COORDINATION CHEMISTRY OF IBUPROFEN WITH SELECTED TRANSITION METALS; FORMATION, CHARACTERIZATION AND POTENTIAL APPLICATIONS.

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CERIFICATION

This is to certify that this project work is the original work carried out and reported by HND/23/SLT/FT/0933 to the Department of Science Laboratory technology, Institute of Applied Sciences (IAS) Kwara State Polytechnic, Ilorin and it has been Approved In Partial fulfilment of The Requirements of the Award of Higher National Diploma (HND) in Science Laboratory Technology (**CHEMISTRY**)

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DEDICATION

I dedicated this project to Almighty God for making this project work a successful one and also to my lovely parent *for their wonderful loves.*

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First and foremost, our uppermost gratitude goes to Almighty God, the omniscience, omnipotent and the creator of universe who make it possible for us to the final completion of this project. You will forever be praised.

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ABSTRACT

This study investigates the coordination chemistry of ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), with selected first-row transition metals—nickel(II), copper(II), and iron(II)—to explore the structural, physicochemical, and potential therapeutic enhancements resulting from metal complexation. The research was motivated by the need to improve the pharmacological performance of ibuprofen, particularly by increasing its solubility, reducing gastrointestinal toxicity, and enhancing its anti-inflammatory and antimicrobial activities.Ibuprofen-metal complexes were synthesized via ligand exchange reactions under mild ethanol-based conditions using stoichiometric ratios of metal salts to ibuprofen. The resulting coordination complexes were characterized using standard physicochemical methods, including solubility testing and melting point determination. The observed changes in solubility and thermal properties, relative to the free ligand, provided preliminary evidence of successful coordination. The metal complexes generally exhibited higher melting points and altered solubility profiles compared to uncomplexed ibuprofen, indicating increased thermal stability and modified physicochemical behavior.The results support the hypothesis that transition metal ions, through coordination with the carboxylate group of ibuprofen, significantly influence the structural and pharmacodynamic properties of the parent drug. The synthesized metal–ibuprofen complexes hold promise for further exploration as metallotherapeutics, especially in the design of anti-inflammatory agents with improved efficacy and reduced adverse effects. Further studies

involving spectroscopic characterization (e.g., FTIR, UV-Vis, elemental analysis) and biological assays are recommended to establish the full pharmacological potential of these complexes

