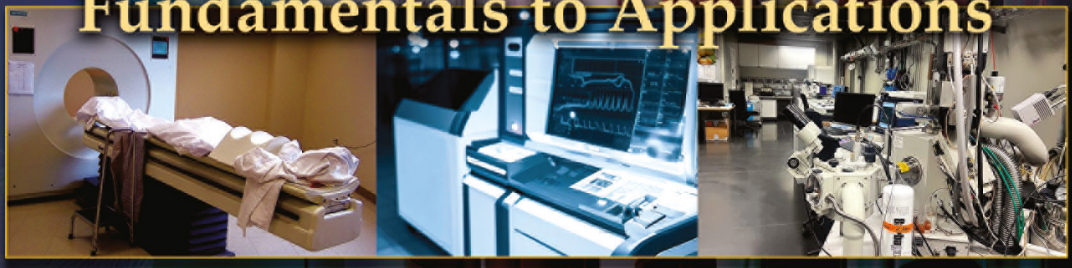
NANOSCIENCE AND NANOTECHNOLOGY FOR SMART PREVENTION, DIAGNOSTICS AND THERAPEUTICS

Fundamentals to Applications



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Preface

Within the realms of biomedical research and technology, the implementation of nanoscience and nanotechnology is acquiring an ever-increasing amount of significance. The scope of this multidisciplinary scientific field includes studies of the nanoscale behavior of chemistry, physics, materials science and engineering, biology, and medicine. Fascinatingly, nanoscale dimensions with a high surface-to-volume ratio, simple surface modification, improved physicochemical stability, specialized optical properties, and targeted and controlled release capabilities can result in lower toxicity and higher efficacy, making them more appropriate for efficient smart prevention, diagnosis, and treatment. Further, nano-dimensional materials interact efficiently with biological functional molecules (such as proteins, nucleic acids, carbohydrates, lipids, and complexes) to answer numerous day-to-day difficulties that are related to a bio-medical theme. This is a significant advancement in the field. In addition, the impact that the nanomaterial has on optical, photothermal, electrical, electronic, and magnetic parameters paves the way for the development of smart and intelligent technologies. These technologies are based on external stimuli to combat preventive, diagnostic, and therapeutic issues in a commendable manner. This can be achieved by combining the nanomaterial's optical, photothermal, electrical, electronic, and magnetic parameters.

This book focuses on the fundamental features of various nanomaterials that are related to the development of biomedical technologies. These fundamental qualities are broken up into three parts: prevention, diagnostics, and therapeutics. When it comes to infectious diseases, prevention is of utmost importance. Highly advanced nanomaterials including silver, titanium, graphene-based filters, and copper nanoparticles are used to fight infectious illnesses. Once the symptoms have been recognized in the patients, through the use of effective and straightforward nanodiagnostic techniques, the diseases can be accurately localized in either a qualitative or quantitative manner. Nanodiagnostics tools currently dominate the field of biomedical diagnostics because of their high degree of accuracy,

low requirement for samples and reagents, user-friendliness, portability, and capacity to perform point-of-care (POC) applications. Nanomaterials are widely used in imaging due to many factors, including: their signal generation and amplification abilities; the ongoing development of reliant new imaging techniques, such as photoacoustic imaging and Raman imaging; their targeting potential, due to the possibility of functionalizing their surface with cancer-targeting moieties; their multimodality, since some nanomaterials can generate signals for more than one imaging technique); and their affordability.

The most notable area of focus in contemporary therapeutics is the investigation into numerous breakthroughs that have been made possible by applying nanotechnology in the treatment of site-specific cancers. In a similar vein, intelligent nanodrug delivery systems make it possible to improve medicine delivery at a particular point of care while simultaneously underrating the adverse effects that are associated with drugs and drug carriers. In the initial generation of nanocarriers, liposomes and straightforward polymers played important roles. Phospholipids are the building blocks of liposomes. Phospholipids have a hydrophobic tail and a polar head, and they can self-assemble into spheres with a diameter varying from tens to hundreds of nanometers. Liposomes are used to transport lipids throughout the body. Stealth liposomes are liposomes that have been functionalized with polyethylene glycol (PEG) to increase their half-life in circulation. Drugs that are either hydrophilic or hydrophobic can be delivered via liposomes. In most cases, the nanocarriers that are utilized in the process of drug delivery are functionalized by a PEG that has a molecular weight (MW) ranging anywhere from 1 to 40 kDa. This coating is useful for nanocarriers because it decreases the nonspecific interactions that nanocarriers have with serum proteins. These interactions flag nanocarriers for internalization by cells that are part of the reticuloendothelial system (RES). They become less immunogenic as a result, and cells inside the RES absorb them less specifically. As a consequence, their phagocytosis is reduced, which in turn leads to a prolongation of the nanocarriers' duration in circulation. PEG functionalization of nanocarriers can reduce the toxicity of the nanocarriers, as well as prevent them from clumping together. Examples of current nanocarriers include viruses, nanoparticles consisting of gold, magnetic nanoparticles, quantum dots, titanium dioxide, zinc oxide, and silica, graphene, carbon nanotubes and fullerenes, and hybrids of materials (such as lipid-coated or polymer-coated nanoparticles).

