Global Scientific JOURNALS

GSJ: Volume 12, Issue 1, January 2024, Online: ISSN 2320-9186
www.globalscientificjournal.com

SYNTHESIS AND CHARACTERIZATION OF COBALT(II), NICKEL(II) AND SILVER(I) COMPLEXES WITH INDOMETHACIN.

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ABSTRACT

In recent years, significant advances in chemistry have been made in the synthesis, characterization, and application of metal complexes in the biological and pharmaceutical industry. Many efforts to date have concentrated on the study of the role of these coordination molecules, given the wide range of fields in which they have practical application. In this study, Nickel(II) metal, cobalt(II) metal, and silver(I) metal complexes are synthesized with in Hindo, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid (commonly called indomethacin) and characterized by molar conductance, melting point, color and solubility in different solvents to identify properties that will be a crucial in future research applications. A putative structure for the silver indomethacin complex has been presented due to the paucity of data and study on complexes of silver(I) with indomethacin. Thus, it is anticipated that this work will support future research and development of indomethacin-containing metal complexes.

Keywords: synthesis, complex, characterization, nickel-indomethacin, cobalt-indomethacin, FT-IR

1. INTRODUCTION

Metal coordination of bioorganic compounds from both natural and synthetic products is not only gaining recognition in drug design and medicinal inorganic chemistry research, also they are being considered in the improvement of the bioactivity of drugs [1]. Transition metal complexes play key roles in photochemistry, biological systems, materials production, and catalysis. The distinct characteristics of metal ions can be utilized by medicinal inorganic chemistry to create novel pharmaceuticals. [2-3]. Metal complexes have distinct shapes because they can aggregate to a variety of coordination geometries. Depending on the metal and its oxidation state, different values apply to the bond length, bond angle, and coordination site. Furthermore, a broad range of coordination numbers and geometries can be conferred by structurally modifying metal-based complexes to yield a variety of unique molecular species. [4-5].

Metal ions have been an essential component of living organisms acting as complexes or chelates, as well as in the analysis and control methods of drug substances by forming complexes that can be detected by spectral techniques, according to the biological and pathophysiological role of metal ions and ligands with pharmacological effect. [6]. Numerous metals, including Nickel, Copper, Cobalt and Silver, combine to create complexes with a wide range of organic ligands that have significant uses in the pharmaceutical sector. Within the active Centre of vitamin B12 (cobalamin), cobalt is an important bio element that is necessary for numerous biological processes, including the insertion of methyl groups into DNA. [7]. 1952 saw the publication of the first studies on the biological activity of cobalt complexes, which examined Since then, numerous biologically significant cobalt complexes have been discovered, the majority of which have antiproliferative properties. [9][10], antibacterial, antifungal, antiviral [8], and antioxidant action [11][12].

Nickel is a trace element that is required by all living things. When compared to Zn, Cu, and Fe, its concentration in live organisms is negligible..[13], [14], [15], [16], [17], Following the discovery of nickel as an active site metal ion in jack bean urease in 1975 [18] [19], research into nickel's biological roles has increased considerably.[20], [21], [22], Since then, the number of nickel-dependent enzymes has grown dramatically, as has nickel's usage in bioinorganic chemistry. As a result of their biological activity as anticancer agents, Ni(II) complexes have become the focus of bioinorganic chemists' research. [23] antibacterial 14][15][16], fungicidal [24], anti-inflammatory/antioxidant, antileishmanial and their intercalating interactions with DNA. Furthermore, a vast number of nickel complexes of biological importance have been identified. [14][15][16].

Silver complexes are comparable to its lighter homologue copper complexes; Ag(II) complexes are rare and rapidly reduced to the more stable lower oxidation state, however they are marginally more stable than Cu(II) complexes. The yellow diamagnetic (AgF_4^-) is far less stable, fuming and interacting with glass [25]. Ag(II) complexes are more prevalent; like other valence isoelectronic copper(II) complexes, they are often square planar and paramagnetic, which is aided by the stronger field splitting field splitting for 4d electrons than for 3d electrons.

