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Review Article

STRUCTURAL ANALYSIS OF METALLIC MEDICINES

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Abstract:

Indigenous systems of medicine now face the world with many queries as to the safety and efficacy of traditional medicines. Metallic medicines, in particular are still considered as a Pandora's Box in reference to its structure, bio-availability, site of action etc. Ancient health systems has long used metals as a base for numerous medicinal formulas, however recent times requires elaborate scientific validation as to its safety, pharmaco-kinetics etc. Hence the question at hand is in which manner science proves the significance of these medicines to society at large. One such method is to determine the minute structure of these complex compounds posing as a base for further studies. Structure of any material may be examined at many levels. Macroscopic and microscopic findings are very convenient to determine conversely the examination does not stop there. The crystalline structure (monoclinic, cubic etc.), elements present, elemental group as well as the molecular structure are ultimately essential to truly understand these ancient formulas. With reports of concern regarding the safety of traditional medicines surfacing in literature from all parts of globe, it is imperative for the practitioners of indigenous systems of medicine to update themselves about the latest methods and techniques of structural analysis. This paper will briefly describe the different structures to be determined in a metallic compound in addition to the various modes of analysis.

Keywords: Metallic Medicines, Structural analysis, Rasa Shastra

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INTRODUCTION

Metals occur naturally in the environment and maybe found as trace quantities in the atmosphere, soil and water.[1] Continuous exposure to metals may cause serious health hazards in living creatures. Heavy metals, in particular, are known to be unsafe and the severity of its effects fluctuates according to the metal. Yet still, ancient Indian sages deployed the use of metals, following extensive processing, for just about all ailments. According to these ancient sciences, any metal or mineral after due processing will undergo some sort of physical or chemical change that renders these elements suitable for internal administration.

The obvious questions arise, using crude methods, what are the chances of formulating a medicine out of a known harmful substance. Siddhas of Rasa Shastra possessed divine powers that allowed them to understand the changes taking place in a substance when subjected to specific conditions. They developed an elaborate unique science in which a toxic material, for example mercury, is converted to a medicine, which can be

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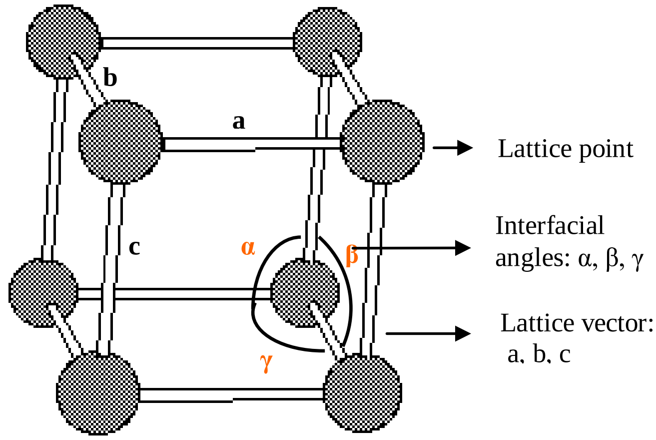
utilized in even incurable diseases. Conversely, the changes which occur in these metals needs to be explained in a manner by which any person can accept the validity of these drugs. Hence, principals of basic chemistry and analytical instruments are essential in the determination of the changes occurring in these metals or minerals.

Structural analysis opens up the doors to further understanding of the conversion that takes place when metals or minerals undergo these specific processes of ancient texts. But before we get into that, first we need to look at the different type of structures that need to be determined and how this information is useful for indigenous systems of medicine. From gross to minute, the crystal lattice, elemental analysis, elemental group and molecular formula with its configuration of atoms provides a clear picture of these complex metallic formulas. The following structures are essential for the understanding of pharmaco-kinetics and pharmaco-dynamics of a drug. Hence an attempt has been made to compile and describe the different structures to be determined in a metallic compound in addition to the various modes of analysis.

