EJTAS
ISSN 2786-7447
EUROPEAN JOURNAL OF THEORETICAL AND APPLIED SCIENCES
OPEN ACCESS
PEER REVIEWED

Role of Gold Nanoparticles in Drug Delivery

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Suggested Citation

Raihan, R., Wafa, A., & Nesar, A. (2024). Role of Gold Nanoparticles in Drug Delivery. *European Journal of Theoretical and Applied Sciences, 2*(2), 869-877.
DOI: 10.59324/ejtas.2024.2(2).78

Abstract:

Recent developments in nanotechnology offer a multitude of approaches for investigating and tracking diverse biological and medical processes at the nanoscale. Nanoparticles can deliver medications directly to cancer cells, aiding in the diagnosis and treatment of diseases like cancer. Gold nanoparticles (AuNPs) are incredibly small gold particles, usually fewer than 100 nanometers in size. They are measured in nanometers. AuNPs are one type of nanoparticle that has shown promise as a medication delivery platform. Their outstanding stability, adjustable chemical and physical characteristics, and biocompatibility make them incredibly beneficial for drug delivery applications. The physical and chemical features of AuNPs' natural characteristics were studied. Localized surface plasmon resonance (LSPR), radioactivity, and a high X-ray absorption coefficient are among the physical characteristics of AuNPs that are commonly used in diagnosis and treatment. Compared to many other nanoparticles, AuNPs can create stable chemical interactions with groups that contain S and N. As a result, AuNPs can bind to a broad range of chemical ligands or polymers used for particular purposes. According to recent research, AuNPs can be easily modified to allow the delivery of pharmaceutical drugs directly to the target tissue. This article provides a brief overview of the more effective synthesis method for AuNPs and how they can be utilized as drug carriers to improve precision medicine.

Keywords: *Gold Nanoparticles, Synthesis, Properties, Applications, Drug Carrier.*

Introduction

Nanotechnology-based platforms have emerged as promising options for the efficient, secure, and patient-friendly treatment of various medical problems throughout the last few decades (Pattnaik & Swain, 2018).

Gold, one of the first metals to be found, has a long and remarkable history of study and use. Early treatises claim that attempts to manufacture colloidal gold back to the fifth and fourth centuries BC by researchers from China, India, and the Arab world (Yadav & Pattnaik, 2023).

Gold (Aus) is applied in targeted medication delivery, theranostic applications, and disease detection. It is also useful in reducing adverse effects, costs, and effort associated with diagnosing and treating illnesses, as well as cutting down the time and resources required (Fig.1) (Thalluri et al., 2023).

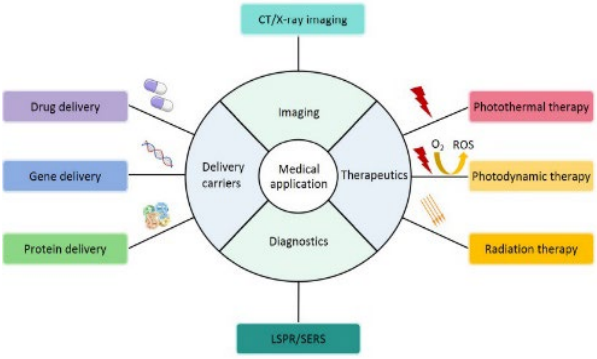

Figure 1. Medical Applications of Gold Nanoparticles
Source: Hu et al., 2020

Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs), demonstrate a potential platform for drug delivery. Because of their exceptional stability, tunable physical and chemical properties, and high biocompatibility, AuNPs are especially beneficial for drug delivery applications in cancer research (Fig. 2) (Sztandera et al., 2018; Yaqoob et al., 2020).