Even in acidic conditions, aqueous Ag^{2+} generated by ozone oxidation of Ag^{+} is a highly potent oxidizing agent. [26].

Metal-NSAIDs complexes have excellent biological activity compared with free NSAIDs because of the synergistic effect between the metal ions and the NSAIDs [27]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic, antipyretic, and anti-inflammatory activity; they also have therapeutic benefits in preventing some cancer types and treating neurodegenerative diseases [28]; NSAIDs are among the most commonly prescribed classes of medication for pain and inflammation [29]. NSAIDs are effective COX-1 and COX-2 inhibitors both in vivo and in vitro, which reduces the production of prostaglandins, prostacyclin, and thromboxane derivatives. [30]

One of the most potent NSAIDs, indomethacin (also known as Hindo, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid) has antipyretic, analgesic, and anti-inflammatory activities. It is a derivative of indoleacetic acid and belongs to the phenyl alkanoic acid family [31]. Indomethacin has been used successfully to treat various types of hemicrania even though it is primarily used for the treatment of arthritis and other joint inflammatory diseases [31]. It's worth noting that during the coronavirus pandemic, indomethacin was proven to have considerable antiviral activity against SARS CoV-2 (COVID-19) in vitro and canine coronavirus in vivo. [32][33]. Nevertheless, bio-inorganic chemists have been able to mitigate its negative side effects by complexing it with -d-block metal ions. [33]

Complexes of indomethacin coordinate via the carboxyl group's oxygen. Additionally, when complexing with Hg(II), Pb(II), Sn(II), and Bi(II), indomethacin functions as a bidented chelating agent. Additionally, when coordinated by IR-UV to Cd(II), Ce(III), and Th(IV), it functions as a monodented ligand. [32]. The coordination of indomethacin towards metal ions has also been reported to be influenced in the presence of co-ligand [33]. A bridging bidentate coordination mode, having a paddle wheel motive, mostly with solvent co-ligand, was observed in most structurally characterized indomethacin complexes [33,34]. Three structurally characterized complexes with indomethacin coordinating as chelating bidentate ligand reported in [34,35]. Also, indomethacin was reported having three different coordination modes in the presence of a nitrogen donor co-ligand in a complex [36]. Monodentate coordination of indomethacin ligand in complexes with known structures are scarce. A thorough survey of literature for mononuclear Cu(II) and Ni(II) indomethacin complexes revealed only five known crystal structures, which were in the presence of imidazole, and pyridine derivatives (4-picoline, 2,2′-bipyridylamine, 2,2′-bipyridine and 1,10-phenanthroline) [35,37].

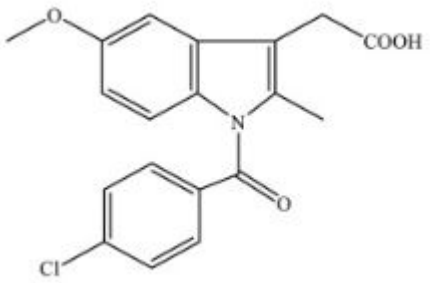

Figure 1. Chemical Structure of Indomethacin (Hindo)

Spyros Perontsis et al (2019) [38] synthesized, characterized and structurally determined in vitro and silico the biological evaluation of divalent and trivalent cobalt complexes with indomethacin and in this study, the interaction of cobalt chloride with the NSAID indomethacin led to the formation of the mononuclear-based polymeric complex $[Co(indo\text{-}O)_2(H_2O)_2(\mu\text{-}Cl)]_n$; in this complex, a unique chlorido ligand bridges the cobalt atoms which is a rather rare case. The presence of a nitrogen-donor co-ligand during the interaction results in a variety of complexes, such as the dinuclear complex $[Co_2(\mu\text{-}indo\text{-}O,O')_2(indo\text{-}O)_2(bipy)_2(\mu\text{-}H_2O)]$ and the mononuclear complexes $[Co(indo\text{-}O,O')_2(bipyam)]$, $[Co(indo\text{-}O,O')_2(phen)]$ and $[Co(indo\text{-}O)_2(Himi)_2]$. In all these complexes, the indomethacin ligands are bound in all possible ways through the carboxylato groups. [38]