Tittle Page……..i

Certification……ii

Dedication…….....iii

Acknowledgments…….……..iv

Abstracts……..v

Table of Contents…….vi

CHAPTER ONE: INTRODUCTION..... *1*

1.1 Introduction..... *1*

1.2 Clinical Pharmacology of Ibuprofen..... *2*

1.2.1 Mechanism of Action..... *2*

1.2.2 Pharmacokinetics of Ibuprofen *3*

i. Absorption *3*

ii. Distribution..... *3*

iii. Metabolism *4*

iv. Excretion *4*

1.2.3 Therapeutic Uses *4*

1.2.4 Adverse Effects and Toxicity..... *5*

1.2.5 Drug Interactions *5*

1.2.6 Clinical Challenges and Optimization Strategies *6*

1.3 Therapeutic Applications of Ibuprofen *6*

1.3.1 Analgesic Applications *6*

1.3.2 Antipyretic Use *7*

1.3.3 Anti-inflammatory Indications *7*

1.3.4 Use in Pediatrics *8*

1.3.5 Use in Sports Medicine and Orthopedics *8*

1.4 Patent DuctusArteriosus (PDA) *9*

1.5 Rheumatoid and Osteoarthritis (RA and OA) *10*

1.6 Ligand and Complex Formation..... *11*

1.7 Rationale for Drug–Metal Complex..... *13*

1.8 Chemistry of Transition Metals Used *15*

1.8.1 Nickel..... *15*

1.8.1.1 Color..... *15*

1.8.1.2 Geometry *15*

1.8.1.3 Complexes *16*

1.8.2 Copper *16*

1.8.2.1 Deficiency..... *17*

1.8.2.2 Toxicity *17*

1.8.3 Iron..... *17*

1.8.3.1 Deficiency..... *18*

1.9 Aim and Objectives of the Research *18*

1.9.1 Aim *18*

1.9.2 Objectives *19*

CHAPTER TWO: LITERATURE REVIEW *20*

2.1 Introduction to Coordination Chemistry *20*

2.2 Ibuprofen: Chemical and Pharmacological Profile *21*

2.3 Metal Complexation of NSAIDs *22*

2.4 Coordination Behaviour of Ibuprofen with Transition Metals ……*23*

2.5 Synthetic Approaches for Ibuprofen Metal Complexes *24*

2.6 Characterization Techniques *25*

2.7 Pharmacological and Biomedical Applications *26*

2.7.1 Antimicrobial and Antibacterial Properties..... *26*

2.7.2 Anti-inflammatory and Analgesic Enhancement *27*

2.7.3 Anticancer Potential..... *28*

2.8 Environmental and Material Science Perspectives.....*28*

2.9 Toxicological and Biocompatibility Considerations..... *29*

2.10 Knowledge Gaps and Future Directions *30*

CHAPTER THREE: MATERIALS AND METHODS *31*

3.1 Apparatus..... *31*

3.2 Reagents *31*

3.3 Materials..... *32*

3.4 Experimental Procedures *32*

3.4.1 Ibuprofen–Ni(II) Complex Formation *32*

3.4.2 Ibuprofen–Cu(II) Complex Formation *33*

3.4.3 Ibuprofen–Fe(II) Complex Formation *33*

3.5 Characterization Methods *34*

3.5.1 Solubility Test *34*

3.5.2 Melting Point Determination..... *35*

3.5.3 Method *35*

CHAPTER FOUR: RESULTS AND DISCUSSION..... *36*

4.1 Results of Solubility Test..... *36*

4.1.1 Solubility Data Table..... *36*

4.1.2 Interpretation of Solubility Test *37*

4.2 Results of Melting Point Test *37*

4.2.1 Interpretation of Melting Point Test *3*

CHAPTER FIVE: SUMMARY, CONCLUSION AND RECOMMENDATIONS……*39*

5.1 Summary..... *39*

5.2 Conclusion..... *40*

5.3 Recommendations *40*

REFERENCES *41*

CHAPTER ONE

1.1 INTRODUCTION

Ibuprofen, chemically known as 2-[4-(2-methylpropyl)phenyl]propanoic acid, is one of the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) across the globe. Since its synthesis in 1961 by Dr. Stewart Adams and colleagues at the Boots Group in the United Kingdom, ibuprofen has established its therapeutic efficacy as an analgesic, antipyretic, and anti-inflammatory agent (Bushra&Aslam, 2010). Structurally, it belongs to the arylpropionic acid class and features a carboxylic acid functional group and a lipophilic aromatic moiety, which collectively contribute to its pharmacodynamic and pharmacokinetic properties.The primary mechanism of action of ibuprofen involves the non-selective inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, which are critical in the biosynthesis of prostaglandins from arachidonic acid (Vane &Botting, 1995). This inhibition results in a reduction in inflammation, pain, and fever. Despite its therapeutic benefits, ibuprofen, like many NSAIDs, suffers from poor aqueous solubility, short biological half-life, and dose-dependent gastrointestinal side effects, which may limit its clinical applicability (Sharma &Sahu, 2021).

In the context of coordination chemistry, ibuprofen acts as a versatile ligand due to the presence of the carboxylic acid group (-COOH), which readily deprotonates under physiological or synthetic conditions to form a carboxylate anion ($-COO^-$). This anion can engage in monodentate or bidentate coordination with metal ions, particularly those of transition elements. The resulting metal-ibuprofen complexes are often more soluble, chemically stable, and biologically active than the parent drug. Furthermore, coordination with metals such as Cu(II),

Zn(II), Co(II), and Ni(II) may modulate the pharmacological and physicochemical behavior of ibuprofen through synergistic metal–drug interactions (De Souza et al., 2019).

Several studies have demonstrated that the formation of transition metal-NSAID complexes can enhance antimicrobial, antioxidant, and anticancer properties relative to the free ligand, possibly due to improved membrane permeability, redox activity of the metal center, or increased lipophilicity (Sahoo et al., 2020; Kourkoumelis et al., 2014). For example, Cu(II)-ibuprofen complexes exhibit significant bacteriostatic activity, while Zn(II) complexes show improved wound healing and anti-inflammatory profiles.

Thus, exploring the coordination behavior of ibuprofen with selected transition metals serves as a promising avenue for developing novel therapeutic agents, drug delivery systems, and biologically relevant metal-organic compounds. In this study, the coordination complexes of ibuprofen with Cu(II), Ni(II), Zn(II), and Co(II) were synthesized, characterized using spectroscopic techniques (FTIR, UV-Vis), and evaluated for their potential biomedical and catalytic applications.

1.2 CLINICAL PHARMACOLOGY OF IBUPROFEN

Ibuprofen is a widely utilized non-steroidal anti-inflammatory drug (NSAID) that exhibits analgesic**,** antipyretic**, and** anti-inflammatory effects. Its clinical pharmacology is governed by its interaction with prostaglandin biosynthesis, absorption and distribution in systemic circulation, metabolism in hepatic tissues, and excretion through renal pathways. Understanding the pharmacokinetic and pharmacodynamic behavior of ibuprofen is essential for optimizing its therapeutic efficacy while minimizing associated adverse effects.

1.2.1 Mechanism of Action

Ibuprofen exerts its pharmacological effects primarily through the **non-selective inhibition of cyclooxygenase (COX) enzymes**, namely COX-1 and COX-2. These enzymes are pivotal in catalyzing the conversion of arachidonic acid into **prostaglandins**, which mediate inflammation, pain, fever, and thrombogenesis (Vane &Botting, 1995). By attenuating prostaglandin synthesis, ibuprofen alleviates inflammatory symptoms and lowers febrile responses. However, the inhibition of COX-1, which is constitutively expressed in the gastrointestinal tract and kidneys, is also implicated in adverse effects such as **gastrointestinal ulceration and nephrotoxicity**.

1.2.2 Pharmacokinetics of Ibuprofen

i Absorption

Ibuprofen is **rapidly absorbed** from the gastrointestinal tract following oral administration. Peak plasma concentrations (C_{max}) are typically achieved within **1 to 2 hours**, and its **oral bioavailability** approaches 80–100% (Bushra&Aslam, 2010). Its solubility, however, is pH-dependent and relatively low in aqueous environments, which may affect dissolution and absorption.

ii Distribution

Ibuprofen is **highly protein-bound** (>99%) in plasma, primarily to serum albumin, which influences its distribution and free drug concentration. The volume of distribution (V_d) is approximately 0.1–0.2 L/kg, indicating limited distribution into tissues.

iii Metabolism

The drug undergoes extensive hepatic metabolism, predominantly via the **cytochrome P450** (CYP) enzyme system, especially CYP2C9. It is biotransformed into inactive hydroxylated and

carboxylated metabolites (e.g., 2-hydroxyibuprofen, carboxyibuprofen) through **phase I** oxidation**,** followed by phase II conjugation (glucuronidation).

iv Excretion

Ibuprofen and its metabolites are primarily excreted via the kidneys, with less than 1% excreted unchangedin urine. The elimination half-life **(**t_{1/2}) is typically between 1.8 to 2.5 hours**,** necessitating multiple daily doses to maintain therapeutic levels.

