AuNPs as an important inorganic nanoparticle applied in drug carrier systems

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ABSTRACT
Gold nanoparticles (AuNPs), as a kind of inorganic nanoparticle, have been gradually recognized as one of the most promising nanomaterials, which is attributed to their unique optical, electronic, sensing and biochemical characteristics. Due to such unique characteristics, AuNPs have been widely applied in biomedical fields such as diagnosis, biosensing and drug delivery. Except for their use in cancer treatment alone with their photothermal ablation of solid tumours, when used with anticancer drugs, AuNPs can exert a dual role in treating cancer. With the advantages of protecting drugs from degradation and leakage in the physiological environment, tuneable modification in size, surface and shape, and biocompatibility, AuNPs can be used as promising drug carriers in anticancer drug design. However, there are still many aspects that need to be improved during the usage of drug carriers in pharmacology including the following aspects: prolongation in the plasma, enhancement in targeting accumulation, improvement in cellular uptake and the control of intracellular release. AuNPs are important drug carriers.

Introduction
Nanotechnology is becoming a trending topic involving many academic disciplines such as chemistry, biology and medicines [1]. The size of nanoparticles, which have important activity compared to the same material in bulk form, is one billionth of a metre [2]. There are many types of common nanomaterials such as nanoparticles, nanocapsules and nanotubes [3]. Nanoparticles, as the most familiar nanomaterials, can be divided into two types, of which the most common one in pharmacology is organic nanoparticles, such as liposomes and polymeric micelles, and the other one is inorganic nanoparticles such as quantum dots (QDs), gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), carbon nanotubes (CNTs) and mesoporous silica nanoparticles (MSNs) [4].

Organic nanoparticles have already been used extensively in the clinical setting. However, adjusting the size and geometry to maintain the organic aggregates below a certain size threshold is challenging, especially in living systems [5]. In contrast, inorganic nanoparticle-based drug carrier systems have more tuneable surface modification and adjustable size strategies. In addition, inorganic nanoparticles exhibit inherent physicochemical properties to transfer irradiated energy to heat or toxic radicals for high temperature, photothermal or photodynamic therapy for solid tumours, and are not susceptible to the environment in the body. Due to these unique properties, inorganic nanoparticles play a significant role in many fields, such as sensing, bioimaging and drug loading [6] and are receiving increasingly more attention from researchers and undergoing extensive research in pharmacy. Inorganic nanoparticles are difficult to degrade in vivo and cause damage to normal human cells, which has limited their usage in pharmacology, but their broad application prospects in the pharmaceutical field should still be recognized.

AuNPs are one type of inorganic nanoparticle which play an important role in pharmacology. When adjusting to a suitable size and shape, AuNPs are also safe and have low phototoxicity. Additionally, they show a unique photophysical property named localized surface plasmon resonance (LSPR), which is caused by the free electron resonance of the free electron cloud’s resonance of its metal lattice when irradiated by resonant frequency photons [7]. Depending on their unique optical versatility and other characteristics, such as tuneable size and shape, convenient surface modification, biocompatibility, flexibility in fabricating different morphological forms, and ease to functionalise with active ligands via Au–S chemical bonds, have made AuNPs as promising drug carriers in cancer theranostics [8–10].

To better employed AuNPs in pharmacology, some surface modification, such as conjugation with polyethylene glycol (PEG) or surface-capped mesoporous silica nanoparticles, should be applied [10]. Through these changes, an ideal nanoparticle drug delivery system, which is inert or undetectable in the plasma while are activated after accumulating at the targeted site to be recognized by tumour cells, could be...
realised [11]. Due to the development of inorganic nanoparticles in pharmaceutics, AuNPs are becoming a desired approach either in stand-alone therapeutics or combined with drugs as carriers for therapeutics [12]. From this perspective, we summarize the current state of knowledge of how inorganic nanoparticles, especially AuNPs, are applied in pharmacology and how AuNPs are optimized to contribute to drug carriers (Figure 1).

Inorganic nanoparticles

Inorganic nanoparticles are particles of metal oxide or metallic composition with an inorganic core and organic shell. Some inorganic nanomaterials have been used for diagnosis, treatment and cancer immunotherapy [13]. Common inorganic nanomaterials applicable in biomedical applications include MSNs, AgNPs, CNTs, QDs and AuNPs (Figure 2) [14].

