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Nanotechnology and Nanomedicine: An Introduction and History

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Outline

Introduction

The ultimate example of nanotechnology can be seen in nature, where biological processes use polymeric nanostructures. When creating and integrating nanostructures into bigger frameworks, researchers take inspiration from supramolecular assemblages seen in nature [1]. The recognition of nanotechnological applications in medicine is credited to Richard P. Feynman, who initially introduced this interdisciplinary science to medical contexts during the 1950s [2]. The term "nanotechnology" was first employed by Norio Taniguchi in 1974 [3]. Nanoparticles, typically ranging in size from 1 to 100 nm, have some ambiguity concerning their upper size limit [4]. Historically, the earliest utilization of nanotechnology can be traced back to the 4th century AD, as evidenced by the Lycurgus cup displayed at the British Museum in London [5]. The cup's colour transforms from olive green to ruby red due to the presence of gold and silver nanoparticles.

Exploration of nanotechnology in medicine garnered attention from the 1990s onward, with substantial growth in the early 20th century, owing to groundbreaking advancements in microscopy techniques [6]. Nanotechnology stands as the most extensively researched field in contemporary drug discovery and delivery, marked by the escalating number of publications and patents from both the industrial and academic sectors worldwide [7]. Noteworthy milestones in the development of nanomedicines include the creation of high-resolution microscopes, such as the ultramicroscope in 1902, the immersion ultramicroscope in 1912, the transmission electron microscope in 1931, the field emission electron microscope in 1936, the field ion microscope in 1951, the scanning probe microscope in 1980, the scanning tunnelling microscope in 1981, and the atomic force microscope in 1982 [8].

While, the word nanomedicine can be defined as, “the design, development, and application of nanoscale materials, devices, and techniques for the molecular and cellular diagnosis, treatment, and prevention of diseases. Nanomedicine is a multidisciplinary field that combines nanotechnology and medicine.”

The potential for using nanomaterials in healthcare applications is highlighted by recent advancements in nanoscience. Pharmacological delivery involves the use of nanomaterials to protect pharmacological entities *in vivo* [9]. This ensures that bioactive molecules are consistently absorbed across biological barriers, hence limiting medication access to targeted areas [10]. Nanoparticles have been created using a variety of building elements, providing chances to alter the surface to alter stability, drug release, and targeting. The paper delves into the latest developments in stimulus-responsive polymeric nanoparticles, which have the ability to regulate drug release in reaction to either external or natural stimuli. It is especially concerned with the planning and development of these clever medication delivery systems [11].

The convergence of nanotechnology and medicine first emerged in the early 20th century, and their collaboration has endured to the present day. Nanomedicine initially manifested as simultaneous progress in numerous scientific domains, encompassing biotechnology, cell and molecular biology, chemistry, engineering, and physics [12]. Paul Ehrlich's groundbreaking work in targeted pathogen treatment and the introduction of the "magic bullet" concept through chemotherapy, epitomized by the creation of Salvarsan in the early 20th century, underscored the efficacy of precisely directed drug therapy [13]. This pivotal development significantly influenced the course of drug synthesis, emphasizing specificity. Subsequently, the field of biomaterials achieved significant milestones in the ensuing decades, characterized by research on biopolymers leveraging electron microscopy and X-ray diffraction techniques [14]. Additionally, Watson and Crick's revelation of the DNA structure in

the 1950s, accompanied by further explorations into the genetic code, illuminated the precise molecular mechanisms underpinning life processes. In the 1960s and 1970s, scientists at ETH Zurich commenced experimentation with nanoparticles for pharmaceutical applications [15].
Simultaneously, novel insights into cell membrane structure and function enhanced comprehension of membrane transport. Noteworthy examples include the examination of ion channels via the patch clamp technique. The identification of membrane receptors and ion channels unveiled the intricacies of highly regulated signalling pathways within the body, offering potential targets for specific pharmaceutical interventions [12]. Another significant milestone was the discovery of reverse transcriptase in 1970. As the field of immunology progressed, scientists delved into the complexities of the immune system, encompassing its cellular and molecular constituents. In the 1970s, the synthesis of monoclonal antibodies enabled precise targeting of molecules, opening doors to genetic engineering [16]. Scientists also gained a deeper understanding of the intricate nature of proteins as molecular machinery. Moreover, diagnostic tools like microchips and microsensors emerged, providing swift, cost-effective, and high-throughput screening capabilities [17].
Furthermore, to reach the nanoscale, various techniques can be employed, that may include, chemical synthesis, biological synthesis, and physical synthesis [18]. While there are two major classes that nanomaterial production can be divided into: i. Top-Down approach and ii. Bottom-Up [4]. In traditional methods, excess use of chemicals and energy caused the nanomaterials to be very expensive, while involving the production of various toxic by-products to the environment. To Overcome these issues, various new developments have been introduced, that we will talk about in this chapter and the coming chapters.

