Advances in Nano-biomaterials and their applications in Biomedicine

Yogita Patil-Sen[1,2]

[1]The Sterile Services Decontamination Unit, Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust, National Health Service, Bolton, BL6 4SB, UK

[2]School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, PR1 2HE, UK

Abstract

Nanotechnology has received considerable attention and interest over the past few decades in the field of biomedicine due to the wide range of applications it provides in disease diagnosis, drug design and delivery, biomolecules detection, tissue engineering and regenerative medicine. Ultra-small size and large surface area of nanomaterials prove to be greatly advantageous for their biomedical applications. Moreover, the physico-chemical and thus, the biological properties of nanomaterials can be manipulated depending on the application. However, stability, efficacy and toxicity of nanoparticles remain challenge for researchers working in this area. This mini review highlights the recent advances of various types of nanoparticles in biomedicine and will be of great value to researchers in the field of materials science, chemistry, biology and medicine.

Introduction

Nanotechnology refers to one of the most innovative technologies of modern times that highlights the design and development of materials and structures having dimension from 1-1000 nanometres (1). At this size scale, the physico-chemical and biological properties of materials are very different from those of larger scale bulk materials. Because of their ultra-small size, large surface area and large surface to volume ratio, nanomaterials own characteristic physical, chemical, biological, and mechanical properties that can be applied for a broad category of applications. Thus, nanotechnology has enriched almost every field of science, including physics, chemistry, biology, computer science and engineering, and has revolutionized virtually all areas of our day-to-day life including food, clothing, cosmetics, electronics, energy, environment and medicine (2).

The application of nanotechnology in medicine, referred to as nanomedicine, has opened a myriad of opportunities in healthcare including those in disease diagnosis (3, 4), drug, gene and vaccine delivery (5-7), in vivo imaging (8, 9), tissue engineering and regenerative medicine (10, 11) which have shown huge potential in enhancing many aspects of human health. Nanomaterials have been used in many therapies such as in the treatment of cancer (5), diabetes (12), infection (13) and inflammation (14). The most recent utilization of nanomaterials reported in medicine is as a carrier system in m-RNA based Covid-19 vaccine (15, 16).

Nanomaterials are classified as zero-dimensional like nanoparticles (NPs), one-dimensional such as nanotubes and nanorods, and two-dimensional like nanofilms, nanolayers (17). Nanoparticles, made of lipids, polymers, metals, cell membrane coated particles are the most common structures that have been widely explored for their biomedical and pharmaceutical applications. However, most of these NPs are still at the research stage and only a handful of these have managed to clear the clinical stages and succeeded the FDA approvals (18). The clinical trials for many NPs seem to fail at the later stages due to toxicity. The physico-chemical properties such as size and shape of NPs determine their *in vivo* distribution and toxicity,

targeting ability and hence their biological fate (19, 20). Surface properties such as surface charge and hydrophobicity also influence their blood circulation and biodistribution (20, 21). Moreover, the physico-chemical and surface characteristics affect the stability of NPs and their interaction with cells and hence their cellular uptake. The properties of NPs are dictated by the synthesis methods and conditions (22). Thus, the control over the particle size, shape, morphology, and surface characteristics is of utmost importance to optimize the therapeutic efficacy and hence the applicability of NPs in biomedicine. Developing a nanoparticle system which is biocompatible, safe, stable, and effective is still a challenge to overcome for researchers. Further, there are key issues relating to complexity in large scale manufacturing, cost and regulatory standards which are hindering their translation and commercialization (23, 24). This article provides a brief review of various types of NPs, their synthesis methods, properties, and important applications in biomedicine. The current challenges associated with these systems for their use in medicine are also discussed.

Synthesis of NPs

Two main methods employed for synthesise of NPs involve top-down and bottom-up approach (25). Both the approaches include physical, chemical, and biological methods. Top-down is a simple strategy that involves breaking down of the bulk material to form tinier nanoparticles using mechanical or electrical methods (26, 27). Techniques such as ball milling, micromachining, lithography (photo, electron beam, nanoimprint, soft, nanosphere, block copolymer) are commonly employed in fabricating nanomaterials using top-down method. Due to the mechanical and electrical methods used during miniaturization of the particles using top-down approach, the surface structures generated show crystallographic impairment.

