



CODEN (USA): IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**Available online at: <http://www.iajps.com>**Review Article****A STUDY ON THE APPLICATIONS OF COORDINATION  
COMPLEXES AND THEIR BIOLOGICAL USES****Mir Shabeer Ahmad**

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**Abstract:**

*Coordination compounds and organometallic complexes in cell biology offer diverse opportunities for manipulating biological processes. The examples that have been highlighted here are only representative of the significant opportunity that metal complexes offer for exploring the chemical biology of living cells. In describing the principles and trends involved in the design, functionality, and reactivity of inorganic complexes in this context, we hope to inspire further research in the area. In many cases, a creative approach can extend a seemingly simple motif across several applications*

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*Please cite this article in press as Mir Shabeer Ahmad, A Study on the Applications of Coordination Complexes and Their Biological Uses, Indo Am. J. Pharm. Sci, 2014; 1(6).*

**INTRODUCTION:**

Transition metals readily react with halogens to form binary compounds of various colors, for example: green-black ferric chloride ( $\text{FeCl}_3$ ), deep blue cobalt chloride ( $\text{CoCl}_2$ ), and golden yellow nickel bromide ( $\text{NiBr}_2$ ). These compounds dissolve in water to give brightly colored solutions-but of changed colors: yellow solutions (containing  $\text{Fe}^{3+}$  ions), red solutions ( $\text{Co}^{2+}$  ions), and green solutions ( $\text{Ni}^{2+}$  ions). By evaporating the solutions, crystals of these new compounds can be obtained: yellow  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , red  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ , and green  $\text{NiBr}_2 \cdot 6\text{H}_2\text{O}$ . Addition of ammonia to a green nickel solution changes its color to violet, and the compound  $\text{NiBr}_2 \cdot 6\text{NH}_3$  can be crystallized. In all cases these beautiful color changes occur because a new chemical species has formed, and there have been changes in the bonding of the nonmetallic substance to the metal ion. Probably the best-known example of vivid color change is the dissolving of anhydrous white cupric sulfate ( $\text{CuSO}_4$ ) in water to give a blue solution, containing  $[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$ . Addition of ammonia yields the deep blue  $[\text{Cu}(\text{NH}_3)_4]^{2+}$ , which forms crystals that have the formula  $[\text{Cu}(\text{NH}_3)_4]\text{SO}_4 \cdot \text{H}_2\text{O}$ . The neutral molecules  $\text{NH}_3$  and  $\text{H}_2\text{O}$  bond directly to a metal atom by donating a lone pair of electrons to any empty orbital on the metal atom. Anions as well as neutral molecules can bond to a metal atom in this way. These neutral molecules or anions that bond to the metal are called ligands. Further examples of ligands are:  $\text{Br}^-$ ,  $\text{NO}_2^-$ ,  $\text{CO}$ , pyridine,  $\text{P}(\text{CH}_3)_3$ , and  $\text{O}=\text{As}(\text{C}_2\text{H}_5)_3$ . Some ligands can donate two pairs of electrons and are termed bidentate, for example,  $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2$  (ethylenediamine or en), and  $\text{O}_2\text{C}-\text{CO}_2^-$  (oxalate anion)

Coordination compounds are found in living systems and have many uses in the home, in industry, and medicine. We describe a few examples here and in the chemistry. Coordination compounds play many roles in the animals and plants. They are essential in the storage and transport of oxygen, as electron transfer agent, as catalysts, and in photosynthesis. here we focus on coordination compounds containing iron and magnesium. Because of its central function as an oxygen carrier for metabolic processes, hemoglobin is probably the most studied of all the proteins. The molecule contains four folded long chains called subunits. hemoglobin carries oxygen in the blood from the lungs to the tissues, where it delivers the oxygen molecules to myoglobin. Myoglobin, which is made up of only one subunit, stores oxygen for metabolic process in muscle. The porphine molecule from an important part of the hemoglobin structure. upon coordination to a metal, the  $\text{H}^+$  ions that are bonded to two of the four nitrogen atoms in porphine are displaced. Complexes

