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Gold-core silica shell nanoparticles application in imaging and therapy: A review

André F. Moreira[a,1], Carolina F. Rodrigues[a,1], Catarina A. Reis[a,b,1], Elisabete C. Costa[a], Ilídio J. Correia[a,c,*]

[a] CICS-UBI — Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, 6200-506 Covilhã, Portugal
[b] FCT-UNL — Faculdade Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal
[c] CIEPQF — Departamento de Engenharia Química, Universidade de Coimbra, Rua 13 Silvio Lima, 3030-790 Coimbra, Portugal

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ABSTRACT

Nanomaterials have assumed a prominent role in biomedical field during the past years. Particularly, the gold-core silica shell nanoparticles present unique physical and chemical properties that make nanodevices appealing for theragnostic applications. The gold core characteristic X-ray attenuation, surface enhanced raman scattering and tunable absorption in the near-infrared region supports the applicability of these systems in X-ray, photoacoustic and thermal imaging as well as in photothermal and photodynamic based therapies. Additionally, the inclusion of the silica shell stabilizes the gold core, protecting it from premature degradation and aggregation, and also provides additional cargo capacity for therapeutic molecules. Further, both silica and gold are described as biocompatible, inert and nontoxic materials. In this review, an overview of the gold core-silica shell nanoparticles applications in nanomedicine is provided, highlighting the different particle shapes and their application in bioimaging and therapy. Further, the basics of the gold core-silica shell nanoparticles synthesis procedures, general properties, and biosafety are also described.

1. Introduction

In the last two decades, the nanomedicine field has been experiencing an unprecedented expansion with the development of novel nanoparticles designed for improving the diagnosis, monitoring and treatment of several diseases such as cancer [1,2], Alzheimer [3,4] and Parkinson [5,6]. With that in mind, remarkable efforts have been made for assuring the reproducible synthesis of nanomaterials with controlled morphology, surface charge and composition [7,8]. Furthermore, these advances in nanomedicine also resulted in nanoparticles with improved biocompatibility and specificity towards the target tissues [9–11]. Despite of liposomal- and micelle-based nanoparticles present nowadays an increased application in clinical practice [12], inorganic nanoparticles also possess exciting properties that can prompt their application in the clinic [13,14]. Among the wide variety of inorganic nanoparticles reported in the literature, gold nanoparticles assume an increased relevance when biomedical applications are envisioned.

Gold is one of the least reactive known metals and presents resistance against oxidation and corrosion [15]. Further, gold nanoparticles present unique optical properties, due to the surface plasmon resonance phenomenon (*i.e.* the light scattering or absorption in response to the free electrons synchronized oscillation when the particle is exposed to light at their resonance wavelength). The production of gold nanoparticles with different shapes (*e.g.* rods, cubes, triangles, cages, stars or others) has allowed the tuning of the particles' resonance wavelength to the near infra-red (NIR) region, a radiation range where the human body presents almost no absorption (reviewed in detail by Refs. [16–19]). This control over gold nanoparticles surface plasmon resonance has been exploited to apply them as bioimaging and/or photothermal agents [20–25].

Despite the wide scope of applications of gold nanostructures, they also display some limitations that can impair their utilization in biological systems. Gold nanoparticles can interact with compounds containing thiol or disulfide groups through the formation of relatively strong gold-thiolate bonds [26]. This well-known gold binding affinity or the establishment of non-specific interactions triggers the biomolecules adsorption on the nanoparticles' surface [27,28]. Particularly, the adsorption of proteins can induce changes on the nanoparticles' surface properties and thus on their interaction with the human body (*e.g.* nanoparticles uptake, blood circulation time and biocompatibility)

* Corresponding author. CICS-UBI - Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal.
E-mail address: icorreia@ubi.pt (I.J. Correia).
[1] Authors contributed equally to this work.

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[29,30]. Moreover, gold nanoparticles during bioimaging or therapeutic applications can be exposed to high-energy laser pulses and a portion of the incident radiation is converted into heat [31]. In turn, the generated heat can lead to the gold nanoparticle reshaping (*i.e.* melting) and consequently loss of their optical properties [32,33]. Therefore, the post-synthesis modification of gold nanoparticles is highly desirable for surpassing these limitations as well as potentiate gold-based nanoparticles application in nanomedicine [34–36]. From the wide number of materials used in the literature (*e.g.* dextran, poly(isobutylene-alt-maleic anhydride)-graft-dodecyl and poly(ethylene glycol) (PEG)), silica arises as one of the main coating alternatives for gold nanoparticles [37,38]. Nanoparticles produced with this material have been reported as stable colloidal suspensions, chemically inert, biocompatible and ease to modify with different functional groups [39,40]. Further, silica derivatives such as mesoporous silica possess a large surface area and pores that can act as reservoirs for bioactive molecules aimed for therapeutic purposes [1,40]. Such features allow the encapsulation of poorly soluble compounds and simultaneously confer them protection from premature degradation and clearance from the human body [41,42]. In addition, the inclusion of the silica shell also enhances the colloidal stability of gold nanoparticles when they are in contact with biological fluids or irradiated with a specific radiation [43,44]. Silica is also optically transparent to the NIR radiation, often used in photothermal therapy (PTT), which indicates that the silica shell does not compromise the therapeutic capacity of gold-based PTT agents [45,46]. Therefore, the multifunctional potential of gold core-silica coated nanoparticles provides an ideal platform for theranostic modalities combining therapeutic, targeting, and imaging functions (please see Fig. 1).