Approaches to Nanoscale

Basically, there are two major approaches to reaching nanoscale, i. Top-Down and ii. Bottom-Up. In Top-Down, the large materials are broken down into smaller and smaller pieces to reach the nanoscale range, while in Bottom-Up, the atoms or molecules are joined together to reach the nanoscale range. It is noteworthy that since the Bottom-Up approach deals with the manipulation of atoms and molecules, therefore, it needs specialized equipment that can manage the small range, resulting in it being expensive. Therefore, the Top-Down approach is employed on a larger scale, since it is inexpensive and easy as managing and controlling atoms and molecules is difficult. **Figure 1.1** shows the schematics of the Top-Down and Bottom-Up approaches.
For the methods, to achieve nanomaterials, there are various methods, that can be majorly classified into 4 classes. i. Chemical synthesis ii. Biological synthesis iii. Physical synthesis and biochemical (Green) synthesis.
In chemical synthesis, the materials and chemicals used, for the generation of nanomaterials/ nanoparticles, are analytical grade, for instance, Amin, S., generated ZnO nanoparticles using urea as a reducing agent [19]. Due to the chemicals used, the byproducts are quite toxic, and if expelled into the environment, they can cause severe damage to the ecosystem and environment, further, to elaborate, the toxic impacts and behaviour are still under consideration [20]. The advantages of chemical synthesis include strong control over the size and shape of nanomaterial [21], and also time-saving. While in biological synthesis, biological organisms i.e., fungi, algae, bacteria etc are employed to develop nanoparticles by reducing the metal salts that they are exposed to [22]. For instance, Haris, M., and group reported the synthesis of Iron Oxide (IO) nanoparticles using *Oscillatoria limnetica* [23], Kamal, A., et. al., reported the synthesis of Iron and Zinc Oxide bimetallic nanoparticles

using *Aspergillus niger* [24], while various bacterial species including *Pseudomonas aeruginosa*, *Pseudomonas stutzeri* and *Lactobacillus fermentum* have helped in the synthesis of varied shaped IO nanoparticles [25].

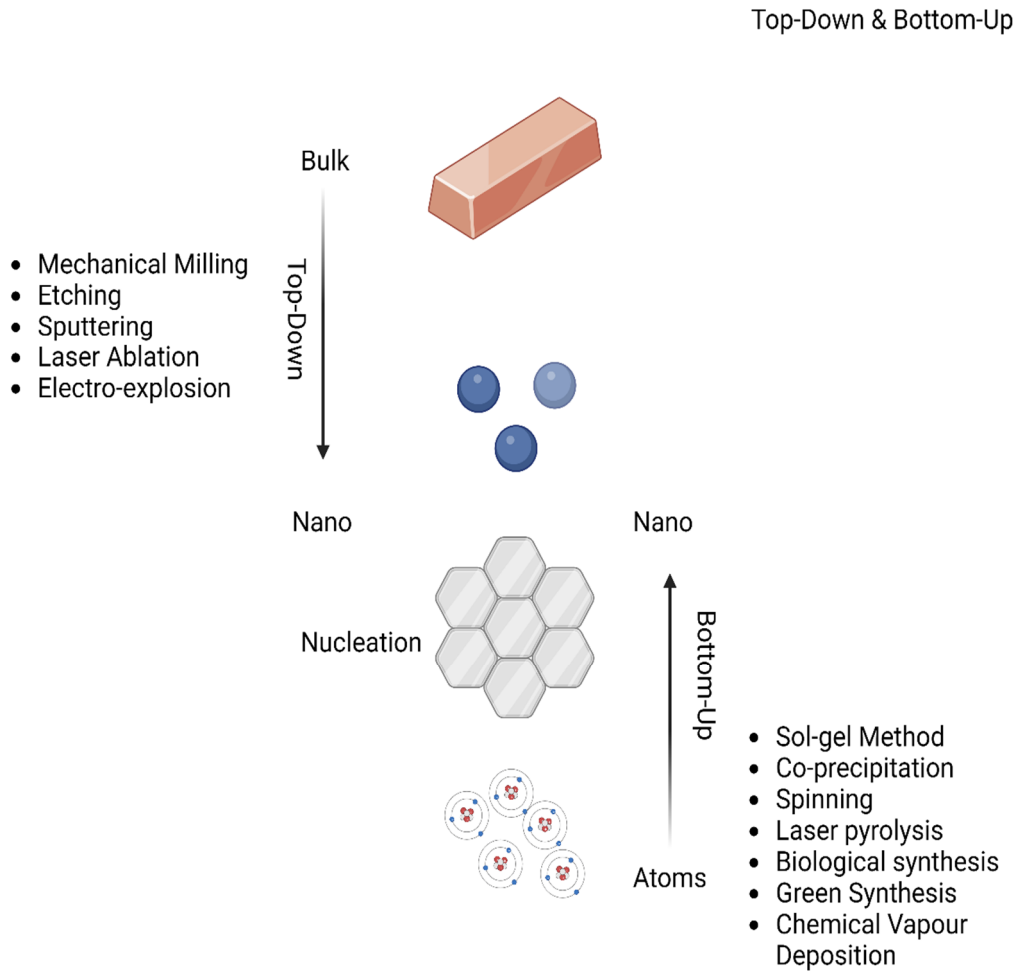

FIGURE 1.1
Top-down and Bottom-Up approaches and the methods used for the synthesis of nanomaterials.

This biological synthesis of nanomaterials is regarded as the safest approach for the synthesis of nanomaterials, but its major drawback is that it lacks control over the size and shape of nanomaterials, since each living organism behaves in a certain way, while another major drawback is low yield and long time. On the other hand, Physical synthesis employs the use of heavy and expensive equipment, for instance, Lévy, A., and group synthesized Gold (Au) nanoparticles using Laser Ablation [26]. This method uses highly energy-consuming equipment, while the lasers are dangerous to human eyes also. Furthermore, if the laser energy and target changes, the size may be

affected and for these types of synthesis, pure metal targets are required which tend to be very expensive, resulting physical synthesis methods to be very uneconomical.
The last type of method, that is currently in trend is biochemical or green chemical synthesis of nanomaterials. In this method, a plant is chosen to take extract either in water or in alcohol, while any part of plant, may it be its bark, stem, leaves, roots, fruits and/or flowers can be taken in either fresh or dried form. The extract serves as reducing agent, while the sugars and proteins inside the extract serve as capping agents, to stabilize the nascent nanoparticles, and avoid their agglomeration. **Figure 1.2** shows the schematics of a green synthesis method.

