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Introduction

Sreekanth Thota[1,2,3] *and Debbie C. Crans*[3]

[1] *Fundação Oswaldo Cruz – Ministério da Saúde, National Institute for Science and Technology on Innovation on Neglected Diseases (INCT/IDN), Center for Technological Development in Health (CDTS), Av. Brazil 4036 – Prédio da Expansão, 8 Andar – Sala 814, Manguinhos, Rio de Janeiro 21040-361, Brazil*
[2] *Universidade Federal do Rio de Janeiro, Programa de Desenvolvimento de Fármacos, Instituto de Ciências Biomédicas, Av. Carlos Chagas Filho, Rio de Janeiro, RJ 21941-902, Brazil*
[3] *Colorado State University, Department of Chemistry, Fort Collins, Colorado 80523, USA*

1.1 History of Metal Complexes

1.1.1 Introduction

Pharmaceutical science, which studies the design, action, delivery, and disposition of drugs, is an important field in drug research. Humans have made several sincere attempts for the search of new drugs in order to cure and control different diseases. Although possible remedial measures are available at present to tackle any disease, scientists are increasingly trying to find superior and more effective drugs [1]. Over the last 50 years some "wonder drugs" have played a crucial role in diminishing the global burden of infectious diseases. New drugs are constantly being screened for their potential biological properties. Among the category of new drugs that are receiving much attention are metal-based drugs [2]. Precious metals have been used for medicinal purposes for at least 3500 years. Among them, gold has played a crucial role in a variety of medicines in China and Arabia [3].

1.1.2 Metal Complexes

Medicinal inorganic chemistry is in the early days of its development, although there are now a significant number of clinical trials involving metal compounds or other agents that interfere with metabolic pathways for metals, both for therapy and for diagnosis [4]. In chemistry, metal complexes are nothing but reactions between metals and ligands [5]. Biomedical applications of several metal coordination compounds in recent years have provided a substantial contribution to the augmentation of more impressive diagnostic and therapeutic agents [6]. Metal coordination compounds and metal ions are known to effect cellular processes in a dramatic way [7]. Metal coordination complexes offer biological and chemical diversity that is distinct from that of organic drugs.

Metal Nanoparticles: Synthesis and Applications in Pharmaceutical Sciences,
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1.1.3 Metal Complexes in Medicine

In the ancient history of medicine, extraordinarily, many metal-based drugs played a crucial role as anti-infective agents. The increasing medicinal application of metals and metal complexes day by day is gaining clinical and commercial significance [8]. The development of metals containing anticancer drugs has been in the 1960s with the synthesis of Platinum compounds. Cisplatin is one of the most extensively used antineoplastic drugs, specifically for the treatment of ovarian and testicular cancers [9, 10]. The success of cisplatin and its analogs has accelerated a resurgence of inorganic medicinal chemistry and the search for complexes of other precious metals [Ru, Va, Zn, Cu, Ag, Gold, Pd] with interesting biological properties [11–17]. Among them, particularly ruthenium compounds have attracted significant attention with two compounds, namely, NAMI-A and KP1019, advancing through clinical trials [18]. Many precious metals and metal compounds have succeeded in the clinic over the last few decades. Platinum compounds are the most extensively used chemotherapeutic agents, silver compounds have been useful as antimicrobial agents, and gold compounds are used widely in the treatment of rheumatoid arthritis. Scientists have been investigating over the past 25 years several metal-based compounds and such return of interest in metal-based drugs can be witnessed in several recent articles [19–24].

1.2 Nanotechnology

1.2.1 Introduction

In today's world, nanotechnology is a relatively new field, but its structural nanometer dimensions and functional devices are not new, and in fact, these materials have much significance. In recent years, we found a plethora of literature explaining the recent advances in nanotechnology [25–33]. Nanotechnology has the potential to provide novel, paradigm-shifting solutions to medical problems. Nanotechnology, which has been defined as the engineering and manufacturing of materials at the atomic and molecular scale, offers exclusive tools for developing safer and more efficient medicines (nanomedicines), and provides several potential advantages in drug formulation and delivery. Nanotechnology refers to an emerging field of science that includes preparation and development of various nanomaterials. Nowadays, nanomaterials are widely used in many fields including biomedicine, consumer goods, and energy production [34–37]. The purpose of nanomaterials in biotechnology combines the fields of material science and biology.

