antimicrobial activity

Introduction:

Although medicinal chemistry was almost exclusively based on organic compounds and natural products during the past three decades, metal complexes have gained a growing interest as pharmaceuticals for the use as diagnostics agents or as chemotherapeutic drugs.^[1-3] Metal ions induce their effects in the complexed form, particularly when the human necessary metals complexed with the drugs as chelating agents. It is very advisable to use metals like Mn, Fe, Co, Ni, Cu, Zn, Mo, etc. in the drug complexes, even though they are required for human body in trace amount to well function the system, they are very important and must present. So there is urgent need for the combination of such metal with drugs to control the diseases.^[4-6] Nausea and vomiting are among common complaints when patients visit their physicians. These symptoms may occur separately or together can result from gastrointestinal disorders to brain tumors, poisoning, or exposure to drugs. Emesis (also known as vomiting) is a reflex that is present to varying degrees in different species and involves forceful expulsion of the contents of the stomach through the mouth. The continuous feeling of gastrointestinal discomfort that one is about to vomit is called nausea. Often nausea precedes the act of vomiting, however, nausea does not always lead to emesis. Metoclopramide (MCP), 4-amino-5-chloro-N-(2-(diethylaminoethyl)-2-methoxybenzamide), is a dopamine antagonist clinically used as antiemetic (useful in treating vomiting) and gastroprokinetic agent.^[7-9] It belongs to the group of medicines called 'dopaminergic' blockers. It is commonly used to treat nausea and vomiting to facilitate gastric emptying in people with gastroparesis and treatment for the gastric stasis often associated with migraine headaches. Recent investigations show that this drug has therapeutic potential and studies show its mechanism of action at receptor and molecular level. There has been the metal-MCP complexes such as Mo and Co.^[10-15] In an attempt to make an effective drug complex, we have carefully chosen Mn(II) as a metal ion and MCP as a drug to make complex. To the best of our knowledge, we have first time synthesized Mn(II)-MCP complex, characterized well and studied its antimicrobial activities.

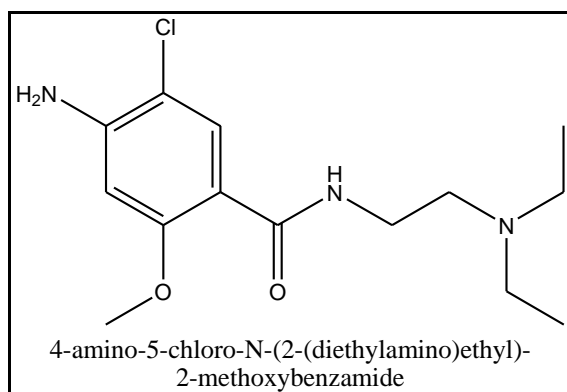


Fig.1 Structure of metoclopramide

Materials and Method:

Synthesis of complex:

All chemicals used were of analytical grade. Pure sample of metoclopramide (MCP) having molecular formula, (C₁₄H₂₂ClN₃O₂) and molecular weight 299.80 g/mol was obtained from pharmaceutical company. Metal salt was of Merck Chemicals. Complex was prepared by dissolving MCP (5mM, 1.5 g) in ethanol and adding this solution to ethanolic manganese chloride (2.5mM, 0.49g). The reaction mixture was refluxed for 2 hrs. The mixture was filtered and dried in oven to obtain creamy powder.

Instrumentation:

Melting points were taken in open capillaries on a melting point apparatus. Ultraviolet (UV) spectra were recorded in the range 200-800 nm on Perkin Elmer UV spectrometer by making solutions in DMSO. The Infra-red (IR) spectra were recorded as KBr pellets in range 4000-400cm⁻¹ on Shimadzu FTIR. Carbon, Hydrogen and Nitrogen were determined on Thermo Fisher Flash Elemental Analyzer. Magnetic moment was carried out by Gouy balance. Conductivity was measured by making solutions in Dimethyl Sulfoxide (DMSO). In order to throw more insight into the structure of the reported complexes, thermal studies on the solid complexes using Thermogravimetric (TG) and derivative thermal analysis (DTA) were performed.

Results and Discussions:

Table 1: Analytical Data of MCP and Mn (MCP)₂·2H₂O Complex:

Ligand and Complex	Ligand :Metal Ratio	Colour	Melting Point	Molecular Weight in g/mol	Molar Conductivity in Ω ⁻¹ cm ² mol ⁻¹
MCP	-	White	147°C	299	
Mn (MCP) ₂ ·2H ₂ O	2:1	creamy	326°C	690	12.50

The molar conductance of the solid complex (Ω⁻¹ cm²mol⁻¹) was measured. The DMSO solubility of the above complex made calculation of molar conductivity of 10⁻³mol dm⁻³ solution at 25°C possible. The data showed that the molar conductance is relatively of low value, indicating the non-electrolytic nature of the complex. Therefore molar conductance confirm the result of elemental analysis and spectral data.