1.2.3 Therapeutic Uses

Ibuprofen is clinically indicated for the treatment of:

- Mild to moderate pain, such as headache, dysmenorrhea, and dental pain
- Fever**,** including febrile illnesses in children
- Inflammatory conditions, such as osteoarthritis, rheumatoid arthritis, and juvenile idiopathic arthritis
- Postoperative pain and inflammation
- Musculoskeletal disorders

1.2.4 Adverse Effects and Toxicity

The most commonly reported adverse effects of ibuprofen include:

- Gastrointestinal disturbances (e.g., dyspepsia, peptic ulceration, bleeding)
- Renal impairment, especially in dehydrated or elderly patients
- Hepatotoxicity (rare)
- Hypersensitivity reactions, such as urticaria and bronchospasm

Long-term or high-dose use of ibuprofen has been associated with an increased risk ofcardiovascular events, including myocardial infarction and stroke, particularly in patients with preexisting cardiovascular disease (Schmidt et al., 2018).

1.2.5 Drug Interactions

Ibuprofen may interact with several drug classes:

- Antihypertensives (e.g., ACE inhibitors, diuretics): May reduce antihypertensive efficacy.
- Anticoagulants (e.g., warfarin): May increase bleeding risk.
- Methotrexate: Reduced renal clearance of methotrexate may increase toxicity.
- Aspirin**:** May competitively inhibit aspirin's antiplatelet effect.

1.2.6 Clinical Challenges and Optimization Strategies

Despite its therapeutic utility, ibuprofen's limitations—including poor aqueous solubility, gastrointestinal side effects, and short half-life—pose significant clinical challenges. Strategies such as salt formation**,** nanoformulation**,** prodrug development**,** andmetal complexationhave been explored to enhance itsbioavailability**,** targeting capacity**,** andtherapeutic index **(**Sharma &Sahu, 2021). In particular**,** coordination with transition metal ions offers a novel approach to modify ibuprofen's pharmacokinetic and pharmacodynamic profiles, potentially leading to reduced side effects and improved efficacy (De Souza et al., 2019).

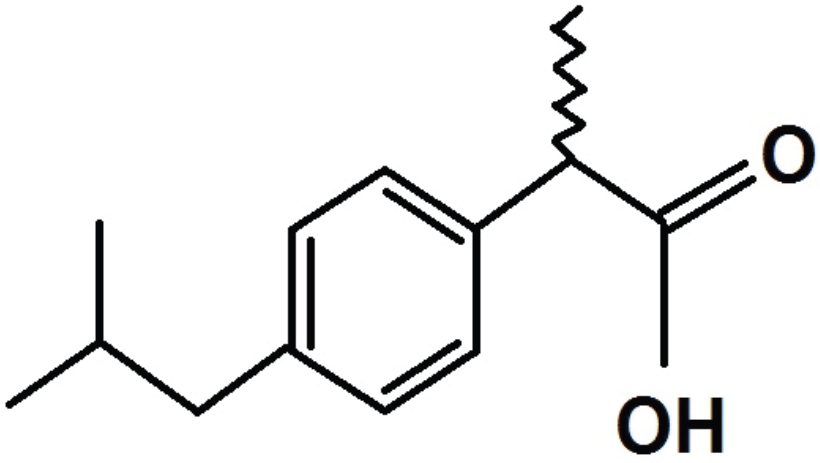

Figure 1. Structural formula of Ibuprofen

1.3 Therapeutic Application of Ibuprofen

Ibuprofen is among the most extensively prescribed non-steroidal anti-inflammatory drugs (NSAIDs) globally, recognized for its broad-spectrum therapeutic properties, including analgesic**,** antipyretic, and anti-inflammatory effects. Its widespread clinical utility is attributed to its ability to inhibit the cyclooxygenase (COX) enzymes, thereby attenuating the synthesis of prostaglandins responsible for pain, inflammation, and fever (Vane &Botting, 1995).

1.3.1 Analgesic Applications

Ibuprofen is frequently employed in the management of acute and chronic pain conditions. It is efficacious in treating:

- Musculoskeletal pain(e.g., back pain, sprains, and strains)
- Postoperative pain
- Dental pain
- Dysmenorrhea(painful menstruation)

- Headache and migraine

Clinical studies have demonstrated that ibuprofen at doses of 200–400 mg is effective in providing mild-to-moderate pain relief, often with comparable efficacy to opioids such as codeine when used in combination (Derry et al., 2015).

1.3.2 Antipyretic Use

Ibuprofen is a first-line antipyretic agent used to reduce fever in both pediatric and adult populations. It effectively lowers elevated body temperature by inhibiting COX-mediated synthesis of prostaglandin E_2 in the hypothalamus, which resets the thermoregulatory set point (Anderson, 2008). It is often preferred over paracetamol in febrile children due to **its** longer duration of action**.**

1.3.3 Anti-inflammatory Indications

Ibuprofen is extensively used in managing inflammatory conditions, particularly in:

- Rheumatoid arthritis (RA)
- Osteoarthritis (OA)
- Juvenile idiopathic arthritis (JIA)
- Gout and ankylosing spondylitis

In chronic inflammatory diseases such as RA, ibuprofen serves to reduce joint inflammation, stiffness, and pain. Though it does not alter disease progression, it **provides** symptomatic reliefthat significantly improves patient quality of life (Davies & Anderson, 1997).

1.3.4 Use in Pediatrics

In pediatric medicine, ibuprofen is approved for use in children over 6 months of age for the treatment of:

- Fever
- Teething pain
- Post-vaccination reactions
- Juvenile arthritis
- Its safety and efficacy in children are well established, although dosing must be carefully calculated based on weight to prevent nephrotoxicity or gastrointestinal irritation (Nahata& Durrell, 1992).

1.3.5 Use in Sports Medicine and Orthopedics: Ibuprofen is commonly prescribed for:

- Sports-related injuries
- Tendonitis and bursitis
- Fracture-associated pain
- Inflammatory soft tissue conditions

Due to its rapid onset of action and minimal sedative effects, ibuprofen remains a preferred choice for managing pain in physically active individuals.