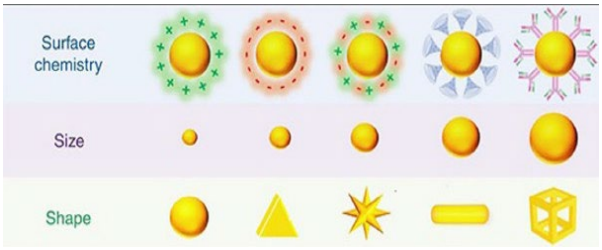

Figure 2. Some Physical Characteristics of AuNPs
Source: Hammami et al., 2021

The success of AuNPs in nanotechnology can be attributed to multiple factors: (i) they exhibit high chemical and physical stability. (ii), they are inherently biocompatible. (iii), their surface can be easily functionalized with organic and biological molecules. (iv), they possess a wide range of optical properties associated with surface Plasmon (Dykman & Khlebtsov, 2012; Hu et al., 2020).

Various shapes of AuNPs including nanoclusters, nanorods, nanoplates, nanoshells, nanocages, and nanostars have been widely studied in various cancers over the last 20 years (Fig. 3) (Yang et al., 2022).

The physical shape of AuNPs is critical as it affects their physical, chemical, and optical properties (Jiang et al., 2011).

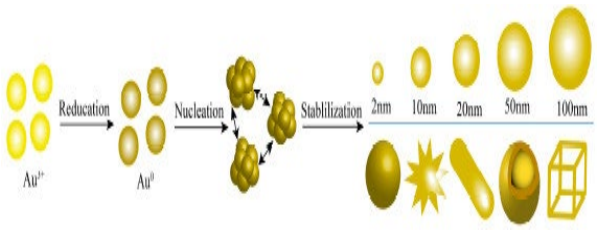

Figure 3. Different Shapes of AuNPs
Source: Huang et al., 2023

Properties of Gold Nanoparticles

AuNPs have distinct properties from bulk gold which is a yellow solid & inert, but gold nanoparticles are wine-red solutions. Interparticle interactions and gold nanoparticle network formation are important factors in determining the characteristics of these nanoparticles (Khan et al., 2014).

Physical Properties

AuNPs' physical characteristics, especially localized surface plasmon resonance (LSPR), radioactivity, and a high X-ray absorption coefficient are widely used in tumor diagnosis and treatment. LSPR can also result in surface-enhanced Raman spectroscopy (SERS), surface-enhanced fluorescence (SEF), photothermal, photochemical, and colorimetric responses (Bai et al., 2020).

Chemical Properties

AuNPs are chemically inert and slightly toxic thus they may pass through the body without causing any adverse responses (Ramanathan et al., 2021).

AuNPs are frequently coated with a layer of polyethylene glycol (PEG) ligands before being administered intravenously as drug carriers (Yang et al., 2022).

Due to their non-porous nature, AuNPs are frequently loaded with payloads via adsorption or chemical bonding to their surface ligands (Vasam et al., 2023).

The surface of AuNPs is readily functionalized by the strong gold–sulfur (Au–S) bonds that spontaneously form through thiol surface adsorption. As Au-S bonds are non-labile, AuNPs remain stable under physiologically relevant pH and salt concentrations (Asiri, 2020; Dong et al., 2020; Yang et al., 2022).

Synthesis of Gold Nanoparticles

Several methods for synthesizing gold nanoparticles have been established, which follow the same norms as other particles (Khan et al., 2014).

1. Top-down: includes physical decomposition

1.1 physical Method

2. Bottom-up:

The self-assembly of gold atoms or molecules into evenly sized AuNPs is cost-effective and easily controlled (Fig. 4) (Hu et al., 2020).

2.1 Chemical synthesis (Chemical reduction) method

- The manufacture of AuNPs via the chemical reduction approach consists of two primary phases. First, tiny clusters are formed when Au3+ is quickly reduced to Au0 by the reducing agent's electrons (Wuithschick et al., 2015). The primary reducing agents include hydrogen peroxide, borohydrides, and citric acid (Daruich De Souza et al., 2019). Secondly, the final size, shape, and rate of growth of AuNPs are all controlled by stabilizing/capping agents. Trisodium citrate dihydrate, sulfur ligands, and surfactants—particularly CTAB—are the principal constituents of these agents (Zhao et al., 2013). The reducing agent and the stabilizing/capping agent can be the same substance (Dong et al., 2020).

- This approach can be characterized as either the Turkevich method, the Brust–Schiffrin method, or the seeding-growth method based on the variations in the synthesis system and conditions (Huang et al., 2023).