Crystals:

Crystals are solids, having in all three dimensions of space, a regular repeating internal unit of structure.[2] The basic structural unit or building block of the crystal structure that defines it by virtue of its geometry and the atom positions within, is known as the unit cell. It is composed of lattice points, which may represent a single atom or consist of tens or even hundreds of atoms.[3] If a line is drawn, connecting these lattice points, a 3-dimensional shape can be observed. These lines are known as lattice vectors. Depending on the arrangement of the lattice points, vectors and the interfacial angles, we find different crystal shapes. (Figure 1)

Figure 1: Unit cell [Primitive Cubic Cell ($a=b=c$; $\alpha=\beta=\gamma=90^0$)]



Vectors are represented by a, b, or c corresponding with the vectors on the x, y and z axis. The interfacial angles correspond with the symbols α, β and γ. When all vectors are of equal length (a=b=c) and all intersect at a 90^0 angle ($\alpha = \beta = \gamma = 90^0$), a perfect cube is formed. This is also known as a cubic primitive cell. Fluctuation in the vectors or angles may produce 7 different possible crystal structures i.e. cubic, monoclinic, triclinic, tetragonal, orthorhombic, rhombohedral and hexagonal. Furthermore, the lattice points may be packed closely together giving rise to the different space lattices i.e. body centered, face centered and side centered. Hence, a total of 14 possible types of lattice arrangements also known as Bravais Lattices (Figure 2) can be found.

A crystalline substance has certain defined characteristics such as a definite chemical composition, melts sharply and exhibits cleavage.[4] All metals posses these characteristics and may be found in any type of crystal arrangement.[5] The most common close packed structures are metals usually found as body centered cubic (BCC), face centered cubic (FCC) or hexagonal close packing (HCP). However, these structures are liable to change if exposed to rapid cooling or high pressure.[6] These two factors may bring about change in the crystal type or the cell volume.

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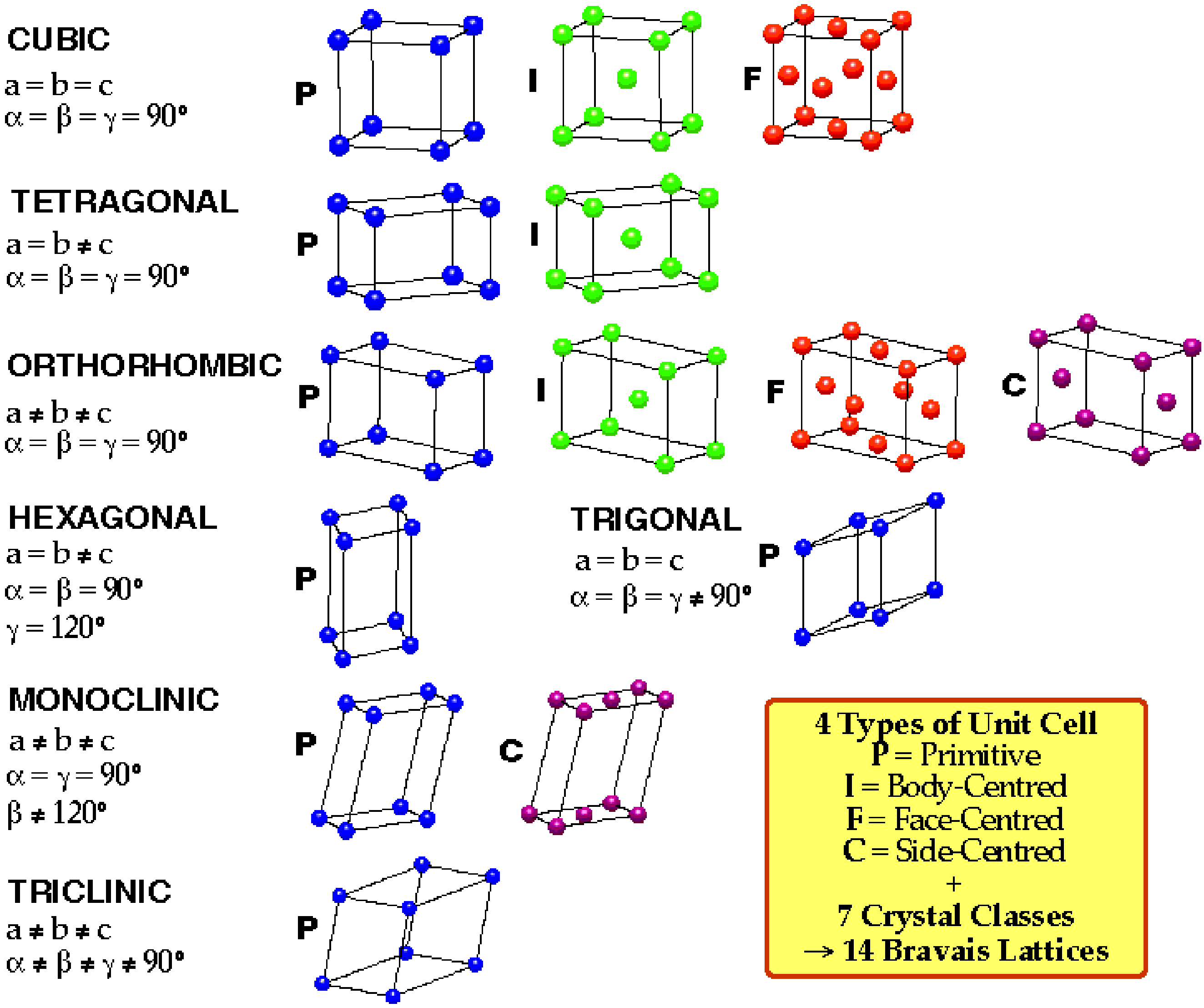
Figure 2: The 14 possible Bravais Lattices (spheres in this picture represent lattice points, not atoms)