This book presents the fundamentals of nanomaterials and discusses the direct applications of nanomaterials to the biomedical sector. In addition, it explores the potential therapeutic applications of nanotheranostics in the

far future. We are deeply grateful to everyone who helped with this book and greatly appreciate the dedicated support and valuable assistance rendered by Martin Scrivener and the Scrivener Publishing team during its publication.

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Arun Thirumurugan
Muthuchamy Maruthupandy
Mercedes Guadalupe López Pérez
Shanmuga Sundar Dhanabalan

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Bio–Nano Interface Technology for Biomedical Applications

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Abstract

Nanoencapsulation protects biologically active compounds from deterioration due to system conditions such as oxidation, temperature, and pH changes, among other interactions that occur at the interface. Thus, biomedical applications of nanometric structures require the evaluation of a complex delivery system, in which the interactions that exist at the biomolecule–nanostructure interface, as well as their physicochemical properties, will determine the scope of the delivery system. A wide range of nanostructured materials exists. However, nanoencapsulation of bioactive compounds is a novelty. One advantage of nanoencapsulation is that nanostructures can be coated with biomolecules such as lipids, proteins, and polysaccharides, resulting in reduced surface energy and providing biological benefits to the organisms they interact with. It is essential to mention several challenges to implementing nanomaterials in biomedicine, among which toxicity and decreased efficacy stand out. These disadvantages occur mainly due to a lack of understanding of the interactions between nanomaterials and their biological environment. Currently, the use of nanomaterials is based primarily on the functionality of biomolecules. While nanomaterials are often designed to take advantage of the functionality of biomolecules, it is important to consider the potential

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impact of biomolecule–nanomaterial binding. Failure to account for such binding could lead to changes in the structure of the biomolecule, resulting in an altered or lost biological function of the compound. Additionally, binding could cause negative interactions between the bionanomaterial and the biological environment. The purpose of this chapter is to show the benefits of nanomaterials in conjunction with biomolecules in providing biological activity to help address various applications in the field of biomedicine, which will help to provide better and timely control of human health; as well as to identify the physicochemical properties of nanomaterials, which allow us to figure out what kind of interactions are involved at the bio–nano interface, due to their influence on the pharmacokinetic system stability associated with some parameters, such as the payload, release, and delivery efficiency. In addition, the effect of the physicochemical properties of nanomaterials and other factors that influence the structure, composition, and function of nanomaterial–bioactive compound complexes will be addressed, leading to a better understanding of the role of bioactive compound–nanomaterial interactions in controlling or predicting the biological fate of nanomaterials.

***Keywords*:** Nanoencapsulation, bio–nano interface, bioactive compounds, fluidized bed

1.1 Physicochemical Properties of Nanoencapsulated Systems

Some physical and chemical aspects of nanoparticle carriers and encapsulated drug molecules have a substantial impact on the basic attributes of nano-sized drug products, such as drug circulation, drug release from site-specific dosage forms, and absorption into bodily membranes. Particle size has a significant impact on the stability of nanoemulsion complex, it has been reported that decreasing particle diameter increases the bioavailability of encapsulated compounds [1, 2]. Therefore, these are chief elements that correlate robustly concerning the stability of the encapsulated system. As a result, the particle characteristics are required to have an appropriate delivery system [3]. Smaller particle sizes provide a greater mass transfer area, leading to an improved drug diffusion rate. Conversely, the rate of drug dissipation within bigger particles is lower, as they offer a reduced mass transfer surface area. Smaller particles, on the other hand, tend to agglomerate when kept and moved [1]. The size of the particles can range from 10 nm (nanoemulsion) to 1 mm (hydrogel droplets). Colloidal reliable encapsulated particles are typically spherical. In contrast, distinct forms, among them cylinders, deformed spheres, or irregular shapes, have

