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Metallic Nanoparticles in Pharmaceutical Applications

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Abstract: *Metallic nano particle is nano sized metals with dimensions (length, width, thickness) within the size range of 1-100nm. In 1857, Faraday first investigated the existence of metallic nano particles in solution. In 1908, Mie gave a quantitative explanation of their colour. Today these nano materials can be prepared and modified with various chemical functional groups which allow them to bind with antibodies, ligands and drugs. Metallic nanoparticles give wide range of application in therapeutic area, biotechnology, vehicles for gene and drug delivery. It provides the readers, detailed information on the synthesis by various methods, characterization, with particular focus on therapeutic application along with potential side effects and their future perspective. Recent headway had opened the way to site-specific targeting and drug delivery by these metallic nanoparticles.*

Keywords: Silver Nanoparticles, Metal Nanoparticle; Catalyst; Gold; Platinum, Gold Nanoparticles, Iron Oxide Nanoparticles.

I. INTRODUCTION

From ancient time to the middle ages, the history of the Nanoparticles has been summarized by Daniel and Astrum. Because of their uniform size and sharp size distribution in Nanometres; metallic nanoparticles have received much popularity. In the field of nanotechnology, metallic nanoparticles have shown Number of properties and it has unlocked many new pathways In nanotechnology. Metallic nanoparticles have specialty with Appropriate functional groups. It can be synthesized and modified That would allow them to bind with ligands, antibodies, drugs [1]. Metallic nanoparticle is nanosized metals with the size range of 10-100nm. Metallic nanoparticles have unique characteristics such as Surface Plasmon resonance and optical properties. Gold solution Does have a golden yellow colour, for example, a solution of 20nm Gold nanospheres has red ruby colour where 200nm nanospheres Has bluish colour. The noble metals, especially silver and gold, Have gained much attention to researchers in various branches Of science and technology namely catalysis, photography, medical Field as anticancer and anti-microbial agents. Faraday (1908) first Recognized the existence of metallic nanoparticles in solution and Mie gave the quantitative explanation of their colour[2].

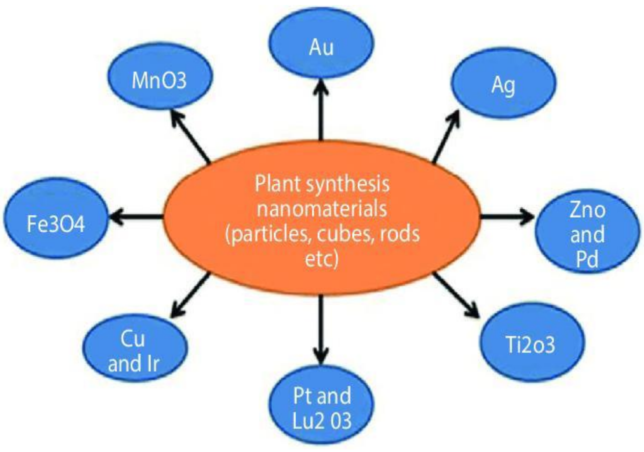

Fig 1. Different types of nanoparticle synthesize from plant resources

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Different Methods for Metallic Nanoparticle Synthesis

Several methods are used for synthesis of nanoparticles (NPs)such as physical, chemical, enzymatic and biological. Physical methods are including plasma arcing, ball milling, thermal evaporate, spray pyrolysis, ultra thin films, pulsed laser desorption, lithographic techniques, sputter deposition, layer bylayer growth, molecular beam epist axis and diffusion flame synthesis of nanoparticles. Similarly, the chemical methods are used to synthesized NPs by electro deposition, sol–gel process, chemical solution deposition, chemical vapour deposition, soft chemical method, Langmuir Blodgett method, catalytic route, hydrolysis, co-precipitation method and wet chemical method. Physical and chemical methods have been using high radiation and highly concentrated reductants and stabilizing agents that are harmful to environmental and to human health[3]. Fig. 1 shows different types of metallic nanoparticles synthesized from plant resources.

II. BIO-REDUCTION MECHANISM

Silver: the biochemical reaction of AgNO3 reacts with plant broth leads to the formation of AgNPs by following reaction[4]. Fig. 2 explains the proposed mechanism of biological synthesis of nanoparticles.

$Ag^{+}NO3^{-}$+ plant extract → Ag^{0} NPs + by products

Gold: the plant extract contains different biomolecules such as proteins, sugars, amino acids, enzymes and other traces of metals. These metabolites are strongly involved in the bioreduction process. The proposed reaction was Au^{+} ions reduction into metallic Au^{0} nanoparticles in the presence of metabolites and redox enzymes[5]. The reaction is given below.