All this may seem vague at the moment, but these concepts maybe applied to verify the changes occurring in metals during shodhana and marana processes. As we know, for samanya shodhana of any metal, it is first heated till red hot, then dipped into specified series of liquids. In addition, during the process of bhasmikarana, the metals are subjected to high pressure, which facilitates transformation to a finer state. This is comparable to rapid cooling and high pressure mentioned above as criteria for change in the structure of the crystal.

Powder X- ray diffraction analysis has shown that some metals in raw state are hexagonal, while after shodhana it transforms to monoclinic. Marana further changes the metal to triclinic and after each puta, the volume of the unit cell decreases.[7] In the instance of sulphur (Gandhaka), originally was an orthorhombic crystal type, but after shodhana it changed to Triclinic. This shodhita gandhaka further processed through mardana 72 times, maintains the crystals structure however decreases the cell volume.[8]

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This indicates that a physical change occurs in metals during these ancient processes. It's established that different crystal lattice has direct relation to the bioavailability of a drug, depending on the compound. By simple manipulation of the crystal type, the action of a drug can be enhanced. Hence determination of the crystal type of a sample would invariably provide insight into the absorption of a drug.

However the study of the crystal type is not conclusive enough to give a clear picture of the pharmaco-kinetics of a drug. In some cases, after processing there is still no change in the crystal type, only change in the cell volume. Ultimately, the analysis of crystal type only provides information as to the arrangement of atoms or molecules present in the formula. Therefore further investigation into the composition of these drugs is necessary leading us to study of molecular composition and its structure.

Molecular Structure:

Molecular structure is the three dimensional arrangement of atoms that constitute a molecule. Certain factors need to be analyzed before the molecular structure of a compound can be determined.

1. Elemental analysis along with percentage/ concentration of each element.
2. Elemental group
3. Molecular formula – molecular configuration

***1. Elemental analysis*:**

The components of a drug are ultimately responsible for its action. Determination of these components and its quantity provides valuable information regarding the composition of a drug. Elemental analysis is a fairly common procedure among indigenous systems of medicine. The elements present in a compound and its percentage can be determined by most spectroscopic methods.