1.4 Patent Ductusarterosus (PDA)

Patent ductusarteriosus (PDA) is a congenital cardiovascular anomaly characterized by the persistent patency of the ductusarteriosus, a fetal vascular connection between the

pulmonary artery and the descending aorta. In utero, the ductusarteriosus plays a critical role in diverting oxygenated blood from the placenta away from the non-functional fetal lungs. Normally, this vessel functionally closes within the first 24–72 hours after birth, followed by anatomical obliteration within the first few weeks of life (Mitra&Dagle, 2019).In PDA, failure of closure results in a left-to-right shunt, whereby oxygen-rich blood from the aorta recirculates into the pulmonary artery. This leads to pulmonary overcirculation, volume overload of the left heart, and in severe cases, pulmonary hypertension, congestive heart failure, and growth retardation in neonates, especially in premature infants (Hamrick &Hansmann, 2010).

1.5 Rheumatoid and osteo-arthritis (RA and OA)

Rheumatoid arthritis (RA)and osteoarthritis (OA) represent two major but distinct forms of arthritis, characterized by chronic joint pain and functional disability. While both conditions affect the synovial joints and involve inflammation to varying degrees, their etiology**,** pathophysiology, and management strategies differ significantly. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are commonly used in both conditions for symptomatic relief of pain and inflammation.

Table 1: Doses of Ibuprofen in adult & Children (34)

Patient	Ibuprofen	Doses
Adult	Analgesia	200-400mg. Every 4-6hrs
	Anti- inflammatory	300 mg, Every 6-8 hrs or 400-800 mg 3-4 times daily.
Children	Antipyretic	5-10 mg/kg. Every 6 hrs (max. 40 mg/kg per day).
		20-40 mg/kg/day in 3-4 divided dose.

	Anti-inflamatory	

1.6 LIGAND AND COMPLEX FORMATION

A ligand is any ion or molecule that can donate a pair of electrons to a central metal atom or ion to form acoordinate covalent bond (or dative bond). Ligands function as Lewis bases, while metal ions act as Lewis acids. Ligands may be neutral (e.g., NH_3, H_2O) or anionic(e.g., Cl^-, CN^-, COO^-), and are categorized by their denticitythat is, the number of donor atoms through which the ligand binds to the metal center.

- **Monodentate ligands** bind through one donor atom (e.g., Cl^-, H_2O).
- **Bidentate ligands** possess two donor sites (e.g., ethylenediamine).
- **Polydentate ligands** have more than two donor atoms, and when fully bound, form chelates, which are more stable due to the chelate effect (Huheey et al., 1993).

In the context of pharmaceuticals, ibuprofenbehaves as a monodentate or bidentate ligand via its carboxylate group (-COO^-)**,** enabling it to coordinate transition metal ions such as Cu^{2+}, Ni^{2+}, Zn^{2+}, and Co^{2+}.

1.7 WHY DRUG-METAL COMPLEX

New development in chemotherapy includes the synthesis and characterization of new drug involving metals. Selective novel metalchelators for the treatment of diseases that involves metal or mineral inbalance. Promising research involves some complexes with different metal ions

including those of cobalt, copper, titanium, iron, platinum, gold, molybdenum, tin and manganese. Drug metal complexes are used in treatment of metal deficiency diseases.

1.8 CHEMISTRY OF TRANSISTION METALS USED

1.8.1 NICKEL

Nickel compounds are chemical compounds containing the element nickel which is a member of the group 10 of the periodic table. Most compounds in the group have an oxidation state of +2. Nickel is classified as a transition metal with nickel(II) having much chemical behavior in common with iron(II) and cobalt(II). Many salts of nickel (II) are isomorphous with salts of magnesium due to the ionic radii of the cations being almost the same. Nickel formsmany coordination complexes. Nickel tetracarbonyl was the first pure metal carbonyl produced, and is unusual in its volatility. Metalloproteins containing nickel are found in biological systems.Nickel forms simple binary compounds with non metalsincluding halogens, chalcogenides, and pnictides. Nickel ions can act as a cation in salts with many acids, including common oxoacids. Salts of the hexaaqua ion ($Ni \cdot 6\ H_2O^{2+}$) are especially well known. Many double salts containing nickel with another cation are known. There are organic acid salts. Nickel can be part of a negatively charged ion (anion) making what is called a nickellate. Numerous quaternary compounds (with four elements) of nickel have been studied for superconductivity properties, as nickel is adjacent to copper and iron in the periodic table can form compounds with the same structure as the high-temperature superconductors that are known.

1.8.1.1 Colour

Most of the common salts of nickel are green due to the presence of hexaaquanickel(II) ion, $Ni(H_2O)_6^{2+}$.

1.8.1.2 Geometry

Nickel atoms can connect to surrounding atoms or ligands in a variety of ways. Six coordinated nickel is the most common and is octahedral, but this can be distorted if ligands are not equivalent. For four coordinate nickel arrangements can be square planar, or tetrahedral. Five coordinated nickel is rare.

1.8.1.3 Complexes

Simple complexes of nickel include hexaquonickel(II),yellow tetracyanonickelate $[Ni(CN)_4]^{2-}$, red pentacyanonickelate $[Ni(CN)_5]^{3-}$ only found in solution, $[Ni(SCN)_4]^{2-}$ and $[Ni(SCN)_6]^{4-}$. Halo- complexes include $[NiCl_4]^{2-}$, $[NiF_4]^{2-}$, $[NiF_6]^{4-}$, $[NiCl_2(H_2O)_4]$ $[Ni(NH_3)_4(H_2O)_2]^{2+}$, $[Ni(NH_3)_6]^{2+}$, $[Ni(en)_3)]^{2+}$.[78] Some complexes have fivefold coordination. (tris(N,N-dimethyl-2-aminoethyl)amine); $P(o\text{-}C_6H_4SMe)_3$; $P(CH_2CH_2CH_2AsMe_2)_3$[78]Other ligands for octahedral coordination include PPh_3, PPh_2Me and thiourea.