This study aims at synthesizing and characterizing Ni(II), Ag(I) and Co(II) complexes using Hindo, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid (commonly called indomethacin). The objective this work is to identify the melting temperatures, molar conductance, solubility in various solvents, and other physical characteristics of indomethacin-mixed ligands for Ni(II), Ag(I), and Co(II) that will be useful in its practical application.

2. MATERIALS AND METHODS

2.1 Reagents and Solvent Used

All the reagents and solvents used was purchased commercially and used without any purification. The reagents used are Ethanol, Distilled water, Nickel (II) Chloride, Silver(I) Chloride, Cobalt (II) chloride, Methanol

2.2 Synthesis of Nickel Complex with Indomethacin

1.8g (0.005mol) of the indomethacin was measured and dissolved properly in 20ml of (90%) ethanol with stirring. While waiting for the dissolution of the indomethacin in ethanol, a solution of cobalt (II) chloride was prepared separately by adding 0.63g (0.005mol) Nickel(II) Chloride in 20ml of ethanol in a flask;

To the indomethacin solution, the green solution of Nickel(II) chloride was added slowly and stirred for 15 minutes. The reaction mixture was refluxed for 3hours and allowed to cool overnight. The crystal formed was filtered, washed with ethanol to remove impurities, dried in a vacuum desiccator and the indomethacin complex was weighted.

$$\text{Molecular Mass of the Ligand} = 357.8\text{g/mol}$$
$$\text{Molecular Mass of the NiCl2} = 129.63$$
$$\text{No of moles} = \frac{\text{Reacting mass}}{\text{Molar mass}}$$
$$= \frac{1.8\text{g}}{357.8\text{g /mol}}$$
$$= 0.005\text{mol}$$

$$\text{Total mass of complex} = \text{mass of salt used} + \text{mass of ligand}$$
$$= 129.63\text{g/mol} + 357.8\text{g/mol} = 487.43\text{g}$$

$i.e$

if 357.8g of the ligand is present in 487.73g of the complex
1.8g of the ligand will be present in (x)g of the complex

$i.e$ $$\text{X(g)} = \frac{487.43\text{g} * 1.8\text{g}}{357.8\text{g}}$$
$$= 2.5g$$

Theoretical yield = 2.5g
Practical yield = 1.1g

$$\text{Percentage yield} = \frac{\text{Practical Yield}}{\text{theoritical yield}} * 100$$

$$\text{Percentage Yield} = \frac{1.1g}{2.5g} * 100$$
$$= 44\%$$

The molar weight of indomethacin is 357.80g, while the molar weight of Nickel(II) Chloride [$NiCl_2$] is 129.63gg. Thus, the molecular weight of the metal complex is 487.43g. With this information the theoretical yield of the complex was calculated to be 2.5g, while the practical yield was measured at 1.1g. the percentage yield is calculated to 44%.

2.3 Synthesis of Cobalt Complex with Indomethacin

1.8g (0.005mol) of the indomethacin was measured and dissolved properly in 20ml of (90%) ethanol with stirring. While waiting for the dissolution of the indomethacin in ethanol, a solution of cobalt (II) chloride was prepared separately by adding 0.60g (0.005mol) Cobalt (II) Chloride in 20ml of ethanol in a flask;

To the indomethacin solution, the blue solution of Cobalt(II) chloride was added slowly and stirred for 15 minutes. The reaction mixture was refluxed for 3hours and allowed to cool overnight. The crystal formed was filtered, washed with ethanol to remove impurities, dried in a vacuum desiccator and the indomethacin complex was weighted.