Listed below are a few instruments that are essential in analysis of the molecular structure of a sample.

- **X-ray Florescence (XRF)** – can detect the elements present in a solid by the x-ray emission phenomenon. The powder of the sample can be analyzed directly without any prior preparation.

- **Atomic Absorption Spectroscopy (AAS) -** Detects elements present in a liquid or powder. Can determine the concentration of a single element on one trial. This may require more time if there are many elements present in the sample.

- **Inductive Coupled Plasma Atomic Emission (ICP-AE)** - Similar to XRF, however the sample must first be dissolved in a lock solvent. Multiple elements maybe detected simultaneously due to high resolution of the instrument, as oppose to single element detection in AAS.

- **Inductive Coupled Plasma Mass Spectroscopy (ICP-MS)** - Detects even minute trace elements present in a sample as well as precise information for further calculation to the elemental group and the molecular formula of the sample. The reading of mass spectroscopy is considered as the "fingerprint" of these metallic medicines.

- **Nuclear Magnetic Resonance (NMR) -** detects both organic and inorganic substances in a sample. Here also the sample should initially be dissolved in a deuterium lock solvent then aspirated into the instrument. This instrument can also be used to determine structure of complicated molecules and molecular structure of solids.

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- **Thermo Gravimetric Analysis (TGA) -** used to determine change in weight in relation to change in temperature. Commonly used in research to test the levels of inorganic and organic components in a sample.

- **Scanning Electron microscopy (SEM) -** can show a picture like image of the components in a mixture.

- **Infrared Absorption Spectroscopy (IR) -** can find specific types of chemical bonds as well as qualitative analysis of organic and organometallic molecules.

Assessment of the elements present in a compound serves as a base for much research, however with this data alone, not much can be concluded about the test substance. Hence further in depth study of the arrangements of the elements, major groups present in the sample as well as the minor elements in trace quantities and its role in the activity of the drug is needed.

***2. Elemental group/ form*:**

An elemental group or form occurs when two or more atoms combine also known as compounds such as oxides, sulfides, bromides, chlorides etc.[9] These forms can also exists in different types depending on the formula for example PbO or PbO_2 are both oxides of lead. Classification of a sample into specific elemental form has become easily accessible. Combination of XRD and XRF finding are sufficient to determine the form of a sample. This information provides much insight into the chemical reactions that may take place once this substance is introduced into a living cell.

It is widely accepted that after extensive processing by ancient methods, the original form of the metal changes. Particularly following bhasmikarana, it is believed that the metal attains an oxide form, which renders it stable. However more than one form in material have been known to exist. For example Tamra Bhasma has been identified as CuO which is the major form present in the bhasma. Yet still forms such as iron sulphide, calcium sulphate, aluminum silicate etc are also present in minor quantities.[10] Such minor elemental forms may also play an important role in the pharmaco-kinetics of a drug. Therefore, generalization of all bhasmas into the oxide group is not sufficient enough to prove its safety or efficacy.

Another example is the difference between Litharge (PbO) and Naga Bhasma. Both are considered as the oxides of lead. Litharge is a known lethal substance whereas Naga bhasma is considered to be non-toxic as per ancient texts. Hence the dilemma, what are the variations between these two substances. Bhasmas are processed with many organic as well as inorganic substances. These ingredients do contribute in producing a complex substance that somehow alters the metal from its original state. Therefore additional information regarding the role of each element present is mandatory to understand these metal complexes.

***3. Molecular formula & Configuration*:**

Molecular formula is the bonding of atoms that constitute a molecule. Its three dimensional arrangement is known as molecular structure or configuration. In order to establish the molecular formula, initially the assessment of elements present in the sample is necessary. Structural formula acts as a minute description of the mixture but in some cases two or more substances have the same formula and different configurations. The arrangement of the atoms in a formula is therefore crucial to differentiate between similar compounds. Investigation by ICP-MS or SEM can show a picture like image of the atomic arrangement thereby providing a "fingerprint" of the sample.