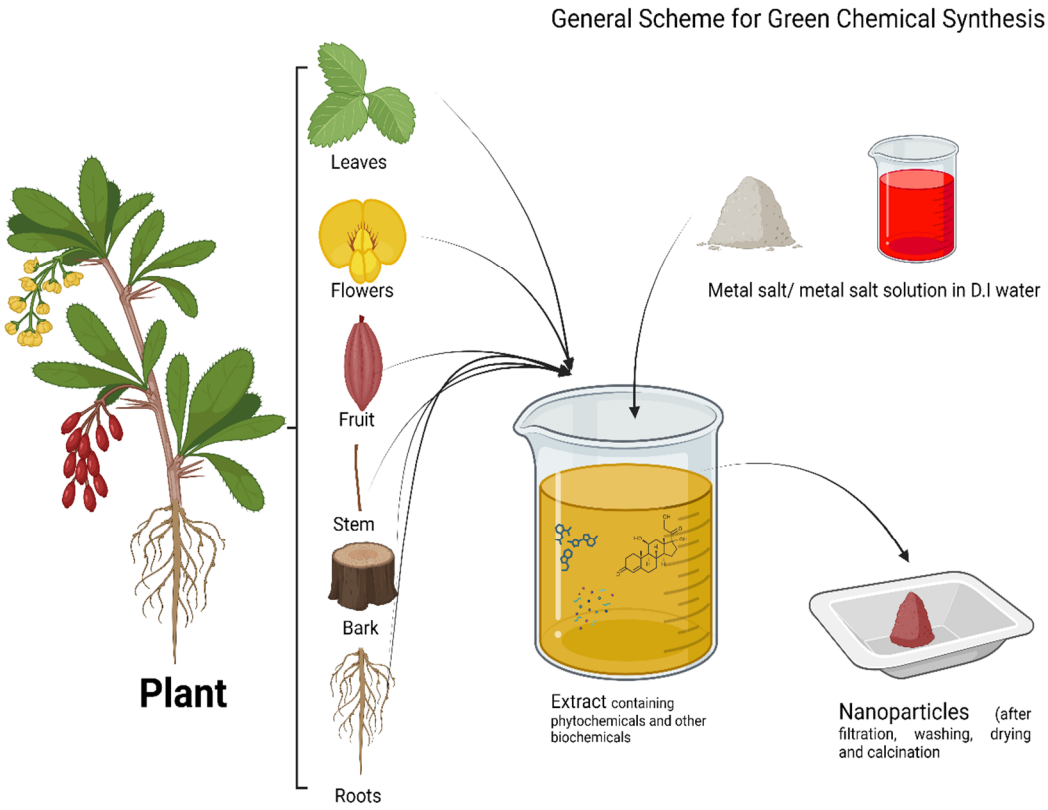

FIGURE 1.2
General schematics of Green Chemical Otherwise Known as Plant Driven Method for Synthesis of Nanoparticles.

For instance, Hassan, D., et. al., and Sani, A., et. al., reported the synthesis of IO and Nickel Oxide (NiO) nanoparticles, using plant extracts of *Callistemon viminalis*, respectively [4, 14]. The reported sizes of IO and NiO nanoparticles were measured to be 22nm and 16.5nm. the materials were investigated for their biomedical applications and their toxicity studies showed them to be very less toxic in lower concentrations, towards human macrophages in haemolytic studies. This methods for synthesis of nanomaterials have gained interest of scientific community in last decade, while this method is ought to be safer, economical and time saving, compared to other methods, but this

method is a bit time consuming compared to chemical synthesis, while is advantages are far more, compared to other synthesis methods.