1.2.2 Development of Nanotechnology

In recent years, disparate products of nanotechnology have played a key role in adding a novel armamentarium of therapeutics to the pipelines of pharmaceutical industries. The nanotechnology fever we are experiencing now began when the

United States launched the National Nanotechnology Initiative [38], the world's first program of its kind, in 2000. Nanotechnology usage may possibly achieve many advantages: (i) improved delivery of poorly water-soluble drugs; (ii) targeted delivery of drugs in a cell- or tissue-specific manner; (iii) drugs transcytosis beyond the tight endothelial and epithelial barriers; (iv) improved delivery of large macromolecule drugs to intracellular sites of action; (v) co-delivery of multiple drugs or therapeutic modality for combination therapy; (vi) improvement in drug delivery through visualization of sites by combining therapeutic agents with imaging modalities [39]; and (vii) real-time read on the in vivo efficacy of an agent [40]. Nanotherapeutics has the potential to actively target tumors, increasing the therapeutic effectiveness of a treatment while limiting side effects. This improved therapeutic index is one of the great promises of nanotechnology [41].

1.2.3 Nanotechnology in Medicine

In pharmaceutical trade, a new molecular entity (NME) that exhibits significant biological activity but meager water solubility, or a very terse circulating half-life, will likely face significant challenges in progress or will be assumed undevelopable [42]. Nanotechnology may revolutionize the rules and possibilities of drug discovery and change the landscape of pharmaceutical industries. In medicine, nanotechnology application may be referred to as nanomedicine that explains various intriguing possibilities in the healthcare sector. The major current and promising applications of nanomedicine include, but are not limited to, drug delivery, *in vivo* imaging, *in vitro* diagnostics, biomaterials, therapy techniques, and tissue engineering [28]. In oncology, nanomaterials can enable targeted delivery of imaging agents and therapeutics to cancerous tissues; nanoscale devices enable multiplexed sensing for early disease detection and therapeutic monitoring. The

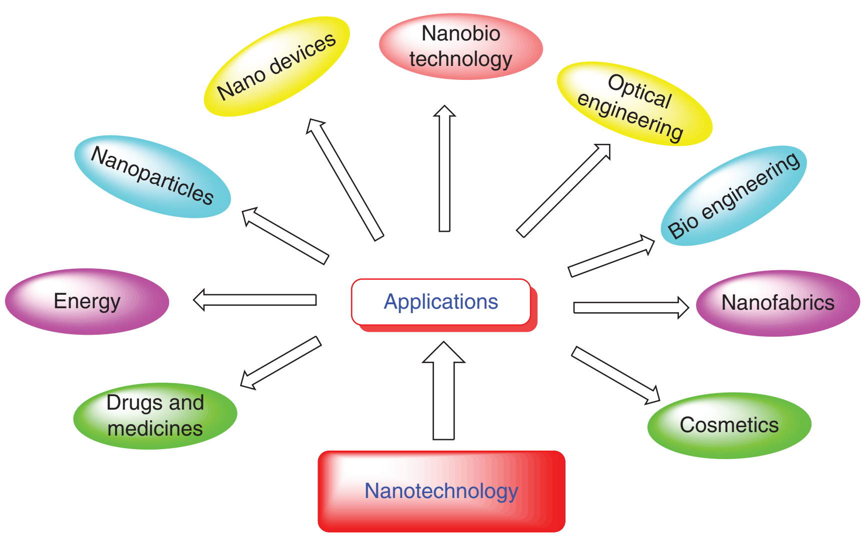

Figure 1.1 Applications of Nanotechnology.

drug delivery field application of nanotechnology is widely expected to change the landscape of pharmaceutical and biotechnology industries in the foreseeable future [40, 43–45]. Nanotechnology attracts scientists because of a wide variety of applications, which includes drugs and medicines, energy, nanoparticles, nanodevices, nanobiotechnology, optical engineering, bioengineering, nanofabrics, and cosmetics (Figure 1.1).