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Such minute structural scrutiny can visibly prove the transformation of metals from its raw state to final medicinal mixture. Even still, there is a possibility of overlooking the minute organic components present in the medicine. Since most of these metals are processed with organic ingredients, they play an important role in the transformation of the metal. Hence it should not be over looked, and its precise role in the final composition of the medicine is important.

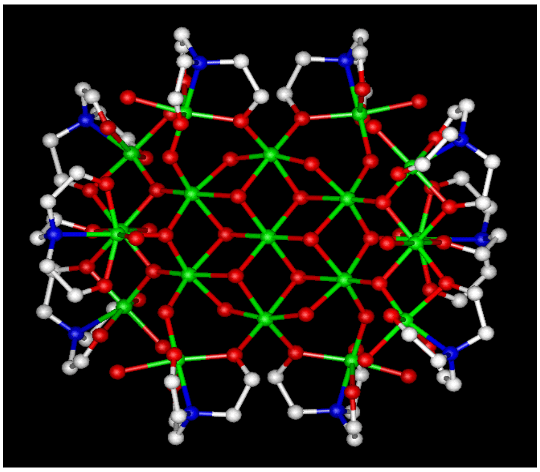
Metallic Species:

Metallomics deals with of the whole array of metallic elements and species in an organism. Speciation of metals describes the geometrical arrangement of a metal and its manner of association with other elements in a complex molecule. This is particularly important when metals are found in combination with organic substances.

The atomic configuration of a metal in a molecule is very important in understanding its reactions to various different environments. For instance, a free metal ion is generally more toxic than a metal ion associated with a large molecule because the free ion tends to cross an organism's cellular membrane more easily.[11]

As seen in figure 3, a mineral ore of iron is trapped within an organic shell. The organic shell acts as a safe store for the destructive free iron species. Such formation may occur when chelating ligands of organic materials "trap" the metal forming a matrix, under controlled conditions.[12] This phenomenon is similar to the reaction that takes place during shodhana of metals. At the stage of heating and dipping into various organic liquids, a chemical change occurs in the metal.

Figure 3: Ore of Iron trapped in an organic shell



We can understand this by measuring the melting point of the metal (in the case of soft metals) after each pouring. If the melting point increases, a chemical as well as physical change has occurred. Chemists believe that during this process, ligands form between the metal and the organic liquids. This may explain the reason why a combination containing heavy metals is able to float on water (varitartva), due to its ligands with organic materials.

Metallic speciation can be determined through a combination of studies with multinuclear NMR, electronic or IR spectroscopy and single crystal X-ray diffraction.[12]

Nano-technology serves as a basis in utility of these metallic species found in ancient metallic medicines. Studies show that if the metallic bhasma is strategically attached forming a shell of a synthetic medicine, it improves the bioavailability of the drug. Yet still such studies have not been accomplished by indigenous systems of medicine. Thus, breakdown of the metallic species present in ancient metallic medicines is crucial to understand how its functions are achieved.

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CONCLUSION

Metallic medicines are the future of indigenous systems of medicine. These complex combinations are very potent and multipurpose drugs. Though these medicines have been employed for centuries, its pharmaco-kinetics and pharmaco-dynamics are still a mystery. In the past few years, much controversy regarding the safety of traditional medicine has surfaced around the world. Many confuse traditional metallic medicines with herbal formulas contaminated with metals. In order to dispel all uncertainty surrounding metallic medicines, a thorough study of its structure and activity is mandatory. Such a task can only be lead by those well versed in traditional pharmaceutics along with correspondence from experts in the field of chemistry. These efforts will be able to prove the safety and efficiency of transformed metals.

An authoritative physician in the department of occupational and environmental health once said, "…metals don't change their characters and each metal will affect an individual differently", non the less a humble attempt was made to illuminate the various methods useful in analyzing metallic medicines and the possible changes that may occur after adequate processing.

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