2.2 Biosynthesis

2.3 Physical Hybridization Methods

- Electrochemical, sonochemical, and photochemical synthesis

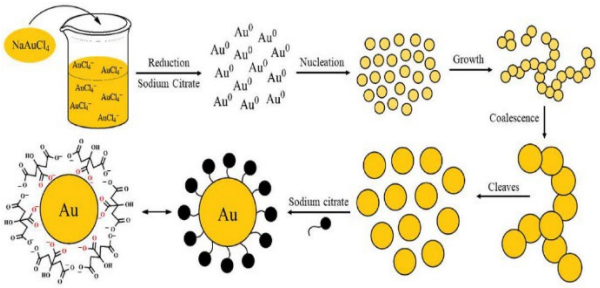

Figure 4. The synthesis process of AuNPs
Source: Huang et al., 2023

Merits of Gold Nanoparticles

- simply create different-shaped Au NPs in diameters ranging from 1 nm to over 100 nm,

- Since Au NPs have a negative charge, many biomolecules, including medications, genes, and targeting ligands, can readily functionalize them.

- Au NPs are harmless and biocompatible.

- AuNPs are harmless and biocompatible

- A specific surface effect, small size, macroscopic quantum tunneling effect, and surface plasmon resonance (SPR) bands are all features of AuNPs (Kong et al., 2017; Yang et al., 2022).

Demerits of AuNPs

There are still many obstacles to overcome in the development process, including immunogenic problems, drug metabolism, safety concerns, in vivo efficacy, biocompatibility and stability, and preparation costs (Yang et al., 2022).

Gold Nanoparticles in Carrier Delivery

The discovery of AuNPs has opened up a world of possibilities for the delivery of selected medications. With a variety of targeting ligands, AuNPs are thought to be the best delivery system for specific drug administration of both new and well-established metastatic tumor medications (Abu-Dief et al., 2021).

Due to their small size, which allows them to passively aggregate at the tumor site, they possess a passive tumor-targeting effect. Moreover, AuNPs can actively target the tumor site and affect tumor cells when associated with specific active substances. For instance, Ramucirumab antibodies connected to gold nanorods target stomach cancers and enhance the medication's anti-cancer properties. Hence, gold nanoparticles can be used as a vehicle to transfer genes and chemotherapeutics to the tumor site, significantly enhancing the effectiveness of the active molecule. AuNPs can modify the tumor microenvironment and stop tumor progression (Connor & Broome, 2018).

Gold Nanoparticles in Drug Delivery

To provide precision therapy for gastrointestinal cancer, AuNPs were utilized to deliver chemotherapeutic medications on target (Yang et al., 2022).

For example, methotrexate has been combined with 13 nm colloidal Au. After an overnight incubation period, the carboxylic groups on the methotrexate molecule can interact on the surface of AuNPs. Moreover, it has been suggested that the concentration of methotrexate bound to Au NPs is greater than that of AuNPs absent at the same volume (Connor & Broome, 2018).

A pH-sensitive linker was used to bind doxorubicin (DOX) with 30 nm AuNPs. This attachment enables the intracellular release of DOX from the AuNPs once they are inside acidic organelles, leading to a sharp rise in intracellular DOX concentration (Fig. 5) (Kong et al., 2017).