derived porphine. Simplified structure of the porphine molecule and the  $\text{Fe}^{2+}$ -porphyrin complex. The dashed lines represented coordinate covalent bonds. From porphine are called porphyrins, and the iron-porphyrin combination is called the heme group. The iron in the heme group has an oxidation number +2, it is coordinated to the four nitrogen atoms in the porphine group and also to a nitrogen donor atom in a ligand that is attached to protein. The sixth ligand is a water molecule, which binds to the  $\text{Fe}^{2+}$  ion on the other side of the ring to complete the octahedral complex. This hemoglobin molecule is called deoxyhemoglobin and imparts a bluish tinge to venous blood. The water ligand can be replaced readily by molecular oxygen to form red oxyhemoglobin found in arterial blood. Each subunit contains a heme group, so each hemoglobin molecule can bind up to four  $\text{O}_2$  molecules.

There are three possible structures for oxyhemoglobin. For a number of years, the exact arrangement of the oxygen molecule relative to the porphyrin group was not clear. Most experimental evidence suggests that the bond between O and Fe is bent relative to the heme group.

The porphyrin group is a very effective chelating agent, and not surprisingly, we find it in a number of biological systems. The iron-heme complex is present in another class of proteins, called the cytochromes. The iron from an octahedral complex in these proteins, but because both the histidine and the methionine groups are firmly bound to the metal ion, they cannot be displaced by oxygen or other ligands. Instead, the cytochromes act as electron carriers, which are essential to metabolic processes. In cytochromes, iron undergoes rapid reversible redox reaction:

**Platinum Compounds in Clinical Trials**

The need for new agents in cancer chemotherapy is apparent from the inability to predictably cure or induce remissions in common tumors such as breast, lung, colon, or prostate cancer. New cytotoxic agents building on our experience and knowledge of the current armamentarium continue to play an important role in the clinical management of cancer. Approximately 28 direct structural analogs of cisplatin entered clinical trials but most have been abandoned through a combination of unacceptable toxicity profile and/or lack of improved or expanded anticancer efficacy.<sup>38</sup> For new, direct structural analogs of cisplatin to find clinical use exceptional properties would need to be found.<sup>38</sup> Currently, there are three principal drugs in clinical trials-the approaches to their development represent examples

of steric control of reactivity, control of oxidation state and ligand lipophilicity aimed at producing orally active agents, and manipulation of new structures to produce structurally new DNA adducts.

### **Nitric Oxide in Physiology and Medicine**

An intriguing aspect of the role of metal complexes in medicine is the role of NO.<sup>272,273</sup> The nitroprusside ion,  $[\text{Fe}(\text{NO})(\text{CN})_5]^{2-}$  is a vasodilator used in emergency situations to treat hypertensive patients in operating theaters.<sup>274,275</sup> The complex is 30-100 times more potent than simple nitrites. The mechanism is considered to be release of NO, an understanding prompted by the emergence of NO as a prominent cell signaling molecule.<sup>273</sup> Related to the biology of NO is production of peroxynitrite ONOO<sup>-</sup> through reaction of NO with O<sub>2</sub>. In this regard, production of peroxynitrite may play a role in many pathological conditions.<sup>276,277</sup> Water-soluble porphyrins and texaphyrins may catalytically react with ONOO<sup>-</sup> and may have clinical utility in peroxynitrite scavenging.

### **Metals in medicine and in food. Synthetic coordination compounds with active drugs as ligands and innovative strategies for their delivery in the tissues**