In bottom-up approach, building blocks i.e. atoms, molecules or smaller particles are added which assemble to form NPs (28, 29). It usually involves a kind of chemical reaction that generally happens in homogenous solution or gaseous phase. There is a greater chance of producing monodisperse NPs with less defects and increased homogenous chemical composition. Various chemical methods such as chemical reduction, electrochemical reduction or oxidation, photochemical synthesis, sonochemical synthesis, hydro/solvothermal synthesis, microwave assisted synthesis, microemulsion, co-precipitation, chemical vapour deposition and biosynthesis using bacteria, yeast, fungi, plant extracts are used.

Characterisation of NPs

NPs are characterized by various experimental techniques for their physico-chemical properties (30). Most common parameters such as size and shape can be measured via dynamic light scattering (DLS), and transmission and scanning electron microscopy (TEM and SEM). Surface charge can be measured using DLS. Crystal structure of NPs can be detected via X-ray diffraction technique. Brunauer–Emmett–Teller (BET) analysis is used to measure surface area of NPs. Optical properties of NPs can be examined using UV-visible spectroscopy and thermal properties can be studied via thermogravimetric analysis. Magnetic properties of magnetic NPs can be investigated via techniques such as vibrating sample magnetometry (VSM).

Types of NPs

Liposomes, polymeric nanoparticles, metal nanoparticles and cell membrane coated nanoparticles are some of the most extensively studied NPs (Figure 1) for their use in biomedicine. These are further discussed in the following subsections.

Liposomes

Lipids are an integral part of cell membranes and thus present an ideal biocompatible material to generate nanostructures for biomedical and pharmaceutical applications (31). Liposomes are one such nanostructures, consisting of lipid vesicles having single or multiple concentric lipid bilayers which are bounded in an aqueous space. Liposomes are one of the first nanoparticle platforms to be applied in medicine (32). In addition to their biocompatible and biodegradable composition, liposomes have an unique ability to encapsulate hydrophobic agents within their lamellae and hydrophilic agents in their aqueous core which provides advantage for these systems as a drug delivery vehicle (33-35). However, the major limitation of these systems is lack of structural integrity which leads to instability during storage and leakage of the encapsulated agents (36). The stability and circulation half-life time of the liposomes can be increased by functionalizing liposomes with polymers (37).

Over the last few decades, liposomes have been explored as delivery systems for various bioactive agents such as drugs, antimicrobials and antioxidants as well as genes and vaccines (38-41). Pharmacokinetics and bio-distribution of the encapsulated material can be improved using liposome drug formulations by exhibiting longer circulation time in blood. It is easy to modify the physicochemical properties of liposomes such as size, shape, and surface charge by altering the lipid composition and surface modification agents. Hybrid systems such as lipid-hydrogels and lipid-iron oxide NPs have also been studied for sustained and targeted drug delivery (42, 43). So far, only a handful of the liposomal formulations have succeeded to receive FDA approval which include Doxil and paclitaxel liposome formulations, however, many systems are in clinical trials and have shown promising results (18). Lipid bilayer structure of the liposomes is recognized by the immune system and is rapidly cleared by macrophages, shortening their in-vivo circulation time. Pegylation, i.e. attaching polyethylene glycol (PEG) on the surface of liposome has been shown to increase their stability (37), to prolong the circulation half-time time, and thus, to significantly enhance the therapeutic potential of these NPs (44).

Polymeric nanoparticles

Polymeric NPs are one of the most extensively investigated therapeutic carrier systems for numerous medications including treatments for cancer, cardiovascular diseases, and vaccinations. These are spherical colloidal systems synthesized by a self-assembly of two or more block-copolymer (45, 46). These block-copolymers are biodegradable and biocompatible and consist of two or more polymer chains which differ in their hydrophilicity. The co-polymers spontaneously self-assemble to form a core-shell structure with hydrophobic blocks forming the core to minimize its contact with aqueous environment and hydrophilic blocks forming the shell to stabilize the core

Natural polymers such as chitosan, alginate and dextran have been explored in nanomedicine due to their biocompatible and biodegradable characteristics as well as due to their abundant presence in nature (47). Moreover, synthetic polymers such as poly (lactic-co-glycolic acid) (PLGA), polyglycolic acid (PGA), PEG, N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) and polylactic acid (PLA) have also been extensively studied in translational medicine (48). Rapid clearance from the systemic circulation system before reaching the site of action and inability to differentiate between different cell types are some of the limitations of the polymeric NPs. Surface functionalization or hybridizing the polymeric NPs with lipids and other NPs may circumvent the drawbacks associated with these NPs and improve their in-vivo performance

(49). Despite their promising properties, very few polymeric NPs, most of which are liposome-polymer systems, have received FDA approval and further research is still needed on many of these systems to enhance their blood circulation time in *in-vivo* applications. Some of the FDA-approved polymeric nanoparticles include paclitaxel-PLGA NPs for metastatic breast cancer, non-small lung cancer and metastatic pancreatic cancer (18). Recently, it is reported that polymeric NPs provide a safe and effective carrier system for delivery of nucleic acids, such as DNA and small interfering RNA (siRNA), by protecting the nucleic acids from cellular uptake and degradation (50, 51).