Factors Impacting Nanoparticles

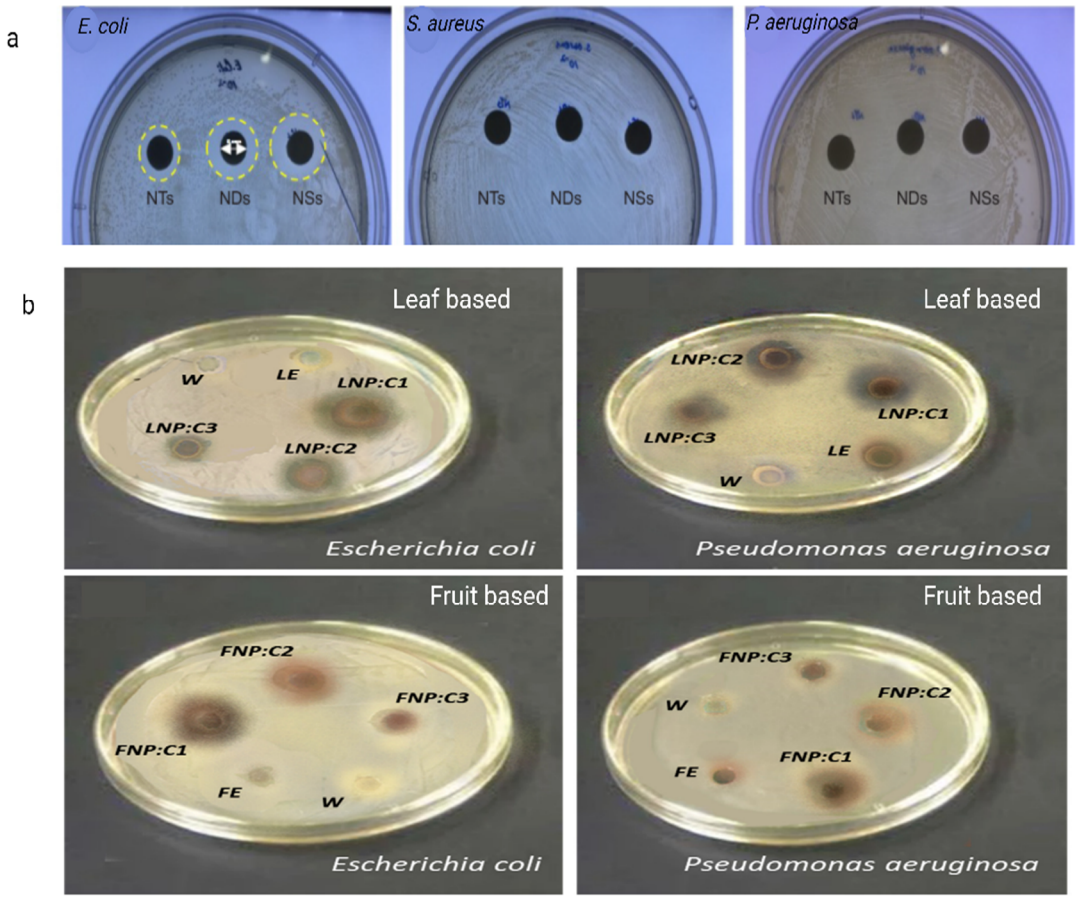

FIGURE 1.3
Impact of shape and size on anti-bacterial properties of Ag nanoparticles. a. shape-based [27] b. size based [28].

Once the nanomaterials are synthesized, they have a specific shape and size distribution. Shape and size play very important role in achieving the desired results for specific application that nanoparticles have been synthesized for, since with their alteration, the surface to volume ratio of nanoparticles changes. Nanomaterials are said to be nano, if at least one of their dimensions falls in between 1 -100nm size range, while there is a great discrimination in between scientists, as for some scientists, a nanomaterial can be in the size range of 1 - 1000nm. These sizes and shapes provide nanomaterials with dramatic properties, that make them suitable for various applications, including in the fields of medicine, electronics, optics, and materials and many more. To analyse the size and

shape of nanomaterials, there are various characterization techniques that are used i.e., X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), and Atomic Force Microscopy (AFM), while to analyse the elemental analysis and other band gap-based studies, Energy dispersive Spectrometry (EDS), X-Ray Photoelectron Spectroscopy (XPS), UV-Visible Spectrophotometry and other are used. We will discuss about these techniques in next topic. As discussed, the shape is a very important factor, in defining the potency of nanomaterials against the bacterial strains. For instance, Cheon, J. Y., and the group, synthesized Ag nanomaterials of various shapes. The shapes of the nanomaterials were sphere, disk and triangular. And the group tested the materials for their anti-bacterial properties against *P. aeruginosa*, *E. coli* and *S. aureus*. The group revealed the spherical shaped Ag nanoparticles lead the potency test against the bacterial strains followed by disk and triangular shaped Ag nanoparticles [27], as shown in **Figure 1.3(a)**. While other factors like size play an important role also. For example, Hassan D. et. al., synthesized, varied sized, pure hematite phased Iron Oxide nanoparticles using plant extract, and found the small sized IO nanoparticles were more magnetic compared to larger sized nanomaterials [4]. Whereas Malik, M., and group synthesized Ag nanoparticles suing leaf and fruit extracts of *Annona squamosa* (commonly known as sugar apple) plant with varied size and studied their biomedical potency against *E. coli* and *P. aeruginosa*. The group found that fruit extracted mediated synthesized Ag nanoparticles were larger than leaf extract mediated Ag nanoparticles. And found that leaf extract based Ag nanoparticles shows higher potency against the tested bacterial strains compared to fruit based [28], as shown in **Figure 1.3(b)**.

There are various factors that can cause these changes in size and shape of nanomaterials. Concentration of precursor salt [29] and/or the concentration of reducing agent [30] is one major actor that can impact the size and shape of the nanomaterials. Furthermore, the newly synthesized nanoparticles are very reactive and due to nucleation, it can combine with others and become larger in size and change their shape, therefore, another addition of a surfactant like chemical can help retaining the size and shape of the nanomaterial. **Figure 1.4** shows an example of nanoparticle with capping agent.

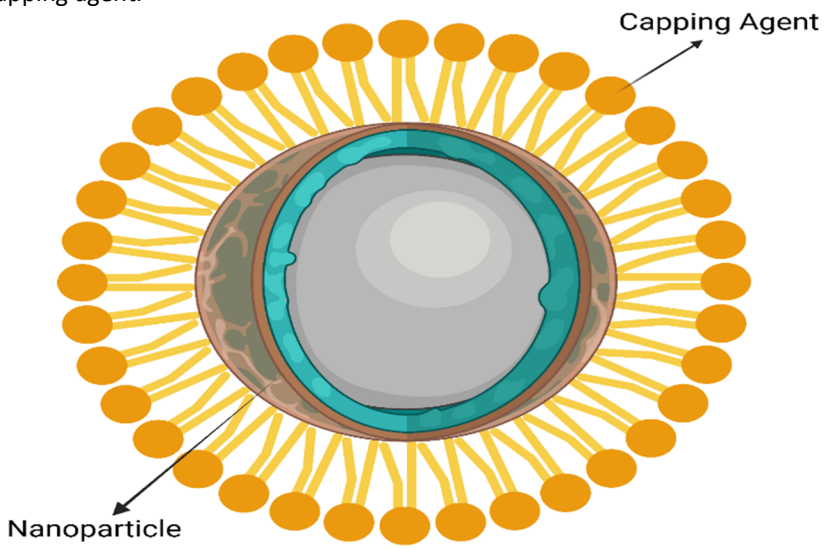

FIGURE 1.4
Nanoparticles and capping agent.

The capping agent has a part that is hydrophobic and other part that is hydrophilic. Hydrophobic part helps in maintaining the size and shape of the nanomaterials.