$HAu^{+}Cl_{4}.4H_{2}0$ + plant extracts →Au^{0}NPs +by products

Platinum: platinum is involved in the following reduction process such as

$H_{2}Pt^{+}Cl2\ .6H_{2}0$ + Plant extracts →Pt^{0}NPs + by products

Copper: the copper nanoparticles are synthesized from plant extracts and the reduction mechanism was proposed by[6].

$CuSO_{4}.\ 5H_{2}O$ + Plant metabolites →Cu^{0}NPs + by products

Zinc oxide: A typical procedure was employed in ZnOnano particles production, the zinc nitrate was dissolved inthe aloe plant extract to produce the nanosized particles. The method is as follows[7]:

Zinc nitrate + Plant extract →ZnO + by products

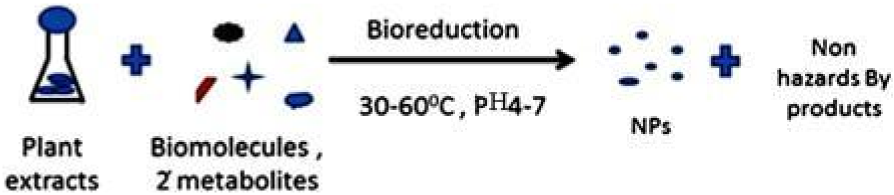

Fig 2. Proposed mechanism of nanoparticle synthesis using plant extracts

2.1 Advantages of Metallic Nanoparticles

1. Enhance Rayleigh scattering
2. Surface enhanced Raman scattering
3. Strong plasma absorption
4. Biological system imaging
5. Determine chemical information on metallic nanoscale substrate[8].

2.2 Disadvantages of Metallic Nanoparticles

1. **Particles instability:** Nanomaterials can undergo transformation, as they are thermodynamically unstable and lie in the region of high energy local minima. This leads to deterioration of quality, poor corrosion resistance, and main concerned is retaining the structure becomes difficult.
2. **Impurity:** While synthesising nanoparticles, nitrides, oxides, formation can aggravated from the impure environment. As nanoparticles are highly reactive, there can also be high chances of impurity as well. In solution form, nanoparticles should be synthesized in form of encapsulation. So, it becomes a challenge to

overcome impurity in nanoparticles.

3. **Biologically harmful:** Nanomaterials has been reported toxic, carcinogenic and cause irritation as they become transparent to the cell dermis.
4. **Explosion:** exothermic combustion can lead to explosion, as fine metal particles act as strong explosives.
5. **Difficulty in synthesis:** while synthesizing nanoparticles, it should be encapsulated, because it is extremely challenging to retain the nanoparticles size in solution form [9].

2.3 Characteristics of Metallic Nanoparticles

a. Large surface energies
b. As compared to bulk they have large surface area to volume ratio
c. Quantum confinement
d. Plasmon excitation[10].

2.4 Applications

A. General Application of Metallic Nanoparticles

Thermal Function

When nanoparticle diameter is less than 10nm, the melting point is also lower than a bulk metal. With low boiling point, electronic wiring can be made with nanoparticles.

Mechanical Functions

Polymers filled with nanotubes leads to improvement in their mechanical properties. And this progress is purely dependent on the filler type and the way with which the filing is conducted. The larger the particle size of the filler, poorer is the properties obtained. Mechanical property of metallic nanoparticles can be improved by mixing the nanoparticles with metals or ceramics.

Magnetic Function

At the nanosized level, pt and gold nanoparticles exhibit magnetic property but as bulk they are non-magnetic. By capping, the nanoparticle surface and bulk atoms can be improvised by interaction with other chemical species. So, by capping with appropriate molecules; this gives the chances to modify the physical property of nanoparticles.

Used as Fuel Cell Catalysts

Fuel cell is a device that directly converts chemical potential energy into electric energy. A PEM (Proton Exchange Membrane) cell uses hydrogen gas (H2) & oxygen gas (02) as fuel. The products of fuel cell are water, electricity, heat.

Used in Materials Science

Nickel nanoparticles are used as electrical conductive pastes, battery materials etc.

Used in Medical Treatment

Healthy cell can be distinguished from cancer cell by the presence of Antibodies joined to the Au nanoparticle.

Used in Paints

Nano titanium dioxide is used in paint to explloit two outstanding properties- photo catalytic activity, UV protection. Addition of nanosilicon dioxide to paints can improve the macro and micro hardness, abrasion, scratch resistant.

Elimination of Pollutants

As metallic nanoparticles is highly active in terms of physical, chemical and mechanical properties. They can be used as catalysis to prevent environment pollution arising from coal and burning gasoline. As they react with toxic gases such as carbon monoxide and nitrogen oxide.