**MSNs**

MSNs are a kind of nanomaterials with pore channels synthesized by silica particles [15]. MSNs with a pore size ranging from 2 nm to 50 nm are employed as excellent candidates in drug carrier and biomedical applications, which is attributed to their unique properties [16,17].

First, the properties of their large surface area and pore volume supplied promising vehicle character for drugs or biological molecules to be loaded into the pore channels. The tuneable pore size and controlled mesoporous structure facilitate the dissolution of drugs and then prevent the crystallization of drugs. Moreover, the exterior and interior surfaces of MSNs are easily modified due to the high density of silanol, which may provide better control of drug loading and release kinetics. Surface modifications may improve the capability to gain hybrid multifunctional smart silica nanoparticles. When equipped with hydrophobic materials, the stability of drugs, especially water insoluble drugs can be extensively improved. The premature release of drug can be limited, and the delivered amount of drug can be elevated.

In addition, controlled and targeted transporting manner can be designed and modified to improve the therapeutic efficacy and minimize the adverse and toxic effects [17]. Finally, MSNs have been increasingly employed as ideal carriers due to their high chemical, thermal and mechanical stabilities over broad ranges of pH and temperature under physiological conditions [18–21].

**AgNPs**

AgNPs are particles composed of silver atoms, usually ranging in size from 1 nm to 100 nm [22]. Many synthetic methods have been developed for the manufacture of AgNPs [23]. The reduction of silver salts by reducing agents is the most common synthetic method [24]. For example, Sood et al. used Ocimum sanctum leaf extract both as reducing agent and as stabilizer. Then, they added the extract to silver nitrate solution dropwise under certain reaction conditions and AgNPs were synthesized [25].

Due to remarkable optical properties, AgNPs have broad application prospects in biomedical and diagnostic testing [26]. Local surface plasma resonance properties of AgNPs are commonly used for electromagnetic enhancement of spectral signals or for ultrasensitive detection of chemicals. For example, Cholula-Díaz et al. used AgNP colloids to detect ascorbic acid in SERS experiments in aqueous solution [24]. In addition, AgNPs have antibacterial effect. Therefore, AgNPs can be used in the preparation of various antibacterial drugs [25,27].

**CNTs**

CNTs are tube skeleton material mainly composed of carbons [28]. The arrangement of atom in a CNT is in a hexagonal form like that of graphite [29]. These atoms in a CNT aggregated to CNTs can be obtained by applying various methods, such as laser ablation method [30].

CNTs are widely applied in biological detection and analysis based on their remarkable intrinsic physical properties.

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Figure 1. The skeleton of this review.
such as superior optical, electrical and thermal properties [28,29,31,32]. Apart from taking advantage of their intrinsic physical properties, one can also benefit from the presence of their inner hollow core and a chosen drug can be simultaneously encapsulated in their interior, while for the biocompatible, dispersible and targeting purposes, the external walls can be modified with various organic materials, such as peptides and substrates. The inner cavity of CNTs can serve as a nanocarrier that preserves the cargo from oxidation or any other unwanted interaction of cargo molecules with biological milieu [33–35]. For example, Zhao et al. [36] designed 300 nm PEGylated multi-walled CNTs which possessed a high doxorubicin (DOX)-loading capacity with high cumulative release within 24 h and a low premature leakage of 10%.

**QDs**

QDs are a kind of nanosized small semiconductor particle equipped with a heavy metal core-shell and an organic coating. Due to their high optical properties and potential toxicity. QDs are not typically used for drug delivery but are generally used as bioimaging agents to monitor certain substances, such as ATP, Cu^{2+}, glutathione (GSH) and prostate protein antigen [37–44].

Graphene quantum dots (GQDs), as an evolutionary graphene relative to semiconductor QDs, show booming applications and potential prospects in terms of bioimaging and photovoltaic devices [45]. Especially in the field of biomedical, GQDs are demonstrated to be excellent nanodrug carriers with the advantage of high stability and low toxicity [46].

**AuNPs**

AuNPs are tiny particles of gold with diameters ranging from 1 to 100 nm. The colour of AuNPs varies from red to purple depending on the size. Typically, the controlled size and shape of AuNPs is synthesized by various physical, chemical and biological means.