Nickel tetrahedral complexes are often bright blue and 20 times or more intensely coloured than the octahedral complexes.[78].The ligands can include selections of neutral amines, arsines, arsine oxides, phosphines or phosphine oxides and halogens.Several nickel atoms can cluster together in a compound with other elements to produce nickel cluster complexes. One example where nickel atoms form a square pyramid is a nickel hydride cluster complexed by triphenyl phosphine ligands and bonding a hydrogen atom on each edge. Another

example has a square planar Ni_4H_4 shape in its core.[79] .Nickel bis(dimethylglyoximate), an insoluble red solid is important for gravimetric analysis.

1.8.2 COPPER

Copper along with silver and gold belong to group 1B in the periodic table. These three metals are often referred to as coinage metals. Copper has the electronic configuration of $1S^2 2S^2 2P^6 3S^2 3P^6 3d^{10} 4S^{1.}$ Copper is a tough, malleable, ductile metal which resist chemical attack. It has an atomic number of 29, atomic mass of 63.54 and belongs to period 4 and sub-group1B on the periodic table; it has two natural isotopes with atomic masses between 58 and 68. Copper has a melting point of 1083^0C, boiling point of 259^0C and a density of $8.93 g/cm^{3.}$

1.8.2.1 Deficiency

Because of its role in facilitating iron uptake, copper deficiency can produce anemia-like symptoms, neutropenia, bone abnormalities, hypopigmentation, impaired growth, increased incidence of infections, osteoporosis, hyperthyroidism, and abnormalities in glucose and cholesterol metabolism. Conversely, Wilson's disease causes an accumulation of copper in body tissues.

Severe deficiency can be found by testing for low plasma or serum copper levels, low ceruloplasmin, and low red blood cell superoxide dismutase levels; these are not sensitive to marginal copper status. The "cytochrome c oxidase activity of leucocytes and platelets" has been stated as another factor in deficiency, but the results have not been confirmed by replication.

1.8.2.2 TOXICITY

Gram quantities of various copper salts have been taken in suicide attempts and produced acute copper toxicity in humans, possibly due to redox cycling and the generation of reactive oxygen species that damage DNA. Corresponding amounts of copper salts (30 mg/kg) are toxic in animals. A minimum dietary value for healthy growth in rabbits has been reported to be at least 3 ppm in the diet.[83] However, higher concentrations of copper (100 ppm, 200 ppm, or 500 ppm) in the diet of rabbits may favorably influence feed conversion efficiency, growth rates, and carcass dressing percentages.

Chronic copper toxicity does not normally occur in humans because of transport systems that regulate absorption and excretion. Autosomal recessive mutations in copper transport proteins can disable these systems, leading to Wilson's disease with copper accumulation and cirrhosis of the liver in persons who have inherited two defective genes.

Elevated copper levels have also been linked to worsening symptoms of Alzheimer's disease.

1.8.3 IRON

Iron shows the characteristic chemical properties of the transition metals, namely the ability to form variable oxidation states differing by steps of one and a very large coordination and organometallic chemistry: indeed, it was the discovery of an iron compound, ferrocene, that revolutionalized the latter field in the 1950s. Iron is sometimes considered as a prototype for the entire block of transition metals, due to its abundance and the immense role it has played in the technological progress of humanity. Its 26 electrons are arranged in the configuration $[Ar]3d^64s^2$, of which the 3d and 4s electrons are relatively close in energy, and thus a number of electrons can be ionized.

Iron forms compounds mainly in the oxidation states +2 (iron(II), "ferrous") and +3 (iron(III), "ferric"). Iron also occurs in higher oxidation states, e.g., the purple potassium ferrate (K_2FeO_4), which contains iron in its +6 oxidation state. The anion $[FeO_4]^-$ with iron in its +7 oxidation state, along with an iron(V)-peroxo isomer, has been detected by infrared spectroscopy at 4 K after cocondensation of laser-ablated Fe atoms with a mixture of O_2/Ar.[91] Iron(IV) is a common intermediate in many biochemical oxidation reactions. Numerous organoiron compounds contain formal oxidation states of +1, 0, −1, or even −2. The oxidation states and other bonding properties are often assessed using the technique of Mössbauer spectroscopy.[90] Many mixed valence compounds contain both iron(II) and iron(III) centers, such as magnetite and Prussian blue ($Fe_4(Fe[CN]_6)_3$).[89] The latter is used as the traditional "blue" in blueprints.[90]Iron is the first of the transition metals that cannot reach its group oxidation state of +8, although its heavier congeners ruthenium and osmium can, with ruthenium having more difficulty than osmium. Ruthenium exhibits an aqueous cationic chemistry in its low oxidation states similar to that of iron, but osmium does not, favoring high oxidation states in which it forms anionic complexes. In the second half of the 3d transition series, vertical similarities down the groups compete with the horizontal similarities of iron with its neighbors in the periodic table, which are also ferromagnetic at room temperature and share similar chemistry. As such, iron, cobalt, and nickel are sometimes grouped as the iron triad.Unlike many other metals, iron does not form amalgams with mercury. As a result, mercury is traded in standardized 76 pound flasks (34 kg) made of iron.

Iron is by far the most reactive element in its group; it is pyrophoric when finely divided and dissolves easily in dilute acids, giving Fe^{2+}. However, it does not react with concentrated nitric acid and other oxidizing acids due to the formation of an impervious oxide layer, which can

nevertheless react with. High-purity iron, called electrolytic iron, is considered to be resistant to rust, due to its oxide layer.