In this review, a comprehensive overview of the gold core-silica shell nanoparticles applications in nanomedicine is provided. Moreover, the different particle shapes and their application in bioimaging and therapy are summarized, as well as the particles synthesis procedures, general properties, and biosafety.

2. Gold core-silica shell nanoparticles

During the past years, a huge effort has been performed to allow the fabrication of gold core-silica shell nanoparticles in a scalable, controlled and reproducible manner [47–49]. Generally, the production of these nanoparticles can be achieved through two main steps (please see Fig. 2), i) the production of the gold core with the desired size and shape and ii) the synthesis of the silica shell [48,50,51]. The gold cores can be synthesized using different synthetic routes to yield gold nanoparticles with distinct sizes and shapes, as extensively reviewed in Refs. [52–55].

Briefly, gold cores are usually prepared by inducing the reduction of gold salts and consequent gold nucleation and growth in the presence of a stabilizing agent, such as trisodium citrate and cetyltrimethylammonium bromide, to prevent the particles aggregation [53]. The sphere is one of the most stable shapes and can be obtained when the gold core synthesis is performed under thermodynamically controlled conditions [56]. Alternatively, to obtain non-spherical gold-cores the synthesis process must be fine-tuned to favor an anisotropic growth of the gold core by using surfactants that block some of the growing directions (*e.g.* cetyltrimethylammonium bromide) [57,58], halides [59,60] or weak/mild reduction agents [61,62]. Up to date, the rod-like shape remains as one of the most explored gold nanostructures. In general, gold nanorods are produced by using a seed mediated growth methodology [51,63], where small spherical gold spheres (*i.e.* seeds) are synthesized by nucleation and then they are added to a solution denominated of “growth solution”, which is composed of a gold salt (*e.g.* chloroauric acid), silver nitrate and high concentrations of cetyltrimethylammonium bromide to induce the rod-shaped growth [63].

Gold nanostars and nanocages have also been used for biomedical applications. Gold nanostars are also produced by using a seed mediated growth method, however, the particle growth occurs in the surface of poly(vinyl pyrrolidone) coated gold seeds in the presence of dimethylformamide [64]. On the other hand, gold nanocages are prepared by using sacrificial silver nanocubes which are exchanged by gold through a galvanic replacement process [65].

Subsequently, the silica coating of the gold cores is accomplished by using the classic Stöber method or its derivations [48,49]. During the synthesis procedure, the silica precursor (*e.g.* tetraethyl orthosilicate) molecules will start to condensate around the gold core originating the silica shell. The thickness of this silica shell can be tailored by fine-tuning the reaction time and reagent concentrations [48]. In these systems, the optical and electronic properties can be adjusted by varying the shape and size of the gold core as well as the thickness of the silica shell [66,67]. On the other side, the silica coating allows the stabilization of the gold nanostructures as well as the encapsulation of drugs, dye molecules, or other imaging agents either via physical adsorption or covalent attachment [68,69]. Further, silica presents an increased surface area that can be functionalized with antibodies, targeting moieties or even stealth agents [42,69]. Therefore, gold core-silica shell (AuMSS) nanoparticles with different core shapes (*i.e.* spheres, rods, stars and cages) have been employed, in different reports in the literature, for therapeutic and bioimaging applications (please see Table 1) [70–72]. AuMSS nanoparticles have been explored to mediate single or combinatorial therapeutic approaches based on drug delivery, PTT and photodynamic therapy (PDT) [25,73–76]. The possibility to combine different therapeutic functions into one nanoparticle presents benefits, since it improves the therapeutic efficacy, due to possible synergic interactions, and minimizes the side-effects originated

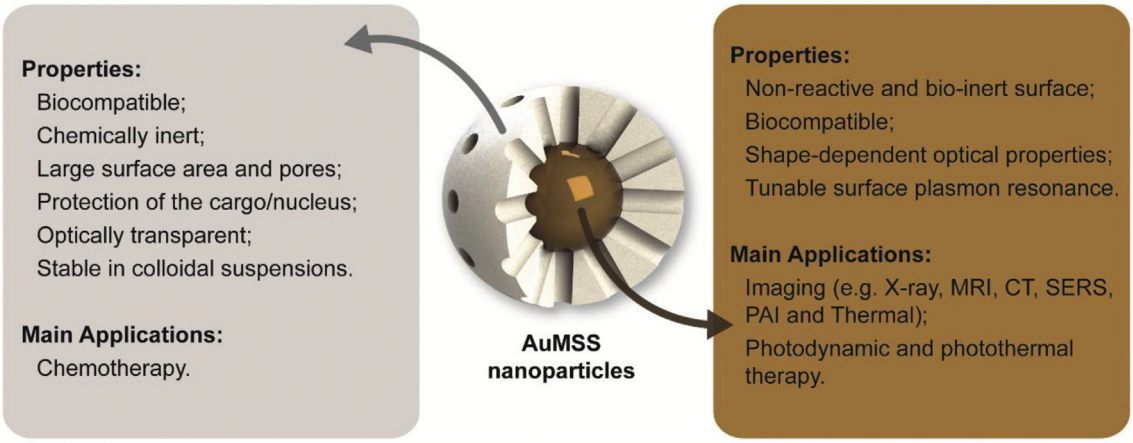

Fig. 1. General properties and main applications of the AuMSS materials.