Chemical synthesis usually uses chemicals and solvents, such as the citrate reduction method using gold chloride and trisodium citrate [47]. Bio-nanoparticle synthesis is a relatively new, eco-friendly and promising area [48]. Many plants have shown potential for the preparation of AuNPs and microorganisms are also capable of participating in the enzymatic reduction of gold ions by secreting many enzymes to prepare AuNPs [49]. AuNPs have generated interest from different research fields, especially in the biopharmaceutical fields. Ease in preparation and modification, precision in controlling the physicochemical properties of particles, unique tuneable optics, unique electronic and SPR characteristics are distinctiveness properties of AuNPs [48,50]. These clear physical and chemical properties make AuNP a great scaffold for many applications in therapeutics, diagnostics, biomarkers, drug carrier and imaging [51].

In addition, AuNPs of various shapes (nanospheres, nanorods, nanoshells and nanocages) have been synthesized. Different shapes of AuNPs usually have various properties, which characterize specific functions in numerous fields. The following is a detailed description of the different shapes of AuNPs.

**Different shapes of AuNPs**

AuNPs with different morphologies could result in distinct uses in biomedicine. The possibility to tune the LSPR towards the near-infra-red region and improve the drug-loading capacity by adjusting the shape of AuNPs is one of the reasons why AuNPs are widely used [51]. The morphologies of AuNPs include gold nanospheres, gold nanorods, gold nanocages and so on [52]. They play an important role in pharmacology (Figure 3).

**Gold nanosphere**

Gold nanospheres (AuNSs), which have received the most attention due to the ease of their synthesis, are AuNPs in the form of spheres [53]. The most common method for synthesizing spherical AuNPs is based on the nucleation and growth process of citrate reduction of HAuCl₄ in aqueous solution [54]. However, this approach has certain limitations such as cytotoxicity and long duration. Many researchers have designed a green method to synthesize AuNSs. For example, Trouiller et al. designed a simple, non-physical method to synthesise small well-defined spherical AuNPs, without any additional reducing chemistry, to achieve rapid synthesis in 30 min [55].

Because of the low cytotoxicity, ease of synthesis, spherical shape with uniform size, good biocompatibility, high tissue permeability and relatively simple surface modifications,
spherical AuNPs are very popular [56]. To efficiently deliver therapeutic agents to human lung cancer cells, Wang et al. produced gemcitabine (Gem)-loaded AuNSs. The results showed that the obtained nanospheres had good biocompatibility, had low cytotoxicity and showed obvious effects, and the efficiency was significantly higher than that of free drugs [57].

**Gold nanorod**

Gold nanorods (AuNRs) are a kind of elongated AuNPs, which can usually be synthesized by the seed-mediated growth method [53]. The preparation method usually consists of mixing the prepared seed solution and the growth solution at room temperature [58].

Due to the anisotropy of AuNRs, two independent SPR bands have attracted considerable research interest. Transversal band and longitudinal bands appear in the visible and near infra-red region (NIR), respectively [59]. The SPR band in the NIR region of AuNRs is converted into heat via the photothermal effect, causing photothermally induced high temperatures and irreversible damage to cancer cells [60,61].

Furthermore, AuNRs are known to exhibit greater fluorescence enhancement than Au nanospheres. Since the LSPR band of AuNRs can be adjusted to match the spectrum of the red/NIR dye, it is more effective in improving the fluorescence of red and NIR dyes to achieve optimal fluorescence enhancement. AuNR-based nanostructures with enhanced red/NIR emission are excellent in bioimaging [62].

**Gold nanocage**

Gold nanocages (AuNCs) are a kind of AuNP that have unique hollow interiors and porous well structures. A common method of preparing AuNCs is a template etching method which still requires further improvement to avoid collapse of the gold shell after removal of the core [63]. Easy preparation of AuNCs by displacement reaction using HAuCl₄ [64–66].

Small molecules can be encapsulated in AuNCs, and the pores on the surface are suitable for small molecules to enter the nanocage. Therefore, AuNCs can be applied to a target site [67]. For instance, Park et al. devised a drug carrier system that contains an anticancer drug in its core loaded with a phase change material in its sheath. The heat generated by NIR causes the phase change of the load to melt, resulting in a rapid release of drug molecules [68]. In addition, functional groups can easily modify their surface to specifically interact with the biological system. Tumour-targeting molecules can readily bind to AuNCs to enhance their tumour accumulation.

The surface plasmon resonance of the NIR region of AuNCs generates heat through the photothermal effect, which causes photothermal-induced hyperthermia and destroy cancer cells. Thus, AuNCs could be drug carriers and photothermal conversion agents. The combination of NIR light-triggered drug release and photothermotherapy shows excellent therapeutic efficacy [69].