Molecular Mass of the Ligand = 357.8 g/mol

Molecular Mass of the CoCl2 = 129.93 g/mol

$$\text{No of moles} = \frac{\text{Reacting mass}}{\text{Molar mass}}$$

$$\text{no of moles} = \frac{1.8\text{g}}{357.8\text{g /mol}}$$

$$= 0.005mol$$

$$Total\ mass\ of\ complex\ =\ mass\ of\ salt\ used\ +\ mass\ of\ ligand$$
$$i.e \quad = 129.93g/mol\ +\ 357.8g/mol\ =\ 487.73g$$

if 357.8g of the ligand is present in 487.73g of the complex
1.8g of the ligand will be present in (x)g of the complex

i.e $$X(g) = \frac{487.73g * 1.8g}{357.8g}$$

$$= 2.5g$$

Theoretical yield $= 2.5g$
Practical yield $= 1.4g$

$$\text{Percentage Yield (\%)} = \frac{\text{Practical value}}{\text{Theoritical value}} * 100$$

$$\text{Percentage Yield(\%)} = \frac{1.4g}{2.5g} * 100$$
$$= 56\%$$

The molar weight of indomethacin is 357.80g, while the molar weight of Cobalt(II) Chloride [$CoCl_2$] is 129.63gg. Thus, the molecular weight of the metal complex is 487.73g. with this information the theoretical yield of the complex was calculated to be 2.5g, while the practical yield was measured at 1.4g. the percentage yield is calculated to 56%.

3. RESULTS AND DISCUSSION

Table.1 Physical properties of the Ni(II) and Co(II) complexes are shown in table 1.0

	Ligand/metal salt	***State***	***Color of salts***	***Color of complexes***	***Physical state***
1	Indomethacin ligand	Solid	White		Powdery
2	Cobalt(II) chloride	Granules	Blue	Pink	Powdery
3	Nickel(II) Chloride	Granules	Green	Light green	Powdery

Solubility test: The solubility test is reported in table 2.0 showed slight solubility between the Ni(II), and Co(II) complex in ethanol and methanol, and solubility with distilled water.
The solubility of a compound is the weight in grams of the solute (complex formed) dissolved in 100gram of solvents at a given temperature.

Small portions of each of the complexes (0.1g) were placed in a test tube and different solvents about 2mls were added to the different test tubes. The solvents used were: water, ethanol, acetone, propanol. In each case, the solubility was recorded. The mixture was shaken vigorously, if all the solute particles dissolved, we have a soluble solution; if some of it

dissolves, we have a sparingly soluble; and if the sample do not dissolve in the solvents, we have an insoluble solution. The same test was carried out in the complex.

Table 2. Solubility test

	Ethanol	**Metanol**	**Water**
Nickel(II)-indo complex	Slightly Soluble	Slightly Soluble	Insoluble
Cobalt(II)-indo complex	Slightly Soluble	Slightly Soluble	insoluble

Melting point: Little amount of the substance was put in a clean dry small capillary tube with one end fused and inserted into the howls of the Stuart SMP3 digital melting point apparatus, the tubes were inserted in a way, in which the visibility on the monitor was clear and then the different samples were heated slowly by pressing the heat up button on the machine. The temperature in which the substance begins to melt was recorded.

Table 3. Physical properties of the metal and its complexes

Ligand Metal Complex	**Molar Ratio (Metal: Ligand)**	**Percentage Yield**	**Physical Nature**	**Melting Point ^{o}c**	**Colour**
Cobalt(II)-indo complex	1:2	56	Powdery	139-142	Pink
Nickel(II)-indo complex	1:2	44	Powdery	146-149	Light green

The nickel and Cobalt complex had a metal: ligand in 2.1 respectively. The melting point of pure indomethacin was 159.9–163.2°C and cobalt and nickel complexes of indomethacin were 139-142 and 146.5–150.1°C, respectively.