Metal nanoparticles

Metallic nanoparticles such as silver NP, gold NP and superparamagnetic iron oxide nanoparticles possess excellent physical, chemical, biological, optical, electronic and magnetic properties which make them suitable in biomedical applications (52-55).

Owing to their intrinsic cytotoxicity, silver NPs have been used as anticancer and antibacterial agents in healthcare. Silver NPs have been applied against various types of cancer cells such as breast cancer, lung cancer, liver cancer (56-58). These NPs have also shown anti-proliferative properties which is attributed to their ability to damage DNA, break chromosomes and disrupt calcium (Ca2+) homeostasis which induces apoptosis (59).

Gold NPs has shown promise both in diagnostic and therapeutic applications (60). These NPs are effective carriers which can transfer chemotherapeutic agents, siRNA, proteins, genes and vaccines (53, 60). Studies have also demonstrated enhanced therapeutic efficacy of gold NPs in photothermal therapy, thus indicating their potential in cancer treatments (61).

Superparamagnetic iron oxide NPs (SPIONs) such as magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3) and hematite (α- Fe_2O_3) have been widely employed in theranostic applications which include, magnetic resonance imaging (MRI) and drug delivery (8, 62). Due to their superparamagnetic properties, SPIONs are increasingly investigated for their potential use in hyperthermia cancer therapy and targeted drug delivery applications (43, 63). By applying external magnetic field SPIONs can be directed specifically to the cancer cells. Moreover, the therapeutic agent can then be released to the target cells by inducing local hyperthermia with an applied AC field.

Although these metal particles are biocompatible and inert, there are concerns related to toxicity of these particles as significant number of particles are retained and accumulate in the body after administration. Therefore, despite promising research in this field, most of the work on metal NPs is still in the preclinical stage.

Cell membrane coated NPs

Cell membrane coated NPs are relatively a new class of NPs which are inspired from biological systems to make nanoparticles with new and enhanced functionalities (64, 65). Cell membrane coated NPs consists of NP core coated with cell membranes isolated from natural cells such as red blood cells, white blood cells, platelets , mesenchymal stem cells, cancer cells and bacterial cells (66, 67). NP core can be polymeric NPs, metallic NPs, or inorganic NPs. Camouflaging NPs using natural cell membranes is a unique top-down engineering strategy that provides a successful transfer of membrane proteins along with the surface chemistry of lipid bilayer (68).

Red blood cell membrane coated NPs have proven to increase circulation time and reduce reticuloendothelial system uptake (69). It was further reported that these NPs not only serve as

carriers but also as detoxification and vaccination platforms. White blood cell membrane coated NPs have shown to inhibit particle opsonization and consequent clearance by macrophage internalization (70). Cancer cell coated NPs have been used for tumour targeting, photothermal therapy (71) and immune response activation (72). Moreover, these NPs can be used in anticancer vaccination and drug delivery applications. Previous research has shown that platelet cell membrane coated NPs have potential applications in targeted drug delivery and pathogen-specific antibiotic delivery (73) whereas bacterial cell membrane coated NPs mainly find applications in vaccine delivery against antimicrobial-resistant bacteria (74). Previous studies using mesenchymal stem cell coated SPIONs suggest the potential of these NPs in diagnostic and magnetic hyperthermia cancer treatment (75).

Thus, lot of progress has been made in the field of cell membrane coated NPs which demonstrate their strong potential for diagnostic and therapeutic applications including those in drug delivery, immune modulation, detoxification, and vaccination. However, complexity and reproducibility issues of the fabrication process of these NPs and their physical instability exhibit a challenge with these NPs.