Table 2: Elemental Analysis of MCP and Mn (MCP)₂·2H₂O Complex:

Ligand and Complex	C%	H%	Cl %	N %	O %	M %
MCP	56(57)	7.35 (7.80)	11.87 (11.95)	14 (14.13)	10.70 (10.78)	-
Mn (MCP) ₂ ·2H ₂ O	49.05 (49.10)	6.42 (6.50)	10.2 (10.34)	12.26 (12.30)	9.34 (9.40)	9.34 (9.55)

Table 3: UV Spectra of Mn (MCP)₂·2H₂O Complex:

Mn (MCP) ₂ ·2H ₂ O	(cm ⁻¹)	nm	assignment
Band 1	14706	680	⁶ A _{1g} → ⁴ A _{1g} (G)
Band 2	20833	480	⁶ A _{1g} → ⁴ T _{2g} (G)
Band 3	24721	404	⁶ A _{1g} → A _{1g} + ⁴ E _g (G)

The electronic spectra of Mn (MCP)₂·2H₂O complex showed a series of very weak and some were narrow bands, which is expected because of the only sextet term of the d⁵ configuration in octahedral stereochemistry is the ⁶A_{1g}, consequently, there will be no spin allowed transitions.^[16-17]

Table 4: IR Spectra of Mn (MCP)₂·2H₂O Complex:

Compound	ν N-H cm ⁻¹	ν C=O cm ⁻¹	ν OH cm ⁻¹	ν M-N cm ⁻¹
(MCP)	3305	1596	3396	-
Mn (MCP)₂·2H₂O	3296	1596	3396	435

The molecule of metoclopramide acts as a bidentate ligand. The donor groups are N-H amino nitrogen and tertiary nitrogen. The change is found in frequency of N-H group which is lowered shows involvement of amide group. An additional band at 435 cm⁻¹ shows M-N bond formation is seen in the IR spectra of Mn-metoclopramide complex.^[18]

TG-DTA of Mn (MCP)₂·2H₂O complex:

The complex is stable at room temperature and can be stored for several months without any changes. The obtained complex is studied by thermo gravimetric (TG) and differential thermal analysis (DTA) from ambient temperature to 1000 °C N₂ atmosphere. The TG curves were redrawn as mg (milligram) mass loss versus temperature (TG) curves and in DTA the, difference in temperature between sample and thermally stable and inert reference material is recorded as function of sample temperature or time, when heated or cooled at a controlled rate, which is linear with time.

The thermogram of Mn (MCP)₂·2H₂O shows that the complex is stable up to 245 °C indicating that there is absence of hydrated water molecule. Decomposition starts at 225 °C and finished at 660 °C with three stages. The thermogram of complex shows that the complex is stable up to 245 °C indicating that there is absence of hydrated water molecule. This is confirmed by endothermic peak in DTA curve in this temperature range. The complex starts gradually decomposing till it attains the temperature corresponding to 300 °C. The weight corresponds to two molecules of coordinated water in complex.^[19] After 225 °C there is sharp decrease in weight till 300 °C indicating decomposition of complex further confirmed by exothermic peak obtained in DTA curve. Organic part of ligand is lost i.e., side groups of ligand which is calculated to be 37.68% and found to be 36.46% from graph. Then in next decomposition step of complex ranging from 325 °C to 500 °C, the percentage weight loss is 19.70% (cal. 20%). After this complex shows sharp decrease in weight indicating decomposition of complex, confirmed by exothermic nature of peaks obtained in DTA curve. The percentage weight loss is 33.62% (cal. 34.48%) which depicts that rest part of the ligand is decomposed and metal oxide is left as residue.

Antibacterial Screening:**Agar well diffusion method**

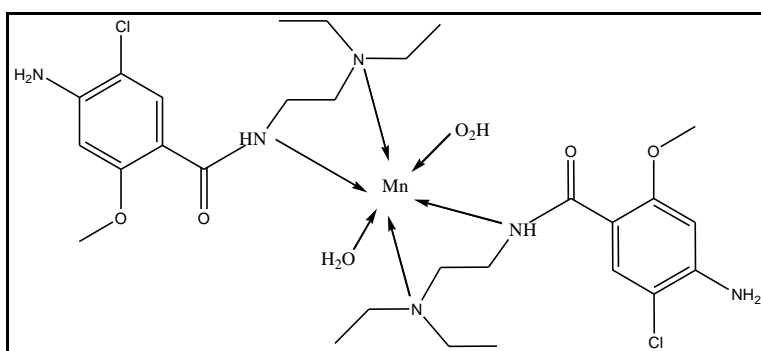
7g of nutrient agar was weighed into a 250 ml conical flask. 250ml distilled water (sterilized for 24hrs) was mixed with agar and it was covered properly with cotton wool and foil paper so as to avoid contamination. The solution was then heated for 15mins so as to dissolve the nutrient agar. It was sterilized for 24hrs in an autoclave. The nutrient agar was then introduced into the petridish and was allowed to set properly. 1cm hole was bored at the center of the plate with the aid of hole borer and was allowed to remove the cracked hole so as to view the bottom of the petridish. This was left in incubator for 24hrs to allow the outgrowth of microorganisms. The zone of inhibition of complexes and ligand was determined in mm. DMSO was used as control. The bacterial species against *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis*) and *Bacillus megaterium* (*B. megaterium*) were used as test organisms.

Table 5:Antibacterial activity zone of inhibition in, mm.

Compound	<i>E. coli</i>	<i>B.subtilis</i>	<i>B.megaterium</i>	<i>S. aureus</i>
MCP	13.10	13.14	-	11.20
Mn (MCP) ₂ ·2H ₂ O	12.34	15.80	16.00	12.10

Conclusion:

The novel synthesis of the metal complex of metoclopramide with Mn (II) was made for the first time. The complex formation has been confirmed by UV and FT-IR spectroscopy, TG-DTA and physical analyses which has revealed the formation of complex was in 2:1 stoichiometry to metoclopramide and Mn(II) further showed that metoclopramide is bidentate ligand. The complex showed a diverse antimicrobial activity as compared to ligand which is attributed to formation of metal chelate. This study will definitely lead to a pharmaceutical research related to metoclopramide.

**Fig. 2 Proposed structure of Mn (MCP)₂·2H₂O complex****References:**

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