Silver-indomethacin complex: For silver metal complex with indomethacin, Ayad et al [39] reported silver nitrate as a good agent in precipitating indomethacin from its alcoholic solutions. Despite the rarity of the silver indomethacin complex, Ayad et al. reported that when silver nitrate was added to a neutral indomethacin solution, a white precipitate was produced. The quantitative assessment of indomethacin's micro qualities was based on this precipitation. Ayad et al proposed the structure of Silver-indomethacin complex as

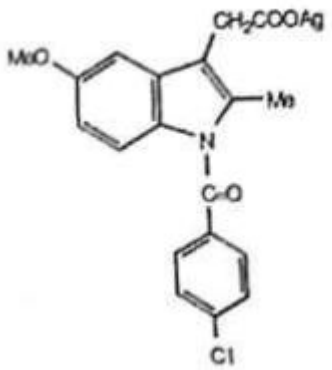

Figure 2. Ayad et al Proposed structure of silver indomethacin complex [39]

3.1 UV AND IR SPECTRA OF COBALT COMPLEXES

Due to the difficulties in producing crystals with sufficient diffraction quality, there are less structurally characterized Co(II)-indomethacin complexes. As a result, it is crucial to determine these complexes' structural details in order to comprehend their roles fully. There are extremely few reported tetrahedral geometry examples in structurally characterized Co(II) complexes of NSAIDs. [40-43].

IR spectra of the complexes of indomethacin exhibited the shift in absorption of the carboxyl group [39]. The shift in the longer wavelength area indicated that the carboxyl group of indomethacin was heavily involved in the complexation with cobalt. Donating electrons to the transitional atoms lowered the energy state and therefore longer wavelength shifting [44].

Williams et al [45] reported that the IR spectra of complexes of indomethacin exhibited a shift in absorption in the carboxyl group. The change in the longer wavelength region indicated a significant contribution from the indomethacin carboxyl group to the complexation with manganese and cobalt. Donating electrons to the transitional atoms lowered the energy state and therefore longer wavelength shifting. (table 4)

Table 4. IR spectra of Co(II) complex with indomethacin

Wavelength, cm^{-1}		Vibrations
I	ICO	
840.01, 925.85	852.55,918.13	C-C stretch
657.74, 753.22	660.63, 756.11	C-CL stretch
925.85	918.13	Carboxyl OH bending
1691.6	1680.03	Indicate carbonyl group
1717.64	-	C=O conjugation of -COOH
3425-2400		
2832.46	2843.12	C-H Stretching
2915.46, 2927.03, 2965.61	2934.74	OH conjugation of -COOH
3021.54	3002.25	Aromatic CH stretching

(I) Indomethacin, (ICO) cobalt-indomethacin complex

Perontosis et al [43] recorded that in the IR spectra of the complexes, the absorption band at 3430 cm^{-1} which is attributed at the ν(O-H) vibration of the free indomethacin disappeared revealing the deprotonation of the ligand. Furthermore, the bands at 1717(*vs*) cm^{-1} and 1228(s) cm^{-1} in the IR spectrum of Hindo that were attributed to the stretching vibrations $\nu(C{=}O)_{carboxylic}$ and $\nu(C\text{-}O)_{carboxylic}$ of the carboxylic moiety (-COOH) of Hindo, respectively, shifted in the IR spectra of the cobalt-indo complex to the regions 1584–1600 cm^{-1} and were attributed to the antisymmetric, $\nu_{asym}(CO_2)$, and the symmetric, $\nu_{sym}(CO_2)$, stretching vibration of the Carboxylato group, respectively.