**Application of AuNPs**

AuNPs are suitable for several biomedical applications due to their relative inertness in biological environments. Furthermore, AuNPs can be used as drug carriers since several methods can be used to readily modify the AuNP surface for attachment of a ligand, drug or other targeting molecule [70]. Previously, AuNPs have made great progress in biological sensing, diagnosis and cancer therapy.

**Biological sensing and diagnosis**

AuNPs have been widely used to develop various biosensors for molecular diagnostics. The optical properties of AuNPs allow for the expression of intense colours under light, which can be adjusted by varying their size and shape [71]. AuNP-based biosensors may play an important role in future clinical diagnosis [72]. For instance, Pannico et al. reported that AuNPs can be used as a surface-enhanced Raman spectroscopy (SERS) sensor for in vivo cellular uptake and localization. SERS experiments have shown that tumour cells take up a significant number of nanoparticles compared to normal cells. This largely different behaviour may be used for diagnosis [73].

In addition to AuNP-based optical biosensor, there are non-optical biosensor, including electrochemical biosensors and piezoelectric biosensors [74–77].

**Cancer therapy**

**Chemotherapy**

AuNPs can also be applied in pharmacology as drug carriers due to their many unique properties [78,79]. In addition, there are some specific morphologies of AuNPs such as gold nanocages, hollow gold nanoshells and hollow nanosphere [80]. Thus, pores on the surface of the hollow nanostructures
are suitable for small molecules to enter and to encapsulate small molecules. For example, Xin et al. synthesized Al(III) phthalocyanine chloride tetra sulphonic acid (AlPC₄₄) delivery systems with AuNRs to improve the limited PDT effect. AlPC₄₄, which binded to AuNRs, had a significant anticancer effect, since AuNRs are not only fit for AlPC₄₄ delivery but also exhibit enhanced singlet oxygen production effects and photothermal effects directly induce apoptosis [81].

Khutale and Casey developed a gold nanoparticle drug carrier system for intracellular delivery of DOX, which is composed of a multifunctional gold nanoparticle-based drug delivery system (Au-PEG-PAMAM-DOX) [82]. The combination of DOX and the AuNP drug carrier system can provide a promising platform for intracellular delivery of various anticancer drugs. Ren et al. designed a synergistic delivery system using NIR responsive hollow AuNPs to realize sequential release of inhibitor/DOX [83].

**Photothermal therapy**

AuNPs convert light energy (NIR) into heat due to their unique surface plasmon resonance, which causes high temperatures. Therefore, photothermal conversion therapy, called plasma photothermotherapy, has emerged because it can be used to ablate cancer cells [84]. Singh et al. synthesised a biodegradable liposome gold nanoparticle for photothermal therapy. The AuNPs enabled the system to specifically absorb NIR light (780 nm) by SPR and convert light energy into heat. The photothermal transduction efficacy of Au-liposome nanoparticles showed an obvious temperature rise, causing irreversible cell damage [85].

Drug carriers and photothermal therapeutics also require AuNPs to participate in the synthesis. Therefore, AuNPs could be designed for chemo-photothermal synergistic therapy [86]. Chuang et al. synthesized a nanocomposite coated with human serum albumin (HSA) showing promising combined effects of photothermal and chemical treatments without adverse side effects [87].

**Optimization of AuNPs in pharmacology**

Over the past few decades, immense amounts of research have proven that the drug delivery process of AuNPs could be summarized in the following order: An ideal nanoparticle drug delivery process should be inert or undetectable in the plasma but activated upon tumour site accumulation to be recognised by tumour cells [11]. However, when AuNPs are used as drug carriers, there are many things that can be improved. It is well known that the in vivo manner of various AuNPs is affected by their surface and size [88]. To make AuNPs function better as drug carriers, various optimisation strategies of AuNPs have been developed. The following aspects will be described: prolongation in the plasma, enhancement in targeting accumulation, improvement in cellular uptake and the control of intracellular release (Figure 4).

**Prolonged plasma circulation**

AuNPs as drug carriers have been restricted by their short circulating half-lives in the bloodstream. It has been reported that such limitation is due to the clearance of AuNPs by macrophages. The clearance is accepted to be primarily attributed to opsonin adsorption on the surfaces of AuNPs, leaving them susceptible to cells of the mononuclear phagocyte system [89]. Therefore, a number of studies on long-circulating AuNPs developed in the past have concentrated on decreasing their clearance by macrophages and the reticuloendothelial system (RES) [90–92] (Figure 3).