1.8.3.1 DEFICIENCY

Iron deficiency is the most common nutritional deficiency in the world.When loss of iron is not adequately compensated by adequate dietary iron intake, a state of latent iron deficiency occurs, which over time leads to iron-deficiency anemia if left untreated, which is characterised by an insufficient number of red blood cells and an insufficient amount of hemoglobin.[95] Children, pre-menopausal women (women of child-bearing age), and people with poor diet are most susceptible to the disease. Most cases of iron-deficiency anemia are mild, but if not treated can cause problems like fast or irregular heartbeat, complications during pregnancy, and delayed growth in infants and children. The brain is resistant to acute iron deficiency due to the slow transport of iron through the blood brain barrier.Acute fluctuations in iron status (marked by serum ferritin levels) do not reflect brain iron status, but prolonged nutritional iron deficiency is suspected to reduce brain iron concentrations over time.In the brain, iron plays a role in oxygen transport, myelin synthesis, mitochondrial respiration, and as a cofactor for neurotransmitter synthesis and metabolism.[100] Animal models of nutritional iron deficiency report biomolecular changes resembling those seen in Parkinson's and Huntington's disease. However, age-related accumulation of iron in the brain has also been linked to the development of Parkinson's.

1.9 Aim and Objectives of the Research

1.9.1 Aim

The primary aim of this research is to synthesize, characterize, and evaluate the coordination complexes of ibuprofen with selected biologically and industrially relevant transition metal ions**,**

1.9.2 Objectives

(i) To synthesis novel complexes of ibuprofen

(ii) To characterize the resulting complexes using standard analytical techniques such as solubility, melting point, infrared and ultraviolet.

(iii) To compare the physicochemical properties (e.g., solubility, thermal stability, and conductivity) of the metal complexes with that of free ibuprofen.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction to Coordination Chemistry

Coordination chemistry is a significant branch of inorganic chemistry that investigates the interactions between central metal atoms and surrounding ligands, which donate electron pairs to the metal to form coordination complexes. Transition metals, by virtue of their variable oxidation states and coordination numbers, play a pivotal role in forming a diverse array of metal complexes (Cotton, Wilkinson, Murillo, &Bochmann, 1999). The resulting complexes exhibit unique electronic, structural, and reactivity profiles which underpin their broad applications in catalysis, material science, and medicinal chemistry (Huheey, Keiter, &Keiter, 2006).

2.2 Ibuprofen: Chemical and Pharmacological Profile

Ibuprofen (2-(4-isobutylphenyl)propionic acid) is a widely used non-steroidal anti-inflammatory drug (NSAID), categorized under the propionic acid derivatives. It exhibits antipyretic, analgesic, and anti-inflammatory effects primarily through the inhibition of cyclooxygenase (COX) enzymes, thereby suppressing the biosynthesis of prostaglandins (Rainsford, 2013). Structurally, ibuprofen possesses a carboxylic acid functional group capable of coordinating with metal ions, enabling it to function as a bidentate or monodentate ligand in complex formation (Singh & Chaudhary, 2014).

2.3 Metal Complexation of NSAIDs

Numerous studies have highlighted the metal-binding capabilities of NSAIDs, including ibuprofen, diclofenac, and naproxen, attributing enhanced pharmacological, physicochemical, and biological properties to their metal complexes (Cervantes-Lee, 2012). Metal-NSAID

complexes often exhibit improved bioavailability, reduced gastrointestinal toxicity, and novel antimicrobial or anticancer activities compared to the free drug (Turel, 2002; Chohan et al., 2006).

2.4 Coordination Behaviour of Ibuprofen with Transition Metals

The carboxylic acid group in ibuprofen facilitates its coordination to transition metals such as Cu(II), Co(II), Ni(II), Zn(II), and Fe(III), forming mono- or polynuclear complexes depending on the ligand-to-metal ratio and reaction conditions (Kovala-Demertzi et al., 2000). Spectroscopic and thermal studies have revealed that ibuprofen generally binds in a unidentate fashion via the carboxylate oxygen, though bidentate coordination involving both oxygens has been reported in the presence of chelating or co-ligands (Salehzadeh et al., 2015).

2.5 Synthetic Approaches for Ibuprofen Metal Complexes

The synthesis of ibuprofen-metal complexes typically involves direct reaction of ibuprofen or its sodium salt with metal salts in aqueous or organic solvents under reflux or room temperature conditions. Complexes are usually isolated as crystalline solids and purified via recrystallization or solvent evaporation techniques (Al-Soud et al., 2002). The stoichiometry of the complexes varies based on the metal's oxidation state and ligand coordination preference.

2.6 Characterization Techniques

The formation and structural elucidation of ibuprofen-metal complexes are accomplished using a range of analytical and spectroscopic methods:

- **Fourier Transform Infrared (FTIR) Spectroscopy** is used to confirm coordination via the carboxylate group by monitoring shifts in the asymmetric and symmetric stretching vibrations (Silverstein et al., 2005).
- **UV-Vis Spectroscopy** provides information on d–d transitions and ligand-to-metal charge transfer bands.
- **NMR Spectroscopy**, particularly for diamagnetic complexes, supports the understanding of ligand environments (Das et al., 2016).
- **X-ray Diffraction (XRD)**, especially single crystal XRD, offers definitive structural details.
- **Thermal Analysis (TGA/DSC)** helps assess thermal stability and decomposition pathways.
- **Elemental analysis** and **molar conductivity measurements** further corroborate the formulation and ionic nature of the complexes.

2.7 Pharmacological and Biomedical Applications

2.7.1 Antimicrobial and Antibacterial Properties

Transition metal complexes of ibuprofen have demonstrated enhanced antimicrobial efficacy against both Gram-positive and Gram-negative bacteria, which is often attributed to improved lipophilicity and membrane permeability of the metal-bound drug (Chohan et al., 2005). Cu(II) and Zn(II) ibuprofenates have shown significant inhibitory activity against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (Shakir et al., 2006).