The synthesis of platinum group metal complexes with pyrimidine and purine derivatives, and non-steroidal anti-inflammatory drugs (NSAIDs) as ligands has acquired new impetus in the past decade. This fact happened because several reasons, some of which are the following. First, on the basis of pure co-ordination chemistry pyrimidines and purines, and NSAIDs are very versatile ligands and show an huge variety of ligating modes as function of the metal and the environmental conditions. Much has to be learnt on this matter even though a big amount of experimental and theoretical work has already been done [1]. The information collected from the preparative, structural and reactivity studies have high significance for several fields which span from the bio-sciences to the material sciences. Second, pyrimidines and purines, often called nucleobase derivatives (to stress their importance in the life of the cell), and NSAIDs have numerous applications as pharmaceutical agents. Third, for this type of drugs the complex formation with specific metals may improve the activity towards certain diseases and hopefully may increase the activity spectrum [1]. The combination of two or more different molecules into the same compound may bring to a multi-therapeutic agent which can be expanded by the synergic action of the metal residue (especially for platinum group metals) once the co-ordination compound dissociate inside the target tissue. Fourth, it has recently been

suggested that photo-activation of DNA thiobases, may offer a novel approach for the treatment of nonmalignant diseases like psoriasis or of superficial tumours that are accessible via phototherapy[2]. Rhodium- and Ruthenium-complexes with thiobases and NSAIDs are not much investigated by the community of inorganic and co-ordination chemists, at least as it is revealed by the small number of structures deposited at the Cambridge Structural Database (CSD) (Release November 2005, ca. twenty structures). On continuing our project on co-ordination chemistry of platinum group metal complexes with active drugs as ligands, we recently performed the synthesis and characterization of some new compounds. The highlights of this research together with a brief analysis of the works by other will be presented to the Emory students. Treatment of diseases with natural and synthetic materials has been an aspiration of mankind since the dawn of human development. From the use of willow-bark to the marketing of aspirin, a steady move from folk remedies to the use of chemistry and biology to develop new therapies has been observed. In terms of metal-containing drugs, the platinum-containing drug cisplatin has long been the most effective metal-containing anticancer drug on the market.

However, severe side effects of conventional drugs are associated with the inability to distinguish between healthy and cancer cells. Hence, a concerted world-wide effort is in progress to discover and characterize new drugs that may distinguish between healthy and cancer or other diseased cells. New techniques of drug delivery are sought and the use of natural products, proteins, antibodies, and synthetic polymers as drug delivery devices capable of targeting a diseased site is being investigated.

These issues are nicely illustrated by macrocycles such as porphyrins, phthalocyanines, and related systems. Some of these compounds exhibit selective absorption by cancer cells and have the ability to photosensitize formation of singlet oxygen. These attributes have led to the development of alternative cancer treatments known as photodynamic therapy. Sadly, many potentially good new therapeutic agents often never leave the designers' laboratory due to some pharmacological problems associated with its in vivo use. The use of drug delivering devices, including water-soluble synthetic polymeric drug delivery systems, may help overcome many pharmacological drug-related problems, including those of solubility, specificity, and biocompatibility, factors that currently prevent many potentially good therapeutic agents from reaching clinics.

The focus of this special issue is the synthesis, characterisation, physical studies, and application of synthetic metal-containing complexes and natural occurring proteins in serious human diseases such as

cancer, diabetes, arthritis, viral disease, malaria, and tuberculosis with special focus on the following; porphyrins, phthalocyanines, and related complexes in photodynamic cancer therapy; proteins, enzymes, and synthetic polymeric drug delivery systems in the treatment of cancer and other diseases; coordination and organometallic compounds in cancer, arthritis, malaria, and viral disease. Towards these goals, L. Josefsen and R. Boyle describe in their review article the development and application of metal-based photosensitisers, including porphyrins and phthalocyanines, in photodynamic therapy. Four other publications highlight different aspects of porphyrin-based macrocyclic photosensitisers. S. Lee et al. focus on the cellular uptake and toxicity of thiotetra (ethylene glycol)

monomethyl ether-functionalized porphyrazines. J.-Y. Liu et al. focus on in vitro photodynamic activity of novel amphiphilic zinc(II) phthalocyanines bearing oxyethylene-rich substituents. E. Antunes and T. Nyokong highlight the syntheses and photophysical properties of tetraazatetrabenzcorrole photosensitizers. Sakamoto et al. present a fundamental study of zinc bis(1,4-didecylbenzo)-bis(2,3-pyrido)porphyrazine for application in photodynamic therapy of cancer.

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