The differential $\Delta\nu(CO_2)$ [= $\nu_{asym}(C{=}O)$ - $\nu_{sym}(C{=}O)$] is frequently utilized to evaluate the carboxylato ligands coordination mode [41]. The value of $\nu(CO_2)$ was determined in the range 206-244 cm^{-1} for Co-Indo complex, which is greater than that obtained for the sodium salt of

indomethacin ($v(CO_2)$ = 192 cm^{-1}), indicating an asymmetric coordination mode of the indomethacin ligands [46,47].

3.1.1 UV-VIS

Sukul et al [48] reported that Indomethacin and metal complexes of indomethacin (chloroform solutions at room temperature) showed characteristic absorbance pattern. Cobalt complexes of indomethacin demonstrated hypsochromic and hypochromic shift [48].

Table 5. UV-VIS of Co(II)-indomethacin

Compound	λmax, nm	Absorbance, au
I	319.15	0.496
ICU	320.5	0.103

a (I) Indomethacin, (ICO) cobalt-indomethacin complex,

The electronic (UV-vis) spectra of complexes 1-5 in DMSO solution and as nujol mull are identical, demonstrating that the structure is stable in solution[49]. An absorption band at 317-325 nm in the complexes' UV spectra is linked to an intraligand transition mediated by the indomethacin ligand. Two low-intensity bands were found in the visible part of the spectra at 530-560 nm and 485-495 nm, which are typical of high-spin cobalt complexes. [49]

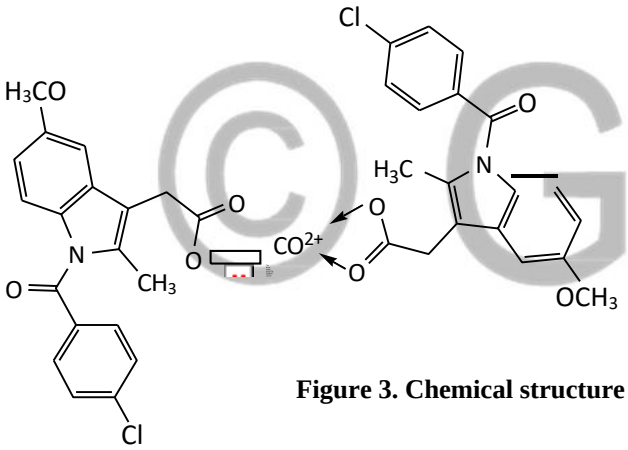

Figure 3. Chemical structure of Cobalt indomethacin [43]

3.2 UV AND IR SPECTRA OF NICKEL INDOMETH COMPLEX

IR spectra: Dupeyrón et al [50] reported that the carboxyl group absorption band in the free indomethacin ligand was observed at 1712 cm^{-1} (vC=O), while the asymmetric aromatic stretching band (C-O) was observed at 1223 cm^{-1}. [45]. These bands shifted to a shorter and higher wavelength in the complexes and were present at 1605 cm^{-1} (ν_{asym}), 1367 cm^{-1} (ν_{sym}), in Ni. This confirmed the carboxyl group of the indomethacin was involved in coordination [50]

Robinson J. W. et al [51] recorded that in the IR spectra of complexes nickel indo complexes with Methanol as oxygen donor $[Ni(indo\text{-}O)_2(MeOH)_4]$, these bands shifted towards the range 1599-1584 cm^{-1} and 1422-1362 cm^{-1} and were attributed to the antisymmetric, $\nu_{asym}(CO2)$, and the symmetric, $\nu_{sym}(CO2)$, stretching vibration of the carboxylato group, respectively, revealing the binding of indomethacin to Ni(II). The variable $\Delta v(CO2)$ is defined as

[= $\nu_{asym}(CO2)$ - $\nu_{sym}(CO2)$]. could be applied to elucidate the carboxylato ligands' coordination mechanism.

The $\Delta\nu(CO2)$ of $[Ni(indo\text{-}O)_2(MeOH)_4]$ is higher than that of the sodium salt of indomethacin ($\Delta\nu(CO2)$ = 192 cm^{-1}), indicating a monodentate binding mode for the indomethacin ligand. It lies in the range of 215-237 cm^{-1} [52]. The binding of the carboxylate ligand in the complex was confirmed by the presence of M-O observed in 430 cm^{-1} in the Nickel complex. [53].