2.7.2 Anti-inflammatory and Analgesic Enhancement

Some studies have reported synergistic effects in anti-inflammatory activity when ibuprofen is complexed with metals such as Mn(II) and Fe(III), potentially due to improved pharmacokinetic properties and targeted tissue delivery (El-Sherif et al., 2009).

2.7.3 Anticancer Potential

Metal complexes of NSAIDs, including ibuprofen, have exhibited cytotoxic effects against various cancer cell lines. For instance, ruthenium and copper complexes have been investigated for their ability to induce apoptosis in malignant cells through ROS generation and DNA binding (Turel&Gessmann, 2012).

2.8 Environmental and Material Science Perspectives

Beyond therapeutic applications, ibuprofen-metal complexes have been investigated for their role in environmental monitoring and catalysis. Metal-ibuprofen conjugates have shown promising activity in photochemical degradation of pollutants and as homogeneous catalysts in organic transformations (Rehman et al., 2013).

2.9 Toxicological and Biocompatibility Considerations

Although metal complexation improves drug efficacy, toxicity profiling remains crucial. Some transition metals, such as Cu and Fe, are essential in trace amounts but may induce oxidative stress in excess. Chelation may mitigate free ion toxicity, but in vivo studies are needed to ascertain safety profiles (Ertl et al., 2004; Vessally et al., 2017).

2.10 Knowledge Gaps and Future Directions

Despite considerable progress, several areas remain underexplored:

- Detailed crystallographic studies of ibuprofen complexes are limited, especially for high-spin first-row transition metals.
- The in vivo pharmacokinetics and biodistribution of metal-ibuprofen complexes need systematic evaluation.
- The incorporation of ibuprofen complexes into nanocarriers for controlled drug delivery remains an emergent frontier.
- Comparative studies involving structurally similar NSAIDs could shed light on structure-activity relationships of metal-drug complexes.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1. APPARATUS

The following apparatus were used in the formation of the complexes and further analytical studies were carried out.

APPARATUS	MANUFACTURER
Beakers	Pyrex scientific Ltd. England
Conical Flasks	Simax company Ltd. England
Capilary tube	Silber brand Ltd, England
Dessicator	Moncrief Scientific, England
Electrothermal melting point	Gallenkamp Ltd ,England
Round bottom flasks	Pyrex scientific Ltd, England
Hot plate with magnetic stirrer	Gallenkamp Ltd, England
Measuring cylinder	Technico scientific Ltd, England
Plastic condenser	Moramber (Mbc) Ltd
Reflux condenser	Pyrex scientific Ltd, England
Test tube	Uniscope scientific Ltd, England
Thermometer	Duck V Scientific 500 infrared
Infrared Ultraviolet	Jenwoy 6405 UV spectrophotometer

3.2 REAGENTS

The following reagents were collected from chemistry department, Kwara State Polytechnic.

Reagent	Manufacturer
Nickel SulphateHexahydrate (MS=262.71g/mol)	J.T Barker Chemical C.O Philliburg
Copper Sulphate(MS=159.60 g/mol)	Eagle Scientific England
Iron SulphateHeptahydrate (278. 02g/mol.)	East Aglia, Chemicals Hadheigh
Ethanol	East Aglia, Chemicals Hadheigh
Methanol	East Aglia, Chemicals Hadheigh
Distilled water	

3.3 MATERIALS

Ibuprofen

Molecular formular= $C_{13}H_{18}O_2$

Molecular Mass=206.29g/mol

Source BIORAJ Pharmaceuticals, Ilorin.

3.4 EXPERIMENTAL PROCEDURES

All apparatus were cleaned thoroughly before use. The retort stand was set properly and a round bottom flask clamped to it. This was further positioned onto the hotplate with a magnetic stirrer. A reflux condenser was fixed into the round bottom flask containing the solution and clamped onto the retort stand. Water pipes were connected, one into the inlet and the other into the outlet with both connected to full bucket of water and an empty bucket respectively.

3.4.1 IBUPROFEN Ni(ii) COMPLEX FORMATION

3.52g of ibuprofen was weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water using a clean dried round bottom flask.

2.38g of $NiSO_4.6H_2O$ was also weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water in a beaker.

The Nickel solution was added to the ibuprofen solution and shaken vigorously for it to mix well. The magnetic stirrer was placed in the mixture and it was refluxed for 1 hour after which the solution was allowed to cool and a light blue color was observed. The resulting solution was filtered using a filter paper. The precipitate was then washed off with methanol.

The complex obtained was weighed and put in a container which was labeled IBNi(ii) complex.

The weight of the complex obtained was 1.7g of methanol.

3.4.2 IBUPROFEN Cu (ii) COMPLEX FORMATION

3.52g of ibuprofen was weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water using a clean dried round bottom flask.

1.6g of $CuSO_4$ was also weighed and was then dissolved in $10cm^3$ of distilled water in a beaker. The magnetic stirrer was placed in the mixture and it was refluxed for 1 hour after which the solution was allowed to cool and a light green color was observed. The resulting solution was filtered using a filter paper. The precipitate was then washed off with methanol. The complex obtained was weighed and put in a container which was labeled IBCu(ii) complex. The copper

solution was added to the ibuprofen solution and shaken vigorously. The weight of the complex obtained was 3.5g.

3.4.3 IBUPROFEN (Fe) FORMATION

3.52g of ibuprofen was weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water using a clean dried round bottom flask.

3.8g of $FeSO_4$ was also weighed and was then dissolved in $10cm^3$ of distilled water in a beaker. The magnetic stirrer was placed in the mixture and it was refluxed for 1 hour after which the solution was allowed to cool and a light brown color was observed. The resulting solution was filtered using a filter paper. The precipitate was then washed off with methanol. The complex obtained was weighed and put in a container which was labeled IBFe(ii) complex. The copper solution was added to the ibuprofen solution and shaken vigorously. The weight of the complex obtained was 3.2g.