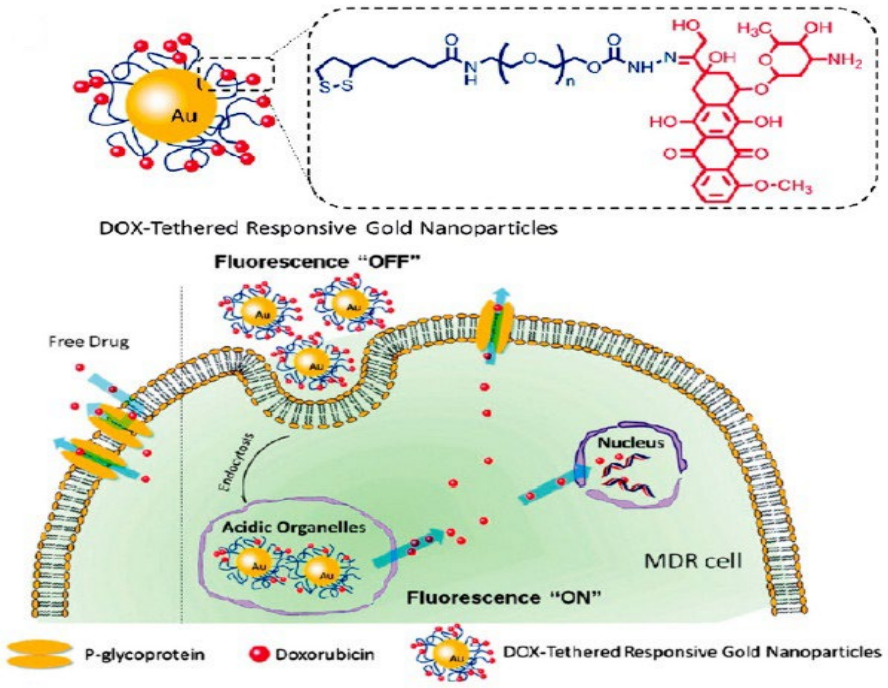

Figure 5. Intracellular Release of Doxorubicin Attached with AuNPs
Source: Kong et al., 2017

Here are more examples of medications that can be delivered to the body by AuNPs:

1. Trastuzumab (Tmab) and AuNPs were mixed (T-AuNPs) to form new nanocomposites that target human epidermal growth factor receptor-2 (HER2) and cause autophagy in gastric cancer cells that are both Tmab-sensitive and Tmab-resistant (Kubota et al., 2018).

2. AuNPs deliver epigallocatechin gallate (EGCG), an anti-tumor medication, to gastric cancer cells and tissues which suppresses proliferation while having no adverse effect on normal epithelial cells (Yuan et al., 2018).

3. Encapsulating AuNPs with cisplatin and glucose, cisplatin can be successfully delivered into head and neck squamous cancer (HNSCC), resulting in inhibiting tumor cell development and improving radiation sensitivity in HNSCC (Davidi et al., 2017).

4. The surface of the AuNPs was coupled with gemcitabine (GEM) to create AuNPs-Gem, which has a strong antiproliferative effect on PDAC cell lines and can deliver GEM into cancer cells selectively.

5. To target pancreatic ductal adenocarcinoma (PDAC), the GNPs were modified using Plectin1-targeted multifunctional peptides (Pal et al., 2017).

6. (DOX) coupled to pH-sensitive linker-coated AuNPs via an acid-labile linkage demonstrated much more drug accretion than free DOX in multidrug-resistant MCF-7/ADR cancer cells (Jiang et al., 2011).

7. A pH-dependent doxorubicin release was demonstrated by spherically-shaped AuNPs functionalized with chitosan and folate-linked chitosan, and manufactured using sodium tripolyphosphate as a linking agent (Goddard et al., 2020; Sathiyaseelan et al., 2021). AuNPs in the drug delivery system (Tab.1).

Table 1. Drug Delivery Applications for Gold Nanoparticles

Therapeutic agent administered	Aim of delivering	Degree of evidence
5- fluorouracil, and doxorubicin	Targeted delivery	Glioblastoma cell model
Doxorubicin, and aptamers	Targeted delivery	A 549 and 4T1 cell
Doxorubicin	Extended delivery	MDA-MB-468, βTC-3, and HFb cell lines
Withaferin A	Targeted delivery	Murine melanoma cells, Chinese hamster ovary, and mouse embryonic fibroblast cells
Betulinic Acid	Targeted delivery	Human Caco-2, HeLa and MCF-7 cancer cell lines
Doxorubicin	pH-dependent targeted delivery	Human breast, cervical, and hepatocellular carcinoma cell lines
Linalool	Targeted delivery	breast cancer cell line
Doxorubicin	Targeted delivery	HeLa cells
EGFR siRNA	Lung cancer treatment	BEAS-2B, and A549 cells
Bcl-2 siRNA and doxorubicin	Breast cancer treatment	Triple-negative breast cancer, and MCF7 cell line
siRNA	Targeted controlled release	Immune deficient mice bearing A549 tumor xenograft
siRNA	Topical delivery	Normal human keratinocytes, spontaneously immortalized cells

Source: Thalluri et al., 2023

Delivery of Gold Nanoparticles to Tumor Tissue

AuNPs coupled with targeted molecules can effectively deliver tumor-targeting medications through passive and active targeting (Fig. 6)

(Huang et al., 2023). Currently, some AuNPs medications are under trial to be used in tumor therapy (tab. 2).

