



Synthesis and Spectroscopic Characterization of Copper-Theophylline-Dicarboxylic Acid Complexes

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Abstract

This study investigates the synthesis and characterization of copper complexes of theophylline, a xanthine derivative with therapeutic relevance, using dicarboxylic acids such as isophthalic acid (ISO), succinic acid (SUC), and terephthalic acid (TER) as auxiliary ligands. The complexes were synthesized via hydrothermal methods and yielded distinct crystalline and powdery products. UV-Vis spectroscopic analysis revealed ligand transitions at 273–275 nm and ligand-to-metal charge transfer (LMCT) bands at 371–471 nm, indicative of robust metal-ligand coordination. Notably, the Cu-Theo-ISO complex exhibited LMCT at 471 nm, while Cu-Theo-SUC demonstrated additional transitions at 544.4 and 599 nm, reflecting variations in coordination geometry influenced by the auxiliary ligands. FTIR spectroscopy confirmed the coordination of copper ions with theophylline and dicarboxylic acids, evidenced by shifts in the N-H ($\sim 3100\text{ cm}^{-1}$) and C=O ($\sim 1658\text{ cm}^{-1}$) stretching vibrations. The synthesized copper complexes displayed improved solubility and stability, critical for enhancing theophylline's pharmacokinetic profile. These findings underline the potential of copper-theophylline-dicarboxylic acid complexes for applications in controlled drug release and bioavailability improvement. Ongoing research aims to explore their biological activities and therapeutic potential.

Keywords: Copper complexes; theophylline; dicarboxylic acids; synthesis; spectroscopy

1. Introduction

Copper coordination complexes have gained considerable attention for their applications in enhancing the pharmacological profiles of essential drugs (Santini et al., 2014; Marzano et al., 2009). These complexes can improve drug solubility, stability, and bioavailability, ultimately leading to more effective therapeutic outcomes in various medical conditions. Copper, a biologically significant transition metal, forms stable complexes with various organic ligands, exhibiting properties such as improved solubility, bioavailability, and stability. These features make copper complexes highly relevant for drug delivery and therapeutic applications. Theophylline, a xanthine derivative known for its bronchodilator and anti-inflammatory effects, has limited clinical use due to its poor water solubility and stability. Researchers have sought to improve these limitations through complexation with transition metals like copper (Ali et al., 2012; Siddiqui et al., 2015; Abosede and Obiyenwa, 2022; Frota et al., 2024a; Frota et al., 2024b). Complexation with metal ions, especially copper, has been shown to overcome these limitations. Copper, as a transition metal, can form stable coordination complexes with various organic ligands, including nitrogen and oxygen donor atoms present in drugs and auxiliary ligands. The inclusion of dicarboxylic acids, such as isophthalic acid, succinic acid, and terephthalic acid, as auxiliary ligands provide additional stability and structural diversity. These



ligands not only enhance the physicochemical properties of the resulting complexes but also introduce functionality that can influence the drug's pharmacological behavior (Chohan et al., 2006).

This study focuses on synthesizing copper-theophylline complexes with dicarboxylic acids, characterizing their structural and electronic properties, and assessing their potential for improving theophylline's therapeutic applications. By combining theophylline with copper ions and auxiliary ligands, the research aims to address solubility and stability issues while exploring new coordination geometries that could enhance controlled drug release and bioavailability. This innovative approach could lead to the development of more effective therapeutic formulations, ultimately improving patient outcomes and expanding the potential applications of theophylline in clinical settings (Novena et al., 2016).

Spectroscopic techniques play a vital role in characterizing these complexes. UV-Vis spectroscopy provides insights into ligand-to-metal charge transfer (LMCT) and d-d transitions, confirming the coordination environment and electronic structure. The information obtained from these spectroscopic methods is crucial for understanding the reactivity and stability of metal complexes in various chemical processes (House, J. E. (2018).

FTIR spectroscopy identifies shifts in characteristic functional groups such as N-H, C=O, and carboxylic groups, providing evidence of metal-ligand interactions. Together, these techniques offer valuable insights into the structural and electronic properties of the complexes (Ali & Mirza, 2012).

The potential of copper-theophylline complexes to enhance drug solubility, stability, and bioavailability has been well-documented. However, there remains a need for comprehensive studies focusing on the role of dicarboxylic acids as auxiliary ligands. This study aims to address this gap by synthesizing and characterizing copper complexes of theophylline with isophthalic acid, succinic acid, and terephthalic acid. The findings provide insights into their coordination behavior, electronic properties, and potential applications in drug delivery.