While another factor that can impact the size and shape of nanomaterials is the temperature and the pressure. By managing the pressure the size and shape of nanoparticles can be managed too [31]. While the altitude causes variation the in temperature, pressure and moisture of in the environment, due to which the altitude can also play a pivotal role in the genesis of nanoparticles, in simple words, the nanoparticles synthesized at sea level can have a specific size and shape and on the contrary, by following same method, the nanoparticles synthesized may vary in size and shape at higher altitude [32]. Furthermore, pH has its own impact on the size and shape of the synthesized material. As mentioned by the Marciniak, L. and group, pH has quite an impact on the size of Ag nanoparticles and explained that on acidic side of pH, specifically pH 6.0, the size distribution obtained was narrowest while at neutral pH (i.e., 7.0) the size distribution was widest, while as the group increased the pH from 8.0 to aa.0, the size distribution did become narrower with increasing pH thus showing decrease in polydispersity of Ag nanoparticles [33]. the results can be clearly seen in **Figure 1.5**, adopted from [33], published under Open access, Creative Commons Attribution CC BY 4.0. Although there can be various factors that can impact the size, shape and dimensions of the nanoparticles, including the size distribution, that is directly related to the physicochemical, electrical, magnetic, biomedical, optical and other properties of the synthesized nanomaterials, but researches can manage to obtain the required size, shape and even phase of the metal oxide or in case of polymeric nanoparticles their size and shape, according to their needs, by manipulating various optimization parameters.

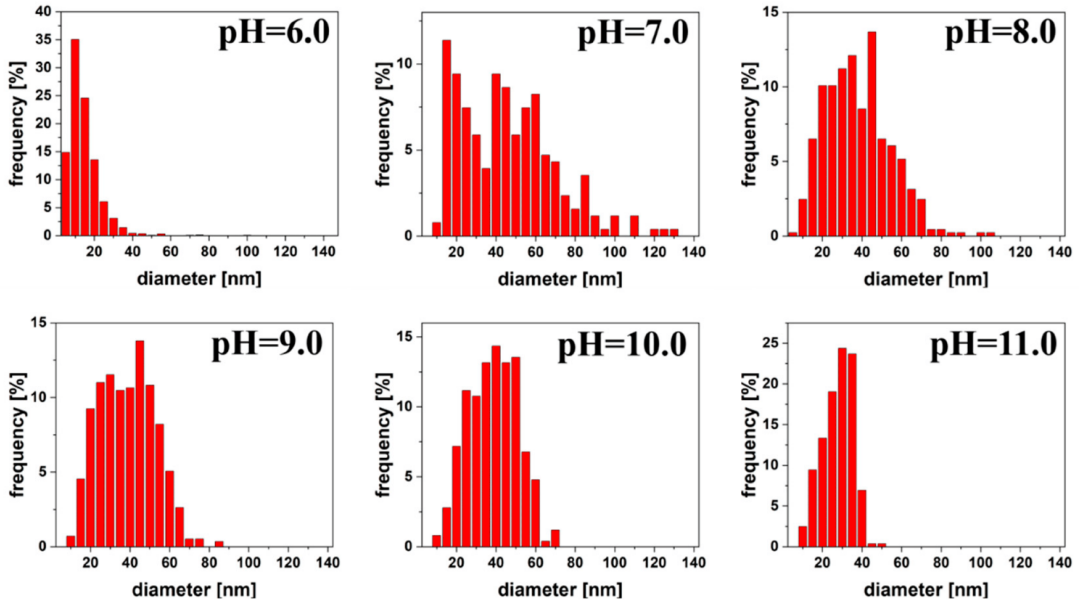

FIGURE 1.5

Impact of pH on the size and size distribution of the nanoparticles. Figure obtained from [33], published under Open access, Creative Commons Attribution CC BY 4.0.

Significance of Size, Shape and Surface

The size, shape and surface of a nanoparticles widely impacts the properties of it, impacting directly the application of the nanoparticle, in the field of application. Due to smaller size the nanomaterials get wider and cleaner bands and specific band gaps, compared to their bulk counterparts. Furthermore, depending on the application, the size of the nanoparticles becomes more and more significant, in case of biomedical applications, the smaller sized nanoparticles are preferred, since they have to cross through the cell wall / cell membrane. For instance, Virmani, I. et. al., reported the synthesis of Au nanoparticles using leaves extract of *Ocimum tenuiflorum* as reducing agents and using chemicals for reduction of Au salt. The reason for the study was to compare the size and toxicity of synthesized Au nanoparticles against cancerous A549, HeLa, H1299, MCF-7 and HEK293 normal cell lines. The group reported that plant extract mediated nanoparticles had size dispersion between 2 to 10nm, on average, with spherical shape, while the chemically reduced Au nanoparticles had size dispersion between 5 to 20 nm with polydisperse nature. The results showed that biosynthesized Au nanoparticles showed IC_{50} Value of 200 µg/mL against the cancerous cell lines, while showing minimal toxicity against the HEK293 cell lines. When compared, chemically reduced Au nanoparticles showed IC_{50} Value of 400 µg/mL against the cancerous cell lines and greater toxicity to normal cell lines, compared with biosynthesized Au nanoparticles. The group mentions the drastic change in toxicity to concentration ration against the cancerous and normal cell lines, is due to difference in size and shape of the nanoparticles, size the smaller sized nanoparticles with spherical shape entered into cells easily via cell membrane and localized into nucleus and/or cytosol [34]. In another research published by Majeed, S. and group mentions the synthesis of IO nanoparticles with size distribution between 19.23 – 30.51 nm, with mediation of bacteria *Proteus vulgaris* ATCC-29905, having spherical shape. The groups study resulted in proving that IO nanoparticles showed greater toxicity against the glioblastoma cell lines U87 MG with IC_{50} Value of 250 µg/mL while showing very less toxicity against L-132 healthy cell lines [35]. Comparatively, Janik-Olchawa, N. and group published the chemical synthesis of 5, 15 and 30 nm sized Io nanoparticles and found that lower sized nanoparticles were having higher dispersion in U87 MG cell lines compared to larger sized nanoparticles [36].