1.3 Nanoparticles

1.3.1 Introduction

Any intentionally produced particle that has a characteristic dimension from 1 to 100 nm and has properties that are not shared by non-nanoscale particles with the same chemical composition has been called a nanoparticle [46, 47]. Nanoparticles demonstrate a particularly useful platform, describing exclusive properties with potentially wide-ranging therapeutic applications [48]. The enormous diversity of nanoparticles was described (Figure 1.2). Nanoparticles made of polymers (NPs) are of particular interest as drug delivery systems because of their synthetic versatility as well as their tunable properties (e.g., thermosensitivity and pH response). Nanoparticles offer exciting prospects for improving delivery, cell

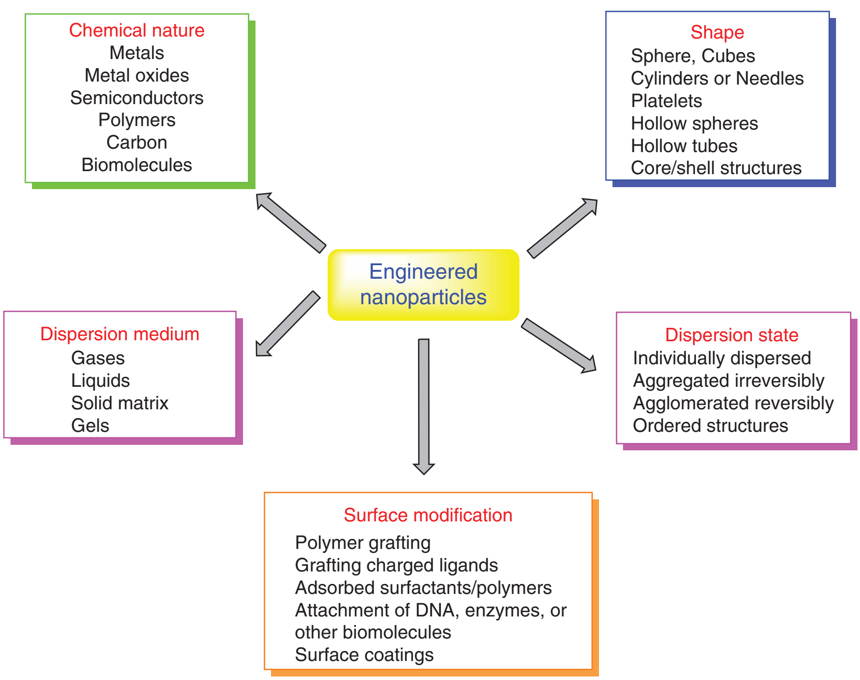

Figure 1.2 Various features of engineered nanoparticles.

uptake, and targeting of metallodrugs, especially anticancer drugs, to make them more effective and safer. Transition metal nanoparticles synthesis has been extensively investigated in recent years because of its many unique physical (electronic, magnetic, mechanical, and optical) and chemical properties. Nanoparticles are often in the range 10–100 nm and this is the same size as that of human proteins.

1.3.2 Development of Nanoparticles

The primary intention in designing nanoparticles as a delivery system is to manage particle size, surface properties, and release of pharmacologically active agents in order to obtain the site-specific action of the drug at the therapeutically optimal rate and dose regimen [49]. Nanoscale particles developed using organic molecules as building blocks have been widely examined for drug and gene delivery. For example, polymer, polymersome, and liposome constructs for controlled release of proteins and polymeric micelles, macromolecules, and long-circulating polymeric nanoparticles are in different stages of clinical and preclinical development [29]. In the 1960s, Bangham and Horne produced the first nanoparticle-based platform for medical application based on liposomes. In the following decades, nanoparticles gathered more scientific and general interest and developed rapidly [50].

1.3.2.1 Liposome-Based Nanoparticles

Liposomes are small sphere-shaped particles, formed by one or more phospholipid bilayers that can be made from cholesterol and natural phospholipids. Depending on the design, they can range from 10 nm up to micrometers [51].

1.3.2.2 Polymeric Nanoparticles

Polymeric nanoparticles might be the most widely used nanoparticle carriers and have been extensively investigated in this regard. They could be formed by biodegradable, biocompatible, and hydrophilic polymers such as poly (D,L-lactide), poly(lactic acid) (PLA), poly(D,L-glycolide) (PLG), poly(lactide-*co*-glycolide) (PLGA), and poly-(cyanoacrylate) (PCA) [52–54].