Metal complexes have been extensively studied for their ability to enhance the pharmacological properties of drugs. Transition metals, such as copper, manganese, and zinc, are particularly effective in forming stable complexes with essential drugs. These complexes often exhibit improved solubility, thermal stability, and targeted drug delivery capabilities (Ali & Mirza, 2012). For instance, copper complexes with Schiff base ligands have shown significant antimicrobial and anticancer activities due to their ability to interact with biological macromolecules like DNA and proteins (Karges et al., 2021).

Theophylline, a xanthine derivative, is an established bronchodilator used to treat respiratory disorders such as asthma and chronic obstructive pulmonary disease. However, its clinical application is limited by poor solubility and bioavailability. Copper-theophylline complexes have been explored as a strategy to enhance these properties. Studies have demonstrated that coordination with copper can significantly improve theophylline's solubility and pharmacokinetics while introducing novel biological activities (Siddiqui et al., 2015).

Dicarboxylic acids are versatile auxiliary ligands in coordination chemistry, offering diverse coordination modes such as chelation and bridging. Isophthalic acid, succinic acid, and terephthalic acid are commonly used to introduce stability and flexibility into metal complexes. These ligands also provide additional donor atoms that contribute to the structural integrity and electronic properties of the complexes (Chohan et al., 2006). The use of these ligands in copper-theophylline complexes could further enhance the drug's solubility, thermal stability, and potential for controlled release.

UV-Vis and FTIR spectroscopy are indispensable tools in characterizing metal complexes. UV-Vis spectroscopy provides insights into ligand-to-metal charge transfer (LMCT) and d-d transitions, which confirm the formation of coordination bonds and the electronic structure of the complexes (Ali & Mirza, 2012). FTIR spectroscopy identifies shifts in characteristic functional groups, such as N-H and C=O, which signify metal-ligand coordination (Siddiqui et al., 2015). These techniques are essential for understanding the structure-property relationships in copper-theophylline-dicarboxylic acid complexes.



2. Materials and Methods

Materials

The metal salt ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) and mebendazole (Meb) were gotten from commercial sources and were used without any further purification. The complexes (materials) were further characterized using the JASCO V-730 Ultraviolet-Visible spectrophotometer, the melting points of the complexes were determined using Stuart melting point (SMP 11) apparatus, and the solubility was determined in from these solvents: methanol, ethanol, distilled water and DMF. The FTIR spectra of the synthesized complex was taken on Shimadzu 8400-S from the region of 4000-400 cm^{-1}

Synthesis

Copper complexes of theophylline with isophthalic acid (Cu-Theo-ISO), succinic acid (Cu-Theo-SUC), and terephthalic acid (Cu-Theo-TER) were synthesized via hydrothermal methods. A typical synthesis involved dissolving 2 mmol of theophylline and 2 mmol of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in 10 mL of aqueous NaOH. Auxiliary ligands (isophthalic acid, succinic acid, or terephthalic acid) were added to the mixture in equimolar ratios (2 mmol), followed by heating in an autoclave at 120–125°C for 10 hours. The resultant mixtures were filtered and allowed to crystallize at room temperature, yielding crystalline or powdery products.

3. Results and Discussion

The complexes were obtained as crystalline (Cu-Theo-ISO) or powdery (Cu-Theo-SUC, Cu-Theo-TER) materials with varying colors, reflecting differences in metal-ligand interactions.

The synthesized complexes displayed distinct UV-Vis absorption bands, indicating successful metal-ligand coordination. The Cu-Theo-ISO complex exhibited ligand transitions at 275 nm and an LMCT band at 471 nm. In contrast, Cu-Theo-SUC showed additional bands at 544.4 and 599 nm, which can be attributed to altered coordination geometries induced by succinic acid. Cu-Theo-TER revealed transitions at 381 nm, consistent with the coordination environment introduced by terephthalic acid. These variations highlight the influence of auxiliary ligands on the electronic environment of copper ions.

Table 1: Physico-chemical and UV-Visible Spectroscopic Data of the Complexes

Complex	Product yield (%)	Colour	Appearance	Ligands Transitions (nm)	Charge Transfer (nm)	Metal-Ligand charge transfer (nm)
Cutheo-Iso	88.3	Blue	Powdery	275	391.4	471
Cutheo	38.5	Green	Powdery	244	315	471
Cutheo-Ter	52.3	Blue	Powdery	273	381	410
CutheoSucc	52.78	greenish blue		273	371	544.4, 599