**PEGylation**

In regard to prolonging time in the plasma, PEGylation (poly(-ethylene glycol) conjugation) immediately comes to mind [93]. PEGylation is a maturation strategy for improving the plasma circulation of AuNPs [94], which provides a steric barrier against conditioning [91,95]. For instance, when DOX was loaded onto hybrid nanoparticles (HN-DOX), in vivo pharmacokinetics indicated that HN-DOX had a much longer cycle time than free DOX. The long cycle times in the plasma can be attributed to effective PEG shielding [96]. However, it has been thought in recent years that PEG will experience accelerated plasma clearance after repeated administration [97,98].

**Modification of zwitterionic materials**

Here, zwitterionic materials can replace PEG to extend the cycle time of the nanoparticles without triggering an immune response [99]. Zwitterions, which are promising ligands for the fabrication of non-interacting nanodrugs, are totally neutral under physiological conditions and can minimise the interaction with biological compositions, such as proteins and cells, and decrease their clearance [100]. Moreover, compared to PEGylated AuNPs, it is reported that AuNPs that have undergone zwitterionic surface engineering exhibited prolonged plasma circulation [98,99]. Thapa et al. designed a mixed droplet containing zwitterionic chitosan (ZC), gold-graphene oxide (Au-GO) and DOX which is very beneficial for prolonging the plasma circulation time of the drug. Furthermore, zwitterionic AuNPs of different types may have different effects [101]. Guével et al. found a significant increase in the plasma half-life using bidentate zwitterionic molecule AuNPs compared to common zwitterionic (GSH) AuNPs [102]. In addition, adjusting the size of the AuNPs is also a great way to prolong the plasma circulation of AuNPs [103].

**Changing size**

Generally, smaller AuNPs have longer plasma circulation time due to the fact that larger AuNPs were more easily cleared by macrophages and the RES [104–106]. Terentyuk et al. selected 15, 50 and 160 nm AuNPs and measured their respective plasma concentrations. The results indicated that 15 nm AuNPs showed significant capacity during long circulation time and concentrations in the plasma were higher than those of 50 and 160 nm AuNPs 24 h after injection [107].
In addition, it was reported that size seemed to be a major factor in the biodistribution in the body and metabolism whether the AuNPs were PEGylated or not [88,105]. Thus, strategies for prolonging the plasma circulation of AuNPs need to consider a combination of surface functional attachments and sizes.

Enhancement of targeting accumulation

In some cases, AuNPs can accumulate in a non-disease site, such as the liver and spleen, after which treatment effectiveness and particle toxicity become problems [108]. Thus, enhancing targeting accumulation of AuNPs becomes a significant issue. There are two ways to deal with this matter.

PEG-decorated Au nanocarriers

One of the two ways is that PEG-decorated Au nanocarriers can passively target the lesion location via an improved permeation and retention (EPR) mechanism [109,110] (Figure 3). However, PEG-modified Au nanocarriers have been questioned for their inability to accumulate in several cancerous tissues. Then, use of the other approach is generally used to enhance targeting accumulation of Au nanocarriers. As known to all, specific receptors overexpressed on the surface of certain diseased tissues can be selectively identified by binding the corresponding targeting agent to the surface of the nanoparticles [111,112].

Recognizable targeting ligands

Hence, the other way is to modify the surface of Au nanocarriers with identifiable targeting ligands, such as lectins or antibodies, low molecular weight molecules such as folate moieties or targeting peptides [113].

Human galectin-3 (Gal-3) recognizes and binds to the β-D-galactoside moiety, which is a particularly attractive lectin. Aykac et al. envisaged a dually functionalized AuNP loaded with the anticancer drug methotrexate and multiple copies of the β-D-lactose unit as a targeting ligand for Gal-3 and β-CD macrocycles as an encapsulating moiety for methotrexate and yielded satisfactory results empirically [114].