In addition to the NPs discussed above, there are many other kinds of nanomaterials researched over the years. These include quantum dots, carbon nanotubes and dendrimers (Figure 1). Quantum dots are fluorescent, spherical nanocrystals made of semiconductor materials which are used as drug carriers, for labelling therapeutic and in imaging and detection (76). Carbon nanotubes contain sp2 hybridized carbon atoms which are arranged in hexagonal lattices. This unique property provides these materials an ability to bind with a broad range of molecules and allowing their wide range of biomedical applications including drug and gene delivery (77, 78), in cancer diagnostics and therapy (79) and in tissue engineering (80). However, in-vivo use of carbon nanotubes is still posing concerns due to their issues relating to toxicity, water insolubility and biocompatibility. Dendrimers are well defined, multi-branched polymeric macromolecules synthesized from either synthetic or natural elements such as amino acids and sugars (81). Dendrimers can enhance the solubility and the bioavailability of various hydrophobic drugs and thus find applications in drug and gene delivery (82) and in treatments of cancer and infectious diseases (81, 83).

Moreover, recent development has shown that nanoparticles such as metallic NPs, polymeric NPs, carbon nanomaterials also have potential in regulating stem cell behaviour and tissue regeneration (84, 85). These nanomaterials can modulate the microenvironments involved in stem cell differentiation (86) and thus can be used to treat various diseases such as cardiovascular disease (87), neurodegenerative disease (88). Although there is a huge promise for nanotechnology in stem cell research, toxicity of certain nanoscaffolds such as carbon nanotubes is still a concern for their applications in tissue regeneration.

Conclusions

Nanoparticles represent a variety of applications ranging from diagnosis and delivery of therapeutics including drugs, genes, and vaccines, to tissue engineering and imaging. Each nanoparticle platform including liposomes, polymeric nanoparticles, metallic nanoparticles, bio-inspired cell membrane coated NPs, quantum dots, carbon nanotubes and dendrimers offers unique set of physico-chemical and biological properties. Thus, these NPs have potential to provide alternative strategy to the conventional treatments for cancer, heart and brain diseases, diabetes, and infectious and respiratory diseases. Although nanoparticles have established a

substantial presence in biomedicine, the field is still in its infancy stage. A large portion of these NPs are still in the research and development stage and have not been able to make the transition from the bench-to-bed. Many NPs seem to fail at the later stages of clinical trials due to severe toxicity, which is governed by their physico-chemical such as size, shape and surface properties like surface charge and hydrophobicity. Development of stable and effective nanoparticles requires a thorough knowledge of physico-chemical features of nanomaterials and their applications. Further strategies to overcome the issues related to manufacturing, costs, and regulatory standards are needed. Moreover, proper understanding about the safety and toxicity of the nanoparticles and the health risk associated with their use is crucial. Continuing the remarkable progress made so far and with the aid of technological and engineering advances, it will be possible for researchers to optimize these therapeutic and diagnostic modalities. Thus, nanoparticles certainly hold a promise to revolutionize the field of biomedicine and present an opportunity to treat a myriad of important human diseases.

Summary points

- Top-down and bottom-up approach, involving different chemical and biological processes, are employed to synthesize the nanoparticles and the physico-chemical and hence, the biological characteristics of the nanoparticles can be manipulated using appropriate synthesis conditions and procedures.
- Ultra-small size (ideally in the range of 0-100 nm), large surface area and large surface to volume ratio are some of the characteristics that govern the physical, chemical, optical, electrical, magnetic, mechanical, and biological properties of the nanoparticles.
- Applications of nanoparticles in biomedicine involve disease diagnosis, delivery of therapeutic agent such as drug, gene and vaccine, in vivo imaging, tissue engineering and regenerative medicine, hyperthermia.