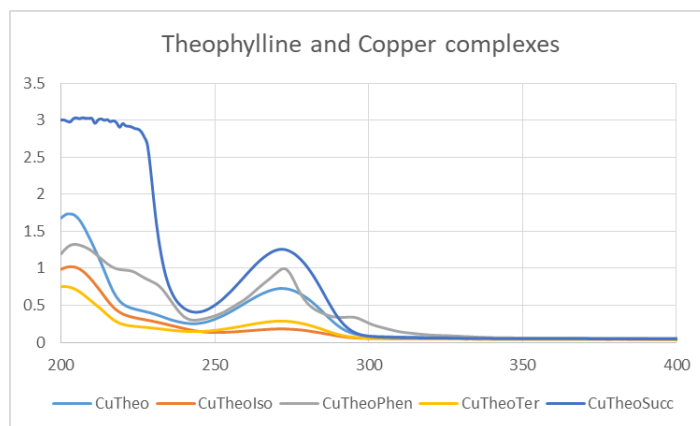


Figure 1: Electronic Absorption Spectra of Mixed Ligands Complexes with Copper



FTIR analysis also confirmed the coordination of copper ions with theophylline and dicarboxylic acids. Shifts in COOH stretching vibrations from $\sim 3345\text{cm}^{-1}$ in free theophylline to $\sim 3365\text{cm}^{-1}$ in the complexes indicated carboxylate coordination. Similarly, the N=H stretching band shifted from 1658cm^{-1} in the free ligands to $\sim 1668\text{cm}^{-1}$ in the complexes, suggesting nitrogen coordination. New bands observed at 1680 and 1632cm^{-1} were attributed to Cu–N and Cu–O stretching vibrations respectively, further confirming metal-ligand bonding.

Table 2: FTIR spectra of theophylline and its copper metal complexes

Cu-Theo	Cu-Theo-Iso	Cu-Theo-Suc	Cu-Theo-Ter	Assignment
3345	3330 sh	3361	3365	COOH
3097		3097		Ar stretch
		1641	1668	N=H stretch
	1680			C=N stretch
1625	1623			C=C stretch
1544				O-H bending of absorbed water

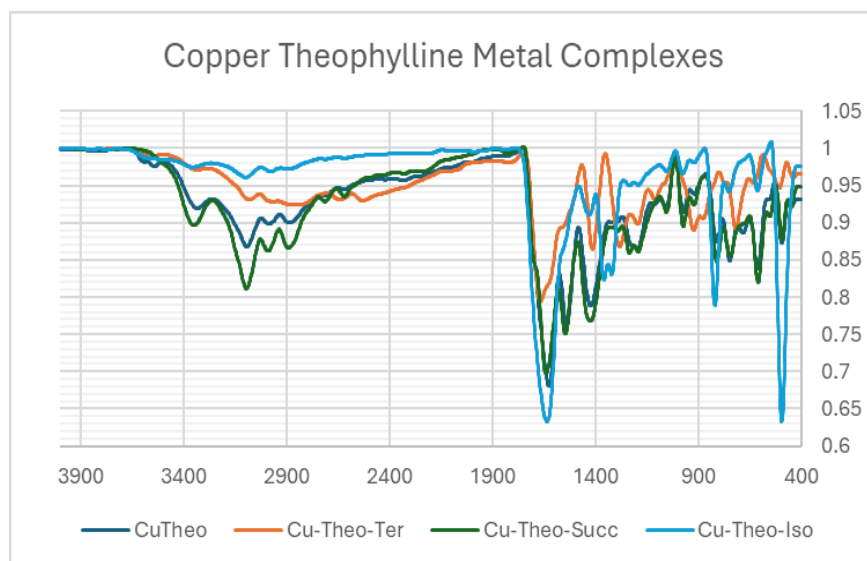


Figure 2: FTIR spectra of Theophylline and copper complexes

The complexes were obtained as crystalline (Cu-Theo-ISO) or powdery (Cu-Theo-SUC, Cu-Theo-TER) materials with varying colors, reflecting differences in metal-ligand interactions. These structural modifications, coupled with improved solubility and stability, underscore the potential of these complexes in enhancing the pharmacokinetic profile of theophylline.

4. Conclusion

Crystalline (Cu-Theo-ISO) or powdery (Cu-Theo-SUC, Cu-Theo-TER) materials with varying colors, reflecting differences in metal-ligand interactions. The successful synthesis and characterization of copper-theophylline-dicarboxylic acid complexes demonstrated the versatility of hydrothermal methods in tailoring metal-ligand interactions. Spectroscopic analyses confirmed robust coordination, with distinct variations induced by the auxiliary ligands. The enhanced solubility and stability of these complexes position them as promising candidates for controlled drug delivery and bioavailability improvement. Further investigations into their biological activities and therapeutic potential are warranted to fully exploit their pharmaceutical applications.



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