AuNPs bind to cancer cell surface receptors and have been used to specifically bind cancer cells [115]. Penon et al. synthesized a gold nanoparticle combined with an anti-erbB2 [111]. Then, they concluded that the anti-erbB2 antibody was

Figure 4. Delivery process of optimized gold nanocarriers in vivo. (a) Two types of optimized gold nanocarriers with drugs. (b) Ideal delivery process of optimized gold nanocarriers with drugs in vivo: prolonged blood circulation, enhancement of targeting accumulation, improvement of cellular uptake and control of intracellular release.
an ideal ligand targeted to breast cancer tissues and realised the PDT treatment of AuNPs [116].

Small molecules, such as peptides can be used as an alternative to targeting agents. Targeting peptides have significant advantages over antibodies, such as lower cost, lower conditioning and lower immunogenicity [117]. Peptides are specific for their target tissues [118]. A structure in which drug was loaded onto the AuNPs and peptides were conjugated holds great potential to increase the target efficacy of chemotherapeutic drugs [49]. For example, the coupling of the gold compound to the targeting peptide (PVCAM-1) enhanced its targeting of the inflammatory synovium during cycling [49].

Folate receptors are overexpressed in malignant tumour sites [119]. Therefore, using folic acid as a targeted ligand can increase accumulation of AuNPs. There are plenty of studies demonstrating that AuNPs conjugate with folic acid to enhance targeting capability [120]. For instance, AuNR, DOX and folic acid were polymerized by a series of physical chemical reactions. The experimental results showed that the FA targeting Au-HNTs-DOX@BSA had decent accumulation around cancer tissues. In addition, there are also many targeting ligands that are designed according to the specific structure of targeting locations [113,119,121,122], such as the strong binding affinity of bisphosphonate ligands for calcium [113]. The discovery or synthesis of more targeting ligands through the special structure of the target site is indispensable to the enhancement of targeting accumulation of AuNPs.

**Improvement in cellular uptake**

The cellular uptake of AuNPs is found mainly to be related to size [123], shape [124], surface charge [125], surface functionality [126], and the interaction of these characteristics. Therefore, improving cellular uptake of AuNPs must start from the above factors (Figure 3).

**Resizing**

Among these influencing factors, size can be the major contributor to cellular uptake [127]. However, there is no consensus on maximizing the optimal particle size for cellular uptake levels [128]. For example, Wong et al. observed that cellular uptake of AuNPs is inversely proportional to particle size [127]. While Yue et al. believed that the cell uptake of 50 nm and 40 nm AuNPs is higher compared to that of 13 nm AuNPs [124]. Moreover, Kumar et al. reported that AuNPs with sizes of 18 nm and 80 nm showed higher gold absorption than those with a size of 40 nm [129].

**Shape modification**

The shape of AuNPs is also an important factor affecting the rate of cellular uptake [130]. It is well known that shapes of AuNPs include gold nanospheres [53], gold nanorods [53], gold nanostar [131], gold nanocage [63] and gold nanoshells. For instance, rod-shaped gold nanoparticles displayed lower cellular uptake efficiency compared to gold nanospherical particles, with the percentage of cellular uptake decreasing with the increase in the aspect ratio [132]. Similarly, cellular uptake of nanospheres increased on a higher scale compared with nanostars [124]. Xie et al. synthesized three different shapes of AuNPs, stars, rods and triangles and then concluded that the cellular uptake efficiency of AuNP was, in order from lowest to highest, stars, rods and triangles [133].

**Surface charge**

In addition to sizes and shapes of AuNPs, many studies have shown that the surface charge of AuNPs played a critical role in modulating cellular uptake [134]. The surface charge of AuNPs includes positively charges [135], negatively charges [136] and neutral charges [137]. Positively charged surfaces preferentially increase cellular uptake due to the negatively charged surface of the cells. For example, Li et al. synthesized AuNPs modified by carboxyl, amine and hydroxyl functional groups with different surface charge treated human bone marrow-derived mesenchymal stem cells (hMSCs) [138]. The results indicated that positively charged AuNPs promoted high uptake of hMSCs. In the same way, Bai et al. reported that the AuNPs significantly reduced cellular uptake with a high-surface negative-charge density [139]. We can infer that the surface charge of targeting cells influences cellular uptake to a certain extent. Liu et al. investigated the cellular uptake behaviours of AuNPs on both positively and negatively charged surfaces in cells. The results indicated that the choice of surface charge of AuNPs to improve cellular uptake should take targeting cell properties into account [134].