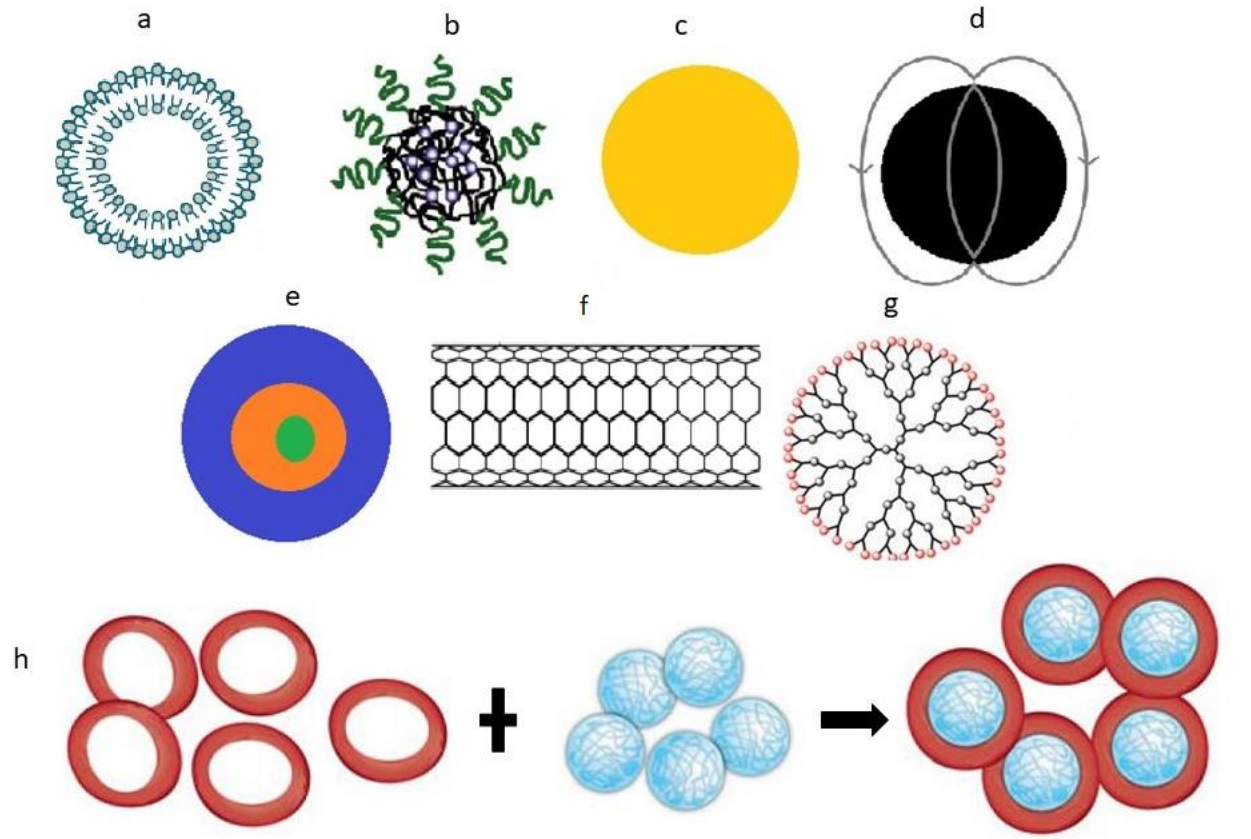

Figure 1: Schematic representation of nanoparticles discussed here, a. liposome; b polymeric nanoparticles; c. gold nanoparticle; d. iron oxide nanoparticle; e. quantum dot; f. carbon nanotube; g. dendrimer; h. red blood cell vesicle and core nanoparticles forming red blood cell membrane coated nanoparticle.

Conflicts of interest

The Author declares that there is no conflict of interest.

References

1. Mansoori GA, Fauzi Soelaiman TA. Nanotechnology — An Introduction for the Standards Community. Journal of ASTM International. 2005;2(6):1-22.
2. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The History of Nanoscience and Nanotechnology: From Chemical–Physical Applications to Nanomedicine. Molecules. 2020;25(1):112.
3. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: application of nanotechnology in cancer therapy. Drug Discovery Today. 2010;15(19):842-50.
4. Bayford R, Rademacher T, Roitt I, Wang SX. Emerging applications of nanotechnology for diagnosis and therapy of disease: a review. Physiological Measurement. 2017;38(8):R183-R203.
5. Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Advanced Drug Delivery Reviews. 2003;55(3):329-47.