been noticed, influencing changes in the properties of particles and the interest compound delivery process [3]. The polydispersity of an enclosed system indirectly shows its aggregation status. Higher polydispersity implies the existence of aggregates, and this can cause destabilization and breakage in emulsion-based encapsulating systems. When the polydispersity of an encapsulating system is lower than 0.2, it is said to be monodisperse; nevertheless, polydispersity under the value of 0.5 is also regarded for pharmaceutical applications [3]. Droplet size is a relevant characteristic of emulsions because it promotes emulsion stability as droplet size and polydispersity decrease. The simplest and most common technique for measuring particle size and polydispersity is dynamic light scattering (DLS) [3]. It measures the intensity fluctuation of dispersed light. This fluctuation is the result of the interference of scattered light by individual particles just because of Brownian motion. The key advantages of DLS are its fast analytical speed, lack of calibration requirements, and excellent sensitivity to submicrometer particles [1]. Generally, the scattering angle is set to 90 degrees in most DLS techniques. For a monodisperse sample, the particle size should not change upon increasing the light scattering angle. Due to the extent of scattering at different angles being affected by particle size, the intensity-averaged mean particle size varies for polydisperse samples [3]. Now, the external charge of captured materials corresponds strongly with their dispersion stability. The zeta potential is frequently employed to analyze the surface charges of encapsulated materials, demonstrating the dominance of electrostatic forces indirectly [3]. In this connection, the use of the zeta potential makes it possible to visualize in encapsulations the influence of the charge of active molecules on the surface properties of the packing material. These enable the investigation of the stability of encapsulated materials besides the study of the electrostatic forces that occur between the active molecules and the encapsulating material. Colloidal stability is usually analyzed from the zeta potential of a nanoparticle. These measurements are performed with a zeta potential analyzer or zeta meter and allow prediction of the storage stability of various colloidal dispersions. To ensure stability and avoid particle aggregation, absolute zeta potential levels must be high, either positive or negative. The zeta potential measurements can be used to estimate the degree of surface hydrophobicity. The zeta (ζ) potential may provide additional details about the material enclosed in nanocapsules or coated on their surface [1]. A study on encapsulation used spray drying as a technique to obtain vitamin E-loaded nanocapsules using modified starches such as

octenyl succinic anhydride (OSA), with two purposes as emulsifier and barrier material. The ζ-potential, size distributions, mean particle size, and polydispersity index (PDI) of the initial and reconstituted nanoemulsions were measured via DLS [1]. The mean particle diameters ranged from 208 to 235 nm. Although the mean hydrodynamic diameters were quite different, the PDI and ζ-potential values were similar. Furthermore, the reconstituted nanoemulsions retained their original trim monomodal distribution with a modest increase in mean particle sizes, according to the authors. It is noteworthy that the reconstituted emulsions kept their polydispersity values (PDI < 0.250) and particle sizes (< 250 nm) indicating that the spray-drying technique had no effect on the nanoemulsions' properties [2]. As a result, the authors reported that OSA-modified starches with low molecular weight are efficacious in producing steady vitamin E nanocapsules for usage in pharmaceutical and food applications [2]. In another study, the authors evaluated the liberation of bioactive compounds with antioxidant and antihypertensive ability from packed extracts of Gulupa and Cholupa peel and seeds in an *in vitro* gastrointestinal model to simulate the process of digestion [4]. The encapsulates were constructed using wall material rice starch enzymatically modified. Characterization of the encapsulates revealed a range of electrical potential values between −6.34 and −6.66 mV. In addition, the DLS method determines the dispersion stability and disclosure PDI measurements from 1.33 to 1.51. The authors mentioned that the increment in the surface charge is due to the phenolic compounds on the particles. They observed that the wrapped extracts had an electronegative charge ζ-potential. As a result, the microcapsules showed high stability, so the encapsulates have an enormous amount of opportunities in the fields of food and medicine [4]. Advanced microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are used to determine the general properties of nanoparticles such as size, shape, and surface charge. Physical stability and in vivo distribution of nanoparticles are important qualities that are heavily influenced by average particle diameter, size distribution, and surface charge. The geometric shape of polymeric nanoparticles is determined using electron microscopy techniques, which is an essential consideration that influences their toxicity. The physical stability, dispersion dispersibility, and *in vivo* performance of nanoparticle drug delivery systems are all determined by their surface charge capability [1, 5]. SEM gives information about a sample's exterior shape, chemical composition, and crystalline structure through direct