1.3.2.3 Metal Nanoparticles

Metal nanoparticles are attractive materials in many fields ranging from physics (hard or soft magnetic materials, optics, microelectronics) to catalysis [55]. Noble metal nanoparticles with spherical shape and sharp size distribution such as gold were formed progressively by the chemical reduction method supported by ultrasonic device [56]. The capability to integrate metal nanoparticles into biological systems has had a huge impact in biology and medicine. Some noble metal nanoparticles have been attracting huge interest from the scientific community owing to their awesome properties and diversity of applications, which include gold and silver [57]. The three important properties of gold nanoparticles that have attracted intensive interest are that they are easily prepared, have low toxicity, and readily attach to molecules of biological interest [58].

1.3.3 Nanoparticles in Science and Medicine

Over the past few years nanoparticles have emerged as a key player in modern medicine. Nanoparticles have significance ranging from being contrast agents in medical imaging to being carriers for gene delivery into individual cells [59]. Nanoparticles represent an extraordinarily charming platform for a distinct array of biological significance. In cancer therapy there has been an enormous amount of interest in the preparation and significance of nanoparticles [60]. NPs can easily be conjugated with biomolecules, and thus, they can act as labels for signal amplification in biosensing and biorecognition assays. These strategies can significantly enhance detection sensitivity; even a single molecule can be detected in an ideal case [34]. The exclusive properties and adequacy of nanoparticles emerge from a peculiarity of attributes, including the similar size of nanoparticles and biomolecules such as polynucleic acids and proteins. Additionally, nanoparticles can be formed with a huge range of metal and semiconductor core materials that convey favorable properties such as fluorescence and magnetic behavior [40]. Nanoparticles can afford significant improvements in traditional biological imaging of cells and tissues using fluorescence microscopy as well as in modern magnetic resonance imaging (MRI) of various regions of the body. MRI technique is extensively used in modern medicine, specifically in the diagnosis and treatment of most diseases of the brain, spine, and the musculoskeletal system. Superparamagnetic iron oxide (SPIO) nanoparticles can also be used to visualize features that would not otherwise be detectable by conventional MRI [61]. Several such SPIO nanoparticles have been used in modern MRI [62, 63]. Nanoparticles have already been used for a wide range of applications both *in vitro* and *in vivo*. Nowadays various nanoparticles are used in biomedicine. A list of some of the applications of nanomaterials in biology or medicine is given below:

1) Drug and gene delivery [64–75]
2) Fluorescent biological labels [76–80]
3) Detection of proteins [81]
4) Biodetection of pathogens [82]
5) Medical imaging [83]
6) Probing of DNA structure [84]
7) Tissue engineering [85]
8) Phagokinetic studies [86]
9) Tumor destruction via heating (hyperthermia) [87]
10) Separation and purification of biological molecules and cells [88]
11) Cancer cell imaging [89]
12) Treatment of cancer [26, 69, 90, 91].

Some of the potential applications of nanoparticles are in antibacterial creams and powders (Ag), biolabeling and detection (Au, Ag, quantum dots), bone growth promoters (hypoxyapatite ceramics), cancer diagnostics and targeted drug delivery (magnetic nanoparticles, metal nanoparticles), biocompatible coatings for implants, cell, receptor, antigen, and enzyme imaging (quantum dots), MRI contrast agents (Fe_2O_3, Fe_3O_4), gene delivery (CNT), and dental composites [92].

The most widely used nanoparticles in everyday life and in research laboratories are silver nanoparticles (AgNPs). This huge degree of AgNP commercialization has been due to their significant antimicrobial and antifungal properties. Many manufacturers claim that potential AgNP toxicity is minimal or nonexistent. In medical practice silver nanoparticles are commonly used as an integral part of both surgical and nonsurgical equipment such as wound dressings, bandages, and catheters [93].

1.4 Nanotechnology-Supported Metal Nanoparticles

Drug loading into NPs can be achieved by three techniques: (i) covalent attachment to the polymer backbone, (ii) adsorption to the polymer surface, or (iii) entrapment in the polymer matrix during preparation of the NPs. In most cases metallodrug polymer systems have been formulated by covalent attachment of the metal-based drug to the polymer backbone. Drug delivery system efficiency can be optimized; for that, carriers must be sufficiently small for the impressive diffusion of the drug-carrier composite into the targeted cellular environment. Hence, metal nanoparticles, owing to their small size, can be excellent candidates as drug carriers [49, 50]. There has been a great deal of development in the field of gold-nanoparticle-mediated cancer therapy *in vitro* and *in vivo* in the last 10 years. In recent years, several metal nanoparticles have been widely used [94–107].

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