6. Gregory A, Williamson D, Titball R. Vaccine delivery using nanoparticles. Frontiers in Cellular and Infection Microbiology. 2013;3(13).
7. Lim S, Park J, Shim MK, Um W, Yoon HY, Ryu JH, et al. Recent advances and challenges of repurposing nanoparticle-based drug delivery systems to enhance cancer immunotherapy. Theranostics. 2019;9(25):7906-23.
8. Cardoso VF, Francesko A, Ribeiro C, Bañobre-López M, Martins P, Lanceros-Mendez S. Advances in Magnetic Nanoparticles for Biomedical Applications. Advanced Healthcare Materials. 2018;7(5):1700845.
9. Wallyn J, Anton N, Vandamme TF. Synthesis, Principles, and Properties of Magnetite Nanoparticles for In Vivo Imaging Applications—A Review. Pharmaceutics. 2019;11(11).
10. Hasan A, Morshed M, Memic A, Hassan S, Webster TJ, Marei HE-S. Nanoparticles in tissue engineering: applications, challenges and prospects. Int J Nanomedicine. 2018;13:5637-55.
11. Fathi-Achachelouei M, Knopf-Marques H, Ribeiro da Silva CE, Barthès J, Bat E, Tezcaner A, et al. Use of Nanoparticles in Tissue Engineering and Regenerative Medicine. Frontiers in Bioengineering and Biotechnology. 2019;7(113).
12. Wong CY, Al-Salami H, Dass CR. Potential of insulin nanoparticle formulations for oral delivery and diabetes treatment. Journal of Controlled Release. 2017;264:247-75.
13. Yuan P, Ding X, Yang YY, Xu Q-H. Metal Nanoparticles for Diagnosis and Therapy of Bacterial Infection. Advanced Healthcare Materials. 2018;7(13):1701392.
14. Jin K, Luo Z, Zhang B, Pang Z. Biomimetic nanoparticles for inflammation targeting. Acta Pharmaceutica Sinica B. 2018;8(1):23-33.
15. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines — a new era in vaccinology. Nature Reviews Drug Discovery. 2018;17(4):261-79.
16. Nanomedicine and the COVID-19 vaccines. Nature Nanotechnology. 2020;15(12):963-.
17. Abd Elkodous M, El-Sayyad GS, Abdelrahman IY, El-Bastawisy HS, Mohamed AE, Mosallam FM, et al. Therapeutic and diagnostic potential of nanomaterials for enhanced biomedical applications. Colloids and Surfaces B: Biointerfaces. 2019;180:411-28.
18. Ventola CL. Progress in Nanomedicine: Approved and Investigational Nanodrugs. P T. 2017;42(12):742-55.
19. Hoshyar N, Gray S, Han H, Bao G. The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. Nanomedicine. 2016;11(6):673-92.
20. Jo DH, Kim JH, Lee TG, Kim JH. Size, surface charge, and shape determine therapeutic effects of nanoparticles on brain and retinal diseases. Nanomedicine: Nanotechnology, Biology and Medicine. 2015;11(7):1603-11.
21. Verma A, Stellacci F. Effect of Surface Properties on Nanoparticle–Cell Interactions. Small. 2010;6(1):12-21.
22. Sajid M, Płotka-Wasylka J. Nanoparticles: Synthesis, characteristics, and applications in analytical and other sciences. Microchemical Journal. 2020;154:104623.
23. Foulkes R, Man E, Thind J, Yeung S, Joy A, Hoskins C. The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives. Biomaterials Science. 2020;8(17):4653-64.
24. Singh D, Dilnawaz F, Sahoo SK. Challenges of moving theranostic nanomedicine into the clinic. Nanomedicine. 2020;15(2):111-4.
25. Biswas A, Bayer IS, Biris AS, Wang T, Dervishi E, Faupel F. Advances in top–down and bottom–up surface nanofabrication: Techniques, applications & future prospects. Advances in Colloid and Interface Science. 2012;170(1):2-27.
26. Yadav T, Yadav rm, Singh D. Mechanical Milling: a Top Down Approach for the Synthesis of Nanomaterials and Nanocomposites. Nanoscience and Nanotechnology. 2012;2:22-48.