visualization by the incident effect of the beam electron. Despite the benefits of morphology and size analyses, SEM provides only a limited amount of information on the particle size distribution and pores [1]. Most electrically insulating samples have a tiny layer of conductive substance on them, such as gold, carbon, other metals, or alloys. Usually, the most common conductive coating used for elemental analysis is carbon, although metallic overlays are more useful for high-resolution electronic imaging applications. With respect TEM operation principle, it is distinct from SEM, even though the type of results obtained are similar. The procedure for TEM samples is elaborate and takes considerable time. Surface features of the sample are obtained when an electron beam is incising on a thin slide of the sample, and the electrons interacting are transmitted through it [1, 5]. Finally, AFM offers some advantages compared to electron microscopy (TEM and SEM); it is based on the calculation force between the material surface and the probing tip. The approach is characterized by simple and easy sample preparation, quick picture capture, and appropriate finest resolution [1]. The analyzed particles need to be immobilized as a first step before viewing, in the case of larger particles is easy to get it due to their sedimentation rate. However, in small particles, the immobilization process faces troubles given to their Brownian motion. In this vein, sample dehydration can solved the troubleshooting, but at the same time, it may originate in cluster formation, lipid crystallization, shrinkage, and other unwanted changes. The main profit of AFM is its proficiency to image non-conductive samples without any specific covering treatment, which allows envisaging of careful biological and polymeric nano- and microstructures [1]. In one of the studies mentioned above [4], along with their characterization of encapsulates of Gulupa and Cholupa husk and seed extracts using modified rice starch as wall material, the authors employed SEM as part of the morphological characterization by obtaining images applied to an accelerating voltage of 12.5 kV and different magnification powers. They reported that the micrographs showed small sizes of 2 to 7 μm with a polyhedral arrangement and irregular shapes [4]. Moreover, it showed a broad range of particle aggregation, swelling, and solid heterogeneity appearance. In addition, some lack of sharpness was observed, with some granules showing barely rough surfaces. These characteristics could be attributed to the frequency of shrinkage due to water diffusion taking more, allowing the structures to shrink and deform to some extent. Therefore, these surface characteristics may be beneficial for improving the rehydration of powders [4].

Zhu *et al.*, evaluated nanoparticles (NPs) produced with xanthan gum and lysozyme, which contained two different peptides: TSeMMM (STP) and SeMDPGQQ (SHP), both containing selenium. TEM was used to notice the nanostructure of each sample. The images of the NPs were acquired at 15k magnifying power and 100 kV accelerating voltage. The NPs were observed to have a spherical morphology with a relatively constant state. NPs sizes were 153 nm somewhat greater than that of NPs-STP (145 nm) and NPs-SHP (148 nm). However, an important feature the authors comment on between TEM and DLS is that the particle size (hydrodynamic diameter in DLS) of NPs, NPs-STP, and NPs-SHP measured by TEM was lower diameter values than that measured by DLS analysis. This is due to sample conditioning in the course of TEM analysis, inasmuch as NPs, NPs-STP, and NPs-SHP are in lyophilized powder form measured, while by DLS average particle sizes measurements of NPs, NPs-STP, and NPs-SHP were in solution [6]. Meanwhile, in another study, Luo *et al.*, used ultrasound treatment to encapsulate within zein and gum Arabic (GA) the peptide TSeMMM (T) with selenium (zein@T/GA), which has immunomodulatory functions, that they obtained from selenium-enriched rice protein hydrolysates [7]. They studied the structural and morphology characteristics of three nanoparticle formulations: zein, zein, and gum Arabian (zein/GA); and the last was zein with gum Arabian and the peptide TSeMMM (zein@T/GA). SEM and AFM were used to determine micromorphological features. To this purpose, zein, zein/GA, and zein@T/GA nanoparticles were examined at 1 mg/mL concentration. The SEM results showed a smooth surface in zein nanoparticles with a majority of spherical shapes and a size distribution particle of 119 nm. Nevertheless, by SEM analysis were noticed aggregation and adherent of NPs. Thus, it was not possible to determine the size distribution. Therefore, information was complemented with the AFM technique. Determining, through 3D and 2D morphology images analysis the average nanoparticle size for zein/GA (90.9 nm) and zein@T/GA (43.7 nm). Moreover, the AFM results suggested that zein@T/GA NPs were smaller and showed less aggregation because the ultrasonic treatment generated changes in the zein structure. Which in turn resulted in the reduction of the nanoparticle size and improved stability of NPs in the system by the gum Arabian capacity to bind to zein via electrostatic interactions to generate more stable NPs. In this sense, the emphasis is on the stable and homogeneous system obtained via ultrasonic process to increase the interactions between the NPs components. The forces that influenced the zein@T/GA NPs formation were dipole-dipole attraction (hydrogen bond), electrostatic repulsion, and hydrophobic interactions. On the other hand, the encapsulation efficiency