3.45 CHARACTERIZATION METHODS

3.5.1 SolubilityTest.

The solubility of the complexes were determined in the following solvents. Ethanol, benzene, methanol, petroleum ether, acetone, distilled water and chloroform

2.5.2 MELTING POINT DETERMINATION

The melting point of the complexes were determined using Gallenkamp melting point apparatus, thermometer and capillary tubes

3.5.3 METHOD

One side of the capillary tubes was sealed and the samples were introduced through the open and to a depth of about 1cm of the tube. The thermometer and the capillary tubes were inserted in the hole provided in the apparatus. The apparatus was switched on and the temperature at which the sample starts to melt and ends was taken as the melting point range of the sample. The melting point temperatures were taken for both the ligand and the complexes.

CHAPTER FOUR

4.1 RESULTS AND DISCUSSION

The following are the results of the analysis conducted on some of the complexes formed

4.1.1 RESULTS OF SOLUBILITY TEST

Complex	Ethanol	Benzene	Methanol	Pet. Ether	Acetone	Distilled water	Chloroform
Ibuprofen ligand	NS	NS	NS	NS	NS	S	NS
IBNi(ii)	SS	NS	NS	NS	NS	SS	NS
IBCu(ii)	SS	NS	NS	NS	NS	SS	NS
IBFe(ii)	SS	NS	NS	NS	NS	SS	NS

Key S= soluble, SS=slightly soluble NS= not solubl

4.1.2 INTEPRETATION OF SOLUBILITY TEST

From the results obtained from the solubility test, it was evident that all complexes and the ligand were slightly soluble in methanol. Solubility of the ligand and the complexes were poor in ethanol , benzene, petroleum ether, acetone and chloroform.

4.2 RESULTS OF MELTING POINT TEST

COMPLEX	MELTING POINT RANGE
IBUPROFEN LIGAND	190-192
IBNi(ii) COMPLEX	158-160
IBCu(ii) COMPLEX	160-162
IBFe(ii) COMPLEX	211-213

4.2.1 INTERPRETATION OF MELTING POINT RANGE

From the results obtained, it showed that the melting point of the complexes were higher than those of the ligand. This shows that there was coordination.

CHAPTER FIVE

5.0 SUMMARY, CONCLUSION AND RECOMMENDATION

5.1 SUMMARY

The coordination chemistry of ibuprofen with transition metals represents a convergence of medicinal chemistry and coordination science, focusing on the ability of ibuprofen to act as a ligand through its carboxylic acid moiety. The literature reveals that ibuprofen readily forms coordination complexes with a wide range of transition metals such as Cu(II), Zn(II), Co(II), Ni(II), and Fe(III), typically through monodentate or bidentate coordination modes. These complexes are synthesized via conventional solution-phase methods and are characterized using a suite of analytical techniques including FTIR, UV-Vis, NMR, XRD, TGA/DSC, and elemental analysis. Studies show that metal-ibuprofen complexes exhibit superior pharmacological activities compared to the parent drug, including enhanced anti-inflammatory, antimicrobial, and anticancer effects. The enhanced bioactivity is often attributed to improved lipophilicity, cellular uptake, and synergistic effects from the metal ions. Moreover, these complexes have demonstrated relevance in environmental and catalytic applications, though biomedical uses remain the primary research focus.

Despite the promising outcomes, the literature also underscores challenges, including limited structural elucidation through single-crystal X-ray crystallography, sparse in vivo toxicological evaluation, and a lack of mechanistic insight into their biological action. These limitations highlight the need for more rigorous and multidisciplinary research approaches.

5.2 Conclusion

The coordination of ibuprofen with selected transition metals is a promising strategy for the development of next-generation therapeutic agents and functional materials. Transition metal complexes of ibuprofen not only retain the parent drug's anti-inflammatory properties but also exhibit enhanced antimicrobial, cytotoxic, and physicochemical properties. The ability of transition metals to modulate the pharmacological activity of ibuprofen stems from their variable oxidation states, coordination geometries, and redox behaviors. While substantial progress has been made in the synthesis and spectroscopic characterization of these complexes, the field is still in its formative stage with respect to translational applications. Most studies are confined to in vitro assessments, and there is a paucity of data regarding pharmacokinetics, in vivo efficacy, and long-term safety. Moreover, detailed structure–activity relationship (SAR) analyses are limited due to the absence of high-resolution crystallographic data.

5.3 Recommendations

Based on the current state of research, the following recommendations are proposed to advance the field of ibuprofen-transition metal coordination chemistry:

1. **Expand Structural Studies Using Crystallography:**

   Advanced single-crystal X-ray diffraction studies should be prioritized to gain precise insights into the coordination environment and geometry of ibuprofen-metal complexes.
2. **Systematic In Vivo Investigations:**

   Long-term pharmacokinetic and toxicological studies are crucial to assess the biocompatibility, metabolism, and organ-specific accumulation of these complexes.

3. **Mechanistic Elucidation of Biological Activity:**

   Investigations should be undertaken to elucidate the exact biochemical and cellular pathways through which these complexes exert enhanced therapeutic effects.

4. **Comparative SAR Analyses:**

   Systematic comparison among ibuprofen complexes with different metal ions will help establish correlations between structure and pharmacological activity.

5. **Integration with Nanocarriers:**

   Encapsulation of ibuprofen-metal complexes in nanocarrier systems such as liposomes or polymeric nanoparticles could improve targeted delivery, reduce systemic toxicity, and enhance therapeutic indices.

6. **Broaden Application Scope Beyond Biomedicine:**

   Exploring the catalytic, optical, and electronic properties of these complexes could lead to applications in environmental remediation and sensor development.

7. **Multidisciplinary Collaborations:**

   Future research should integrate expertise from coordination chemistry, pharmacology, toxicology, and nanotechnology to facilitate the development of clinically viable and industrially relevant metal-based ibuprofen complexes.

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