Table 6. FT-IR wave number bands (*n*) of indomethacin and Nickel complex [49]

I	**Nickel-Indo**	**Comment**
840.01, 925.85	836.16, 918.13	C–C stretch
657.74, 753.22	658.7, 756.11	C–Cl stretch
925.85	918.13	Carboxyl OH bending
1,691.6	1,680.03	Carbonyl group
1,717.64	–	C=O conjugation of –COOH
2,831.55	2,843.12	C-H stretching
2,915.46, 2,927.03, 2,965.61	2,934.74	OH conjugation of –COOH
-	3,406.35	Presence of coordinated H_2O

Sukul et al [54] reported that when using FT-IR, broad and strong signals for the -OH group in the range of 3,700–3,000 cm^{-1} suggested the presence of hydrogen bonding, which may have resulted from the incorporation of water molecules as ligands in the crystal structure. However, the –COOH functional group was lacking in the complexes.

The metal complexes showed distinct changes in the carboxyl group's absorption as well as the stretching and bending of carboxyl OH [54]. The shift towards a longer wavelength indicated that indomethacin's carboxyl group was heavily involved in the complexation process with nickel and chromium [54]. Longer wavelength shifting results from lowering the energy state of the transitional atoms by donating electrons. [55]

UV spectra: Perontsis et al [51] recorded that using different buffer solutions (150 mM NaCl and 15 mM trisodium citrate at pH values regulated by HCl solution), the compounds' UV-vis spectra were also recorded in solution within the timeframe used for the biological tests (up to 72 hours) and in the pH range 6-8. No significant changes (shift of the λmax or new peaks) were observed, suggesting the stability of the complex under these conditions [56].

Table 7. Absorbance (in chloroform) found in UV–Visible spectrum of indomethacin and its complexes [49]

Compound	**λ_{max} (nm)**	**Absorbance**

Compound	λ_{max} (nm)	Absorbance
I	318	0.747
Nickel(II)-indo	319	0.352

Bathochromic and hypochromic shift took place in both the cases of nickel complex, when UV–Vis spectra were analyzed [57].

4.CONCLUSION

Cobalt and Nickel complexes have been successfully synthesized and characterized using FT-IR spectroscopy and UV spectroscopy. The FT-IR spectra of both complexes indicate that the indomethacin ligand coordinates in a monodentate mode through the carbonyl oxygen atom, as evidenced by the [($\nu(COO^-) = \nu_{asy}(CO2) - \nu_{sy}(CO2)$] value. In addition to spectroscopic analysis, the metal complexes were characterized using various physiochemical parameters such as solubility, color, and melting point. These parameters provide valuable information about the properties of the complexes. Further investigations should be carried out to fully analyze the spectroscopic properties of the indomethacin ligand with Co(II) and Ni(II) metals, utilizing nitrogen and oxygen donor agents. These additional analyses will provide a more comprehensive understanding of the complexes' structure and bonding. However, it is important to note that this research encountered a limitation in the form of limited available data on silver indomethacin complexes. Therefore, future studies should focus on characterizing silver indomethacin complexes to expand our knowledge and understanding in this area. The spectroscopic analysis carried out in this study can serve as a basis for further research on silver indomethacin complexes, providing valuable insights into their properties and potential applications. By conducting thorough spectroscopic and physiochemical characterizations, as well as addressing the limitations in the current research, we can advance our understanding of cobalt and nickel complexes with indomethacin ligands. Furthermore, investigating silver indomethacin complexes will contribute to the broader field of coordination chemistry and facilitate the development of novel metal-ligand systems.

Acknowledgements

The authors are grateful to the University Calabar's Department of Pure and Applied Chemistry for providing materials and analytical equipment.

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