Used as Sun Screen Lotion

Nanomaterials are very useful as sunscreen lotions by blocking UV radiation effectively for a prolonged period of time. As prolonged UV exposure causes skin burns. By applying sun-screen lotions containing nano-Tio2 it gives sun protection factor (SPF).

B. Therapeutic Applications of Metallic Nanoparticles

As anti-Infective Agents-

The anti-viral properties of AgNps are more effective then chemically synthesized silver nanoparticles[11]. In one study, metallic nanoparticles have been described as a HIV preventative therapeutic[12]. In a couple of studies, it has been shown that as virucidal agent silver acts directly on the virus by binding to the glycoprotein gp120[13]. This binding in turn prevents the CD4 dependent virion binding which effectively decreases HIV-1's infectivity[14] and it has also been reported that metallic nanoparticles has been effective antiviral agents against herpes simplex virus[15], influenza[16], respiratory syncytial viruses[17].

As anti-Angiogenic

It is well known that angiogenesis is the development of new blood vessels and occurs during normal development and in some disease states. It plays a main role in number of diseases such as cancer, rheumatoid arthritis. In normal conditions, angiogenesis is tightly regulated between various pro-angiogenic growth factors. Under diseased conditions, angiogenic is turned on. Some reviews have reported that these agents have serious toxicities such as fatal haemorrhage, thrombosis, and hypertension. It may be overcome if these nanoparticles alone can be efficacious as an anti-angiogenic agent.

In Tumour Therapy

It has been studied that naked gold nanoparticles inhibited the activity of heparin-binding proteins such as VEGF165 and bFGF in vitro and VEGF induced angiogenesis in vivo[18]. Further work in this area has been reported that onto the surface of AuNPs heparin binding proteins are absorbed [19] and were subsequently denatured[20].The researchers also showed that surface size plays a main role in the therapeutic effect of AuNPs. Mukherjee and colleagues also experimented the effect of gold nanoparticles on VEGF mediated angiogenesis using a mouse ear model injected with an adrenoviral vector of VEGF[21]. A week later, the AdVEGF administration, mice treated with AuNPs developed lesser edema than the same treated mice. Eom and Colleagues revealed the anti-tumour effects of 50nm AgNps In vitro and In vivo.

In Multiple Myeloma

Researchers have designed a nanoparticle based therapy that is effective in treating mice with multiple myeloma. Multiple myeloma is a cancer that affects plasma cells. Mukherjee and group demonstrated that a gold nanoparticle inhibits the VEGF and bFGF dependent proliferation of multiple myeloma cells.

In Leukaemia

B-chronic Lymphocytic Leukaemia (CLL) is an incurable disease predominantly characterized by apoptosis resistance, by co-culture with an anti-VEGF antibody, found induction of more apoptosis in CCL B cells. In CLL therapy, gold nanoparticles were used to increase the efficacy of these agents. Gold nanoparticles were chosen based on their biocompatibility, very high surface area, surface functionalization and ease of characterization. To the gold nanoparticles, VEGF antibodies were attached and determined their ability to kill CLL B cells.

In Rheumatoid Arthritis

Scientists from the University of Wollongong (Australia) have built a new class of anti-arthritic drug which could be used by gold nanoparticles and it has fewer side effects. Rheumatoid arthritis is an autoimmune disease that occurs when the immune system not function properly and attacks a patient's joints. New research has shown that gold particles can invade macrophages, and stop them from producing inflammation without killing them. Journal of inorganic biochemistry it has been published that by reducing the size of gold into smaller nanoparticles (50nm) was able to cause more gold to immune cells with lesser toxicity .

In Photo Thermal Therapy

Gold nanoparticles absorb light strongly as they convert photon energy into heat quickly and efficiently. Photo-thermal therapy (PTT) is an invasive therapy in which photon energy is converted into heat to kill cancer.

In Radiotherapy

Tumours loaded with gold, this absorbs more X-rays as gold is an excellent absorber of X-rays. Thus deposition of more beam energy and results in a local dose which increase specifically to tumour cells. Gold nanoparticles have been more useful to treat cancer disease predominantly characterized by apoptosis resistance, by co-culture with an anti-VEGF antibody, found induction of more apoptosis in CCL B cells. In CLL therapy, gold nanoparticles were used to increase the efficacy of these agents. Gold nanoparticles were chosen based on their biocompatibility, very high surface area, surface functionalization and ease of characterization. To the gold nanoparticles, VEGF antibodies were attached and determined their ability to kill CLL B cells.