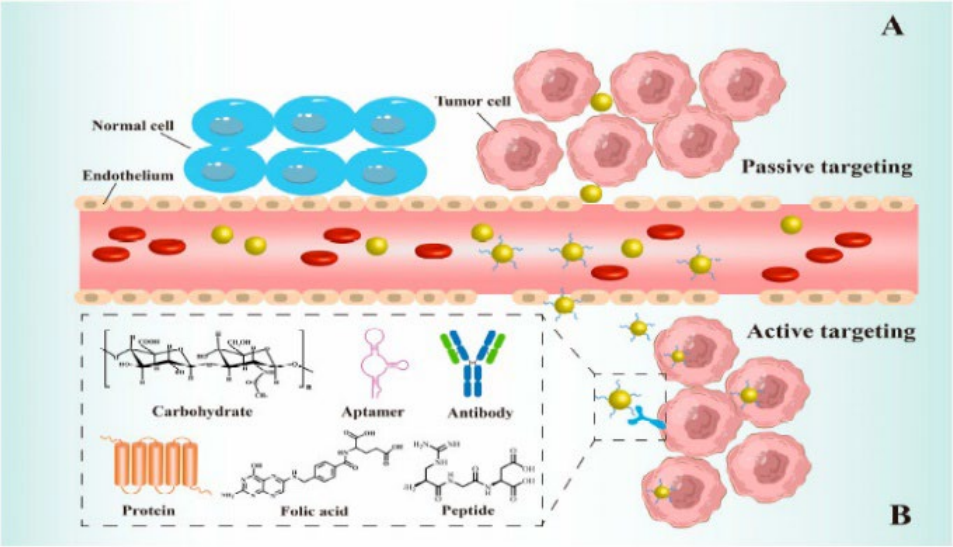

Figure 6. Mechanisms of Targeting Based on AuNPs Delivery.
(A) AuNPs-loaded therapeutic drugs are passively delivered into the tumor by passive targeting, which uses the effect of leaking tumor vasculature-mediated EPR.
(B) The precise binding of AuNPs to receptors on the surface of tumor cells via the functionalization of targeting ligands is referred to as active targeting
Source: Huang et al., 2023

Table 2. Gold Nanoparticles for Tumor Therapy in Clinical Trials

Name	Composition	Physical & Chemical Properties	Usage	Stages
CYT-6091 (Aurimune)	AuNsphere, rhTNF, tPEG	delivery	Melanoma Sarcoma	Phase I complete
Aurolase therapy	AuNshell, Silica, PEG	EPR effect Photothermal conversion	Head and Neck Cancer, Lung and Prostate cancer	Not Applicable
PEGylated gold nanoparticles	AuNRod, PEG	Photothermal conversion	Deep-tissue Malignancies	Human pilot studies
NU-0129	Spherical Nucleic Acid Ausphere	Delivery	Glioblastoma, Gliosarcoma	Early phase I

Source: Bai et al., 2020; Kesharwani et al., 2023

Conclusion

This study addresses AuNPs' drug-carrying design techniques and uses in cancer immunotherapy. The capability of AuNPs to carry a wide range of medications, including cytotoxic and unstable nucleic acid medications, has been demonstrated. Overall, the use of AuNPs in drug administration has advanced significantly, indicating their great promise as useful agents for cancer treatment. The conversion of preclinical technology into useful clinical applications should be one of the next

frontiers of advancement. Despite several AuNP-based medications making their way into phase I and early-stage clinical trials, ongoing discussions about the safety of AuNPs in cellular and animal investigations hinder their advancement.

Conflict of Interests

No conflict of interest.

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