27. Fu X, Cai J, Zhang X, Li W-D, Ge H, Hu Y. Top-down fabrication of shape-controlled, monodisperse nanoparticles for biomedical applications. Advanced Drug Delivery Reviews. 2018;132:169-87.
28. Lu H, Tang S-Y, Yun G, Li H, Zhang Y, Qiao R, et al. Modular and Integrated Systems for Nanoparticle and Microparticle Synthesis-A Review. Biosensors (Basel). 2020;10(11):165.
29. F.A. K. Synthesis of Nanomaterials: Methods & Technology. In: (eds) KF, editor. Applications of Nanomaterials in Human Health. Singapore: Springer 2020. p. 15-21.
30. Mourdikoudis S, Pallares RM, Thanh NTK. Characterization techniques for nanoparticles: comparison and complementarity upon studying nanoparticle properties. Nanoscale. 2018;10(27):12871-934.
31. Patil-Sen Y, Tiddy GJT, Brezesinski G, DeWolf C. A monolayer phase behaviour study of phosphatidylinositol, phosphatidylinositol 4-monophosphate and their binary mixtures with distearoylphosphatidylethanolamine. Physical Chemistry Chemical Physics. 2004;6(7):1562-5.
32. Bangham AD. Liposomes: the Babraham connection. Chemistry and Physics of Lipids. 1993;64(1):275-85.
33. Panahi Y, Farshbaf M, Mohammadhosseini M, Mirahadi M, Khalilov R, Saghfi S, et al. Recent advances on liposomal nanoparticles: synthesis, characterization and biomedical applications. Artificial Cells, Nanomedicine, and Biotechnology. 2017;45(4):788-99.
34. Beltrán-Gracia E, López-Camacho A, Higuera-Ciapara I, Velázquez-Fernández JB, Vallejo-Cardona AA. Nanomedicine review: clinical developments in liposomal applications. Cancer Nanotechnology. 2019;10(1):11.
35. Crommelin DJA, van Hoogevest P, Storm G. The role of liposomes in clinical nanomedicine development. What now? Now what? Journal of Controlled Release. 2020;318:256-63.
36. Maurer N, Fenske DB, Cullis PR. Developments in liposomal drug delivery systems. Expert Opinion on Biological Therapy. 2001;1(6):923-47.
37. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nature Reviews Drug Discovery. 2005;4(2):145-60.
38. Patil-Sen Y. NA, Asawa S., Tavarna T. Nanotechnology: The Future for Cancer Treatment. In: Bose K. CPe, editor. Unravelling Cancer Signaling Pathways: A Multidisciplinary Approach. Singapore.: Springer; 2019.
39. Simão AMS, Bolean M, Cury TAC, Stabeli RG, Itri R, Ciancaglini P. Liposomal systems as carriers for bioactive compounds. Biophysical Reviews. 2015;7(4):391-7.
40. Liu Y, Chen C. Role of nanotechnology in HIV/AIDS vaccine development. Advanced Drug Delivery Reviews. 2016;103:76-89.
41. Madni A, Sarfraz M, Rehman M, Ahmad M, Akhtar N, Ahmad S, et al. Liposomal drug delivery: a versatile platform for challenging clinical applications. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2014;17(3):401-26.
42. Kulkarni CV, Moinuddin Z, Patil-Sen Y, Littlefield R, Hood M. Lipid-hydrogel films for sustained drug release. International journal of pharmaceutics. 2015;479(2):416-21.
43. Patil-Sen Y, Torino E, De Sarno F, Ponsiglione AM, Chhabria V, Ahmed W, et al. Biocompatible superparamagnetic core-shell nanoparticles for potential use in hyperthermia-enabled drug release and as an enhanced contrast agent. Nanotechnology. 2020;31(37):375102.
44. Hoang Thi TT, Pilkington EH, Nguyen DH, Lee JS, Park KD, Truong NP. The Importance of Poly(ethylene glycol) Alternatives for Overcoming PEG Immunogenicity in Drug Delivery and Bioconjugation. Polymers. 2020;12(2).
45. Gu F, Zhang L, Teply BA, Mann N, Wang A, Radovic-Moreno AF, et al. Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. Proceedings of the National Academy of Sciences. 2008;105(7):2586-91.

46. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. Annual review of medicine. 2012;63:185-98.
47. Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z. Polysaccharides-based nanoparticles as drug delivery systems. Adv Drug Deliv Rev. 2008;60(15):1650-62.
48. Sah H, Thoma LA, Desu HR, Sah E, Wood GC. Concepts and practices used to develop functional PLGA-based nanoparticulate systems. Int J Nanomedicine. 2013;8:747-65.
49. Banik BL, Fattahi P, Brown JL. Polymeric nanoparticles: the future of nanomedicine. WIREs Nanomedicine and Nanobiotechnology. 2016;8(2):271-99.
50. Banik BL, Fattahi P, Brown JL. Polymeric nanoparticles: the future of nanomedicine. Wiley interdisciplinary reviews Nanomedicine and nanobiotechnology. 2016;8(2):271-99.
51. Lin G, Zhang H, Huang L. Smart Polymeric Nanoparticles for Cancer Gene Delivery. Molecular Pharmaceutics. 2015;12(2):314-21.
52. Lee SH, Jun B-H. Silver Nanoparticles: Synthesis and Application for Nanomedicine. International Journal of Molecular Sciences. 2019;20(4):865.
53. Carabineiro SAC. Applications of Gold Nanoparticles in Nanomedicine: Recent Advances in Vaccines. Molecules. 2017;22(5):857.
54. Wu K, Su D, Liu J, Saha R, Wang J-P. Magnetic nanoparticles in nanomedicine: a review of recent advances. Nanotechnology. 2019;30(50):502003.
55. Socoliuc V, Peddis D, Petrenko VI, Avdeev MV, Susan-Resiga D, Szabó T, et al. Magnetic Nanoparticle Systems for Nanomedicine—A Materials Science Perspective. Magnetochemistry. 2020;6(1):2.
56. Kawata K, Osawa M, Okabe S. In Vitro Toxicity of Silver Nanoparticles at Noncytotoxic Doses to HepG2 Human Hepatoma Cells. Environmental Science & Technology. 2009;43(15):6046-51.
57. Foldbjerg R, Dang DA, Autrup H. Cytotoxicity and genotoxicity of silver nanoparticles in the human lung cancer cell line, A549. Archives of Toxicology. 2011;85(7):743-50.
58. Jeyaraj M, Sathishkumar G, Sivanandhan G, MubarakAli D, Rajesh M, Arun R, et al. Biogenic silver nanoparticles for cancer treatment: An experimental report. Colloids and Surfaces B: Biointerfaces. 2013;106:86-92.
59. AshaRani PV, Hande MP, Valiyaveettil S. Anti-proliferative activity of silver nanoparticles. BMC Cell Biology. 2009;10(1):65.
60. Singh P, Pandit S, Mokkapati V, Garg A, Ravikumar V, Mijakovic I. Gold Nanoparticles in Diagnostics and Therapeutics for Human Cancer. Int J Mol Sci. 2018;19(7).
61. Pitsillides CM, Joe EK, Wei X, Anderson RR, Lin CP. Selective cell targeting with light-absorbing microparticles and nanoparticles. Biophysical journal. 2003;84(6):4023-32.
62. Y. P-S, V. C. Superparamagnetic iron oxide nanoparticles for magnetic hyperthermia applications. In: (ed.) BS, editor. NanoBioMaterials New York: CRC Press; 2018.
63. Janko C, Ratschker T, Nguyen K, Zschiesche L, Tietze R, Lyer S, et al. Functionalized Superparamagnetic Iron Oxide Nanoparticles (SPIONs) as Platform for the Targeted Multimodal Tumor Therapy. Frontiers in Oncology. 2019;9(59).
64. Li R, He Y, Zhang S, Qin J, Wang J. Cell membrane-based nanoparticles: a new biomimetic platform for tumor diagnosis and treatment. Acta Pharmaceutica Sinica B. 2018;8(1):14-22.
65. Liu Y, Luo J, Chen X, Liu W, Chen T. Cell Membrane Coating Technology: A Promising Strategy for Biomedical Applications. Nano-Micro Letters. 2019;11(1):100.
66. Narain A, Asawa S, Chhabria V, Patil-Sen Y. Cell membrane coated nanoparticles: next-generation therapeutics. Nanomedicine (London, England). 2017;12(21):2677-92.
67. Fang RH, Jiang Y, Fang JC, Zhang L. Cell membrane-derived nanomaterials for biomedical applications. Biomaterials. 2017;128:69-83.
68. Hu CM, Fang RH, Copp J, Luk BT, Zhang L. A biomimetic nanosponge that absorbs pore-forming toxins. Nat Nanotechnol. 2013;8(5):336-40.

69. Hu C-MJ, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proceedings of the National Academy of Sciences. 2011;108(27):10980-5.
70. Parodi A, Quattrocchi N, van de Ven AL, Chiappini C, Evangelopoulos M, Martinez JO, et al. Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions. Nat Nanotechnol. 2013;8(1):61-8.
71. Chen Z, Zhao P, Luo Z, Zheng M, Tian H, Gong P, et al. Cancer Cell Membrane-Biomimetic Nanoparticles for Homologous-Targeting Dual-Modal Imaging and Photothermal Therapy. ACS nano. 2016;10(11):10049-57.
72. Fang RH, Hu C-MJ, Luk BT, Gao W, Copp JA, Tai Y, et al. Cancer Cell Membrane-Coated Nanoparticles for Anticancer Vaccination and Drug Delivery. Nano Letters. 2014;14(4):2181-8.
73. Hu CM, Fang RH, Wang KC, Luk BT, Thamphiwatana S, Dehaini D, et al. Nanoparticle biointerfacing by platelet membrane cloaking. Nature. 2015;526(7571):118-21.
74. Gao W, Fang RH, Thamphiwatana S, Luk BT, Li J, Angsantikul P, et al. Modulating Antibacterial Immunity via Bacterial Membrane-Coated Nanoparticles. Nano Letters. 2015;15(2):1403-9.
75. Lai P-Y, Huang R-Y, Lin S-Y, Lin Y-H, Chang C-W. Biomimetic stem cell membrane-camouflaged iron oxide nanoparticles for theranostic applications. RSC