**Surface functionality**

In addition, surface functionality of AuNPs is also a significant element in improving cellular uptake. Generally, surface modification of AuNPs to improve cellular uptake is similar to the targeting ligand. Yi et al. reported that the glucose-installed targeted AuNPs showed higher cellular uptake compared to glucose-unbound AuNPs [140]. By the same principle, bovine serum albumin is a commonly used ligand as well which can bind to glycoprotein present on the targeting cell membrane [141,142]. Moreover, some studies implied that the interaction of sizes, shapes and surface functionalization can influence cellular uptake of AuNPs [124,125]. In summary, improving cellular uptake depends not only on changes in sizes, shapes and so on but also on the nature of the cells.

**Control of intracellular release**

Ideal drug release of AuNPs should be designed as such a model that drug released from the drug delivery system at physiological conditions is negligible, but drug release was significantly increased and sustained at a specific milieu [143].
**pH control drug release**

The pH of plasma and normal tissue are neutral, while that of the extracellular environment of the tumour is acidic (pH ≈ 6.5–7.0), and the acidity of the endosomes and lysosomes is greater (pH ≈ 5.5–4.5) [144]. In the past several years, many pH-responsive drug carrier systems have been synthesized to initiate drug release in cancer cells due to this particular acidic environment of the tumour site [145]. For example, some acid-sensitive bonds such as amide bonds [146–148] and hydrazone bonds [149,150], are introduced into the AuNPs due to their cleavage in an acidic environment. Khutale et al. designed a new drug carrier system. Under physiological conditions, DOX released in this system is negligible. In contrast, due to amide bond cleavage between DOX and dendrimers, much DOX was continuously released from the drug carrier system after 96 h at pH 4.0 [82]. Wei et al. built the pH-responsive nanodrug Au-DOX. At physiological pH (pH = 7.4), the Au-DOX nanocomposites are relatively stable. At pH = 4.5 (similar to the intracellular pH of cancer cells), rapid release of DOX could be observed due to the rapid rate of hydrolysis of the hydrazone bond [151].

**GSH environment**

GSH is more abundant in tumour cells compared to extracellular cells; thus, an intracellular drug release system is developed based on the combination of GSH-responsiveness [152]. Drug-conjugated AuNPs, which are typically modified by a number of molecular thiol-terminated PEG drugs via a thiol-Au covalent bond, are promising effective nanodrugs; then GSH can be applied to regulate gold-thiol-mediated drug-release [143]. For example, tiopronin-conjugated AuNPs (TPN@GNPs) have GSH-reactive drug release properties and have been developed for the treatment of acute liver injury [153].

**Temperature-controlled release**

AuNPs can be modified with heat-sensitive materials to realise drug release [154]. For example, Lajunen et al. [155] developed liposomal drug carriers which were formulated using a heat-sensitive composition with star- or rod-shaped AuNPs. AuNPs convert light energy into heat and release it into the lipid bilayer, causing an increase in the local temperature that causes double leakage of the liposome and triggers drug release. Phase change material (PCM) is a material with a large latent heat of fusion that melts and solidifies at a certain temperature. There are three forms of PCM: liquid-gas, solid-solid, and solid-liquid. Solid-liquid PCM is now widely used in basic research and practical application [156]. The PCM which is applied in a drug release system should have good biocompatibility and a precise critical solution temperature with a slightly higher melting point than physiological temperature [157]. Lauric acid [158], fatty acid and 1-tetradecanol [156] are frequently used PCMs. Poudel et al. [159] reported a new strategy in which hollow silver-gold nanoshells are encapsulated in hollow mesoporous silica as an effective platform for the release of anticancer drugs. The mesopores were blocked with the heat-sensitive PCM lauric acid to achieve drug-controlled release by photothermal action. In addition, there are also many dual-responsive drug release systems such as pH/near-infra-red dual-triggered drug release [160], GSH/near-infra-red dual-triggered drug release [161], GSH/pH dual-triggered drug release [162] and other responsive drug release systems [162,163].

**Conclusion**

AuNPs have a wide range of applications in current medical and biological research, including diagnostics, therapy, biosensors, immunoassay, targeted delivery of drugs, and bioimaging. In this review, we have described the feature of inorganic nanoparticles and introduced AuNPs, including their shapes, their application in pharmacology and improvement in the drug delivery process. In recent years, little research has investigated the potential of AuNPs to act as stand-alone therapeutic agents. Thus, AuNPs should undergo some surface modification to play an important role in the drug delivery process.

**Disclosure statement**

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