Wile, the surface comes into action, when the nanoparticles are modified on the surface and act as a carrier for various drugs and transport them to deliver at a specific cite to target. To load a drug molecule, the nanoparticles need to be i. smaller in size or as small as possible and ii. With active surface to load the drug. Since the drug molecule will be loaded onto the nanoparticle surface, the average diameter after drug loading increases significantly, which will make it a little difficult for the nanoparticles to move inside the cell, therefore, the smallest sized possible nanoparticles are preferred when it comes to drug loaded nanoparticles for their biomedical applications. Although the size of nanoparticles increases, but in return, it gives nanoparticles an edge of dodging the reticulo endothelial system and stay inside the body for longer period. To back this statement, Ankamwar, B reports in his published chapter that smaller 5 nm sized IO nanoparticles should be the best option for drug carrying purposes since their size is small, but when it comes to naked nanoparticles, 20 to 200 nm sized nanoparticles have highest potency against the cells for *in vivo* applications. Whereas when it comes to the application of a nanoparticle, it should ideally have a hydrophobic surface since t can help the nanoparticle to escape the macrophage capture [37]. He further goes on sand cites Adams, M and group that states that if the nanoparticle's surface is not hydrophobic, that there can be need of some chemical modifications to achieve the hydrophobicity.

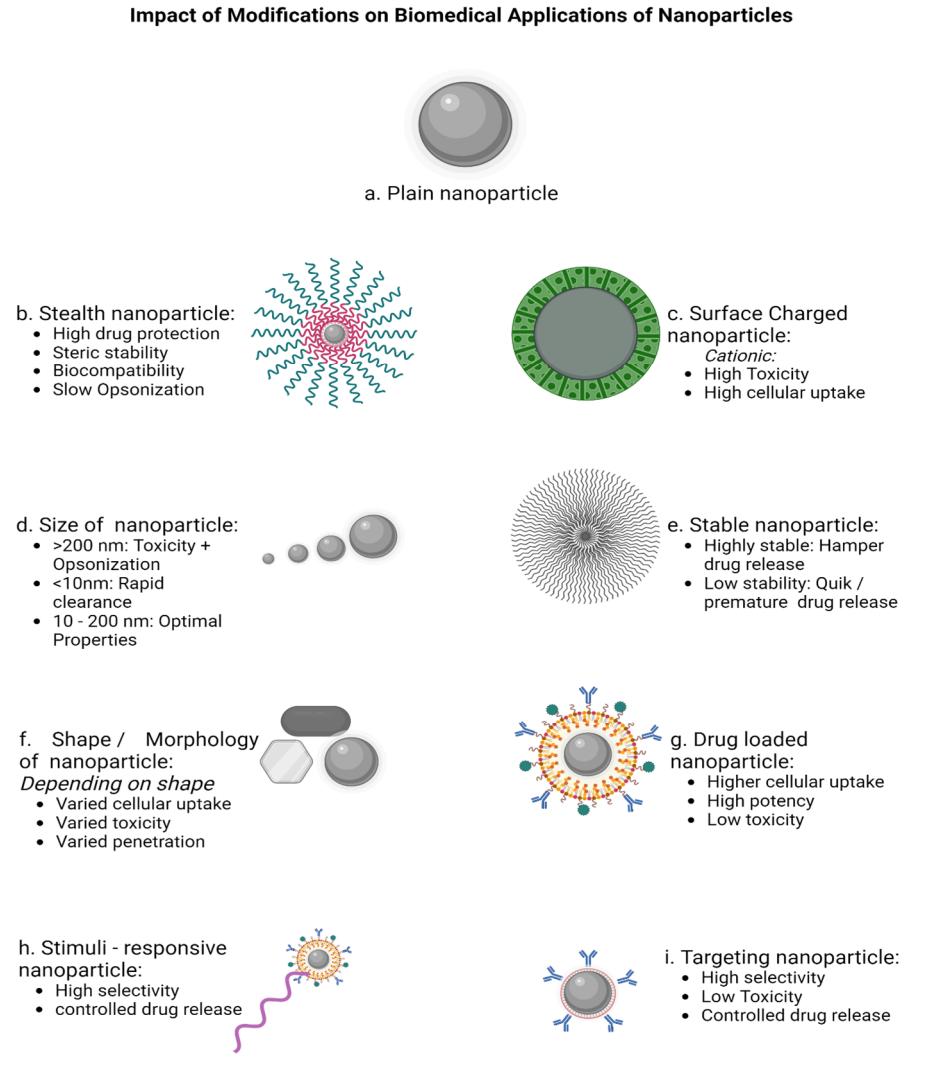

FIGURE 1.6

Various Surface modifications of the nanoparticles and their impact on the biomedical properties. a. shows the naked plain nanoparticle. b. shows stealth nanoparticles, the nanoparticles that have drug loaded inside and protect it, with that they also reduce opsonization but that may cause reduction in nanoparticle's cellular uptake. c. in case of cationic nanoparticle that higher cellular uptake and uncontrolled tissue aggregation due to which toxicity may increase. d. Nanoparticles/nanocarriers in the size range of 20 to 200 nm have optimal cellular uptake and may show high potential with reduced toxicity and reduced chance of clearance. e. A stable nanoparticle should circumvent the barriers and have optimal drug release. f. Nanoparticles with expanded morphology may have higher cellular uptake, lower toxicity and lower clearance with high capacity of drug loading. g. Drug loaded nanoparticles have higher cellular uptake with lower systematic toxicity and high drug availability. h. stimuli-responsive nanoparticles have higher selectivity and can release the loaded drug at the vary specific cite where it is wanted, with low toxicity and higher retention time. i. Targeting nanoparticles have anti-bodies attached onto their surface, resulting in nanoparticles to attack a very specific cite with low systematic toxicity.