Anti-Fungicidal Activities of Metallic Nanoparticles

The fungicidal mechanism of biosynthesized metallic nanoparticles has more potential than commercial antibiotics such as fluconazole and amphotericin. The plant derived Ag nanoparticles have clearly showed the membrane damage in Candida sp. and damage in fungal intercellular components and finally cell function was destroyed [22]. Most of the commercial antifungal agents have limited applications clinically and in addition, there are more adverse effect and less recovery from the microbial disease. Subsequently, the commercial drugs induce side effect such as renal failure, increased body temperature, nausea, liver damage, and diarrhoea after using the drugs. Nanoparticles were developed for novel and effective drug against microbes. The fungal cell wall is made up of high polymer of fatty acid and protein. The multifunctional AgNPs have a promising activity against spore producing fungus and effectively destroy the fungal growth. The fungal cell membrane structure significant changes were observed by treating it with metallic nanoparticles[23].

Anti-Inflammatory Action of Nanoparticles

Anti-inflammatory is an important wound healing mechanism. Anti-inflammation is a cascade process that produces immune responsive compound such as interleukins and cytokinins which can be produced by keratinocytes including T lymphocytes, B lymphocytes and macrophages[24].Various inflammatory mediators such as enzymes, antibodies are secreted from the endocrine system. Other potential anti inflammatory agents such as cytokines, IL-1, IL-2 are secreted from the primary immune organs. These anti-inflammatory mediators induce the healing process[25]. Also, the inflammatory mediators are involved in biochemical pathways and control the expansion of diseases.

Antidiabetic Management of Metallic Nanoparticles

Diabetes Mellitus (DM) is a group of metabolic dysfunction in which person has uncontrolled sugar level in blood. Certain foods and balance diet or synthetic insulin drugs can be prevent the diabetes at certain levels, but the complete treatment of DM is a big challenge. However, the biosynthesized nanomaterials could be alternative drug to cure the diabetes mellitus[26].gold nanoparticles have good therapeutic effects against diabeticmodels. Gold nanoparticles significantly reduce the level of liver enzymes such as alanine transaminase, alkaline phosphatase, serum creatinine, and uric acid in treated diabetes mice. The gold nanoparticles treated diabetic model showed a decrease of HbA (glycosylated haemoglobin) level which is maintaining the normal range[27,28].

Metallic Nanoparticle as Drug Delivery

Most of the chemotherapeutics agents distribute to the whole body results in toxicity and it gives poor compliance by patients, so as targeted delivery of therapeutic agents to tumour cells is a challenge. By active and passive targeting, imaging of tumour cells is done by metallic nanoparticles. Both at surface and inside cells, metallic nanoparticles can interact with bio molecules because of their small size which gives better targeting for therapeutics. Between 10-100nm [29] of different shapes, sizes of gold, nickel, silver, iron [30] metallic nanoparticles have been checked out as diagnostics and drug delivery systems. Gold nanoparticles utility in cancer cells and in xenograft tumour mouse models was experimented and reported the use of non-toxic PEG gold nanoparticles for tumour targeting (in vivo) which were biocompatible and were characterized by SERS (surface enhanced Raman scattering) [31]. But the use of metallic nanoparticles for drug delivery is a concern because after drug administration, some fraction of metallic particles can be retained in the body even though it is inert and biocompatible. These metallic nanoparticles can be easily conjugate with various agents such as peptides, antibodies and DNA/RNA to specifically target different cells [32], with polymers (polyethylene glycol) which are biocompatible to prolong their circulation in vivo for drug and gene delivery applications [33-34]. They can also transform light into heat, thus enabling thermal ablation of targeted cancer cells [35,36]. For the delivery of anticancer drugs such as Paclitaxel [37] or cisplatin, oxiplatin (platinum based drugs); Au nanoparticles have been used as vehicles. This has investigated 2nm Au nanoparticles covalently bind with the chemotherapeutic drug paclitaxel. Gold-gold sulphide nanoshells have been produced as a photo thermal modulated drug delivery system. These nanoshells covered by a hydro gel matrix which are thermo sensitive.

III. CONCLUSION

Metallic nanoparticles in this 21st century are highly Demanded because it can be synthesised through various routes. Metallic nanoparticles synthesis is important because of their ideal Electrical, optical, magnetic and chemical properties. Metal Nanoparticle play a major role in nanotechnology and nanoscience. Metal nanoparticles have been found to play a major role in the medical, biomedical, and pharmaceutical applications of nanotechnology. They proved to be effective in the delivery of drugs, proteins, peptides, and genes.Metallic nanoparticles have wide range of applications such as imaging agents, delivery vectors, synthetic inhibitors and sensors.Metallic nanoparticles development is multidirectional and now it is widely used in cancer treatment

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