These modifications can include the sue of hydrophobic polymers i.e., PEG and/or surfactants [38]. Furthermore, Elsabahy and Wooley state that surface chemistry of nanoparticles plays vital role in biodistribution, toxicity and immunogenicity, while if the nanoparticles having higher positive charge onto their surface, are more likely to be expelled from the blood vessels [39]. **Figure 1.6** shows different modifications of nanoparticle's surface and their impact on cellular uptake. **Idea of Figure 1.6** is inspired from [39].

In **Figure 1.6a**, a plain nanoparticle can be seen, while **Figure 1.6b – i** show various surface changes and modifications that can be done and the impact these changes can put on the cellular uptake of the nanoparticles and the stability and toxicity of the nanoparticles. While it is noteworthy that even a small modification in the size, shape and/or surface shape and charge can cause a drastic change in the application and potential of the nanoparticles in the applied field.

The nanoparticle surface, size and shape also help in determination of surface to volume ratio, hence the higher the number of nanoparticles in a specific volume, higher the cellular uptake will be; thus the question is if the surface morphology of the nanoparticle is smooth or porous. The nanoparticles with porous surface have larger surface area compared to smooth surfaced nanoparticles. the choice of size, shape and surface may help researchers in getting the best results for the required application.

Types of Nanoparticles for Nanomedicines

When it comes to types of nanoparticles, for the biomedical applications, specifically, the nanoparticles can be of various types, specifically divided onto 3 Types i. metal and metal oxides ii. Carbon based (including polymeric) and iii. Hybrid nanoparticles.

These classes of nanoparticles may contain but not limited to, metal and metal oxides of Iron, Nickel, Zinc (Zn), Cobalt (Co), Carbon Nano Tubes (CNTs), Quantum Dots (QDs), Carbon Dots (CDs), PLGA, PEG, PLA and PEGylated metal and metal oxides. The acquisition of a specific type of nanomaterials, with a specific size distribution, shape, and surface morphology needs various optimizations as discussed earlier. But these requirements are studied with the help of various techniques. We will be discussing these techniques and types of nanoparticles, that can be used for their biomedical applications in the coming chapters and with those well will also be discussing the mode of action of a nanoparticle inside a living cell, hindrances, and obstacles a nanoparticle has to face before it can deliver its potency and what are limitations in the field of nanomedicine.

Conclusion

Nanotechnology is leading in the field of biomedical sciences, due to unique and characteristic properties change when a bulk material is reduced to nanoscale range. There are various types of nanomaterials that can be used for their potential biomedical uses, and these materials may include metal and metal oxide nanoparticles, polymeric nanoparticles, and/or hybrid nanoparticles. There are two major approaches that could be used to reach nanoscale, Top-Down and Bottom-Up, while there are several methods that could be employed for the genesis including co-precipitations, green chemical and biological being most employed of all.

References

1. Liu, Y., et al., Nature-inspired supramolecular assemblies for precise biomedical imaging and therapy. Acta Pharmaceutica Sinica B, 2022. 12(10): p. 4008-4010.
2. Bayda, S., et al., The History of Nanoscience and Nanotechnology: From Chemical–Physical Applications to Nanomedicine. Molecules, 2020. 25(1): p. 112.
3. Mehnath, S., et al., Chapter Nine - Biosynthesized/green-synthesized nanomaterials as potential vehicles for delivery of antibiotics/drugs, in Comprehensive Analytical Chemistry, S.K. Verma and A.K. Das, Editors. 2021, Elsevier. p. 363-432.
4. Hassan, D., et al., Biosynthesis of pure hematite phase magnetic iron oxide nanoparticles using floral extracts of Callistemon viminalis (bottlebrush): their physical properties and novel biological applications. Artificial Cells, Nanomedicine, and Biotechnology, 2018. 46(sup1): p. 693-707.
5. Szunerits, S. and R. Boukherroub, Near-Infrared Photothermal Heating With Gold Nanostructures, in Encyclopedia of Interfacial Chemistry, K. Wandelt, Editor. 2018, Elsevier: Oxford. p. 500-510.
6. Somssich, M., A Short History of Plant Light Microscopy. Current Protocols, 2022. 2(10): p. e577.
7. Malik, S., K. Muhammad, and Y. Waheed, Nanotechnology: A Revolution in Modern Industry. Molecules, 2023. 28(2): p. 661.
8. Mappes, T., et al., The Invention of Immersion Ultramicroscopy in 1912—The Birth of Nanotechnology? Angewandte Chemie International Edition, 2012. 51(45): p. 11208-11212.
9. Afzal, O., et al., Nanoparticles in Drug Delivery: From History to Therapeutic Applications. Nanomaterials, 2022. 12(24): p. 4494.
10. Rein, M.J., et al., Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. British Journal of Clinical Pharmacology, 2013. 75(3): p. 588-602.
11. Pourmadadi, M., et al., Novel epirubicin-loaded nanoformulations: Advancements in polymeric nanocarriers for efficient targeted cellular and subcellular anticancer drug delivery. Inorganic Chemistry Communications, 2023. 155: p. 110999.
12. Chehelgerdi, M., et al., Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Molecular Cancer, 2023. 22(1): p. 169.
13. Rubin, R.P., A Brief History of Great Discoveries in Pharmacology: In Celebration of the Centennial Anniversary of the Founding of the American Society of Pharmacology and Experimental Therapeutics. Pharmacological Reviews, 2007. 59(4): p. 289-359.
14. Sani, A., et al., Floral extracts-mediated green synthesis of NiO nanoparticles and their diverse pharmacological evaluations. Journal of Biomolecular Structure and Dynamics, 2021. 39(11): p. 4133-4147.
15. Moreno, J.D., Mind wars: brain science and the military in the 21st century. 2012: Bellevue Literary Press.
16. Liu, J.K.H., The history of monoclonal antibody development - Progress, remaining challenges and future innovations. Annals of Medicine and Surgery, 2014. 3(4).
17. Zarean Mousaabadi, K., et al., Recent developments toward microfluidic point-of-care diagnostic sensors for viral infections. TrAC Trends in Analytical Chemistry, 2023. 169: p. 117361.

18. Hassan, D., et al., Physiochemical properties and novel biological applications of Callistemon viminalis-mediated α-Cr2O3 nanoparticles. Applied Organometallic Chemistry, 2019. 33(8): p. e5041.
19. Amin, S., et al., Zinc oxide nanoparticles coated urea enhances nitrogen efficiency and zinc bioavailability in wheat in alkaline calcareous soils. Environmental Science and Pollution Research, 2023. 30(27): p. 70121-70130.
20. Briffa, J., E. Sinagra, and R. Blundell, Heavy metal pollution in the environment and their toxicological effects on humans. Heliyon, 2020. 6(9): p. e04691.
21. Szczyglewska, P., A. Feliczak-Guzik, and I. Nowak, Nanotechnology–General Aspects: A Chemical Reduction Approach to the Synthesis of Nanoparticles. Molecules, 2023. 28(13): p. 4932.
22. Singh, N.A., et al., Nanoparticles synthesis via microorganisms and their prospective applications in agriculture. Plant Nano Biology, 2023. 5: p. 100047.
23. Haris, M., et al., Oscillatoria limnetica Mediated Green Synthesis of Iron Oxide (Fe2O3) Nanoparticles and Their Diverse In Vitro Bioactivities. Molecules, 2023. 28(5): p. 2091.
24. Kamal, A., et al., Bioinspired Green Synthesis of Bimetallic Iron and Zinc Oxide Nanoparticles Using Mushroom Extract and Use against Aspergillus niger; The Most Devastating Fungi of the Green World. Catalysts, 2023. 13(2): p. 400.
25. Revathy, R., et al., Iron-based magnetic nanomaterials: Sustainable approaches of synthesis and applications. Results in Engineering, 2023. 18: p. 101114.
26. Lévy, A., et al., Surface Chemistry of Gold Nanoparticles Produced by Laser Ablation in Pure and Saline Water. Langmuir, 2021. 37(19): p. 5783-5794.
27. Cheon, J.Y., et al., Shape-dependent antimicrobial activities of silver nanoparticles. International journal of nanomedicine, 2019: p. 2773-2780.
28. Malik, M., et al., Biosynthesis and Characterizations of Silver Nanoparticles from Annona squamosa Leaf and Fruit Extracts for Size-Dependent Biomedical Applications. Nanomaterials, 2022. 12(4): p. 616.
29. Devadiga, A., K. Vidya Shetty, and M.B. Saidutta. Effect of Precursor Salt Solution Concentration on the Size of Silver Nanoparticles Synthesized Using Aqueous Leaf Extracts of T. catappa and T. grandis Linn f.—A Green Synthesis Route. 2017. Singapore: Springer Singapore.
30. Andal, V. and G. Buvaneswari, Effect of reducing agents in the conversion of Cu2O nanocolloid to Cu nanocolloid. Engineering Science and Technology, an International Journal, 2017. 20(1): p. 340-344.
31. Nichols, W.T., et al., Gas and Pressure Dependence for the Mean Size of Nanoparticles Produced by Laser Ablation of Flowing Aerosols. Journal of Nanoparticle Research, 2000. 2(2): p. 141-145.
32. Sharma, M., et al., Inhibition of the bacterial growth as a consequence of synergism of Ag and ZnO: Calendula officinalis mediated green approach for nanoparticles and impact of altitude. Inorganic Chemistry Communications, 2022. 136: p. 109131.
33. Marciniak, L., et al., The Effect of pH on the Size of Silver Nanoparticles Obtained in the Reduction Reaction with Citric and Malic Acids. Materials, 2020. 13(23): p. 5444.
34. Virmani, I., et al., Comparative Anticancer Potential of Biologically and Chemically Synthesized Gold Nanoparticles. Journal of Cluster Science, 2020. 31(4): p. 867-876.

35. Majeed, S., et al., Bacteria Mediated Synthesis of Iron Oxide Nanoparticles and Their Antibacterial, Antioxidant, Cytocompatibility Properties. Journal of Cluster Science, 2021. 32(4): p. 1083-1094.
36. Janik-Olchawa, N., et al., Biochemical changes of macrophages and U87MG cells occurring as a result of the exposure to iron oxide nanoparticles detected with the Raman microspectroscopy. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2022. 278: p. 121337.
37. Ankamwar, B., Size and Shape Effect on Biomedical Applications of Nanomaterials. Biomedical Engineering - Technical Applications in Medicine, 2012: p. 93-114.
38. Adams, M.L., A. Lavasanifar, and G.S. Kwon, Amphiphilic block copolymers for drug delivery. Journal of Pharmaceutical Sciences, 2003. 92(7): p. 1343-1355.
39. Elsabahy, M. and K.L. Wooley, Design of polymeric nanoparticles for biomedical delivery applications. Chemical Society Reviews, 2012. 41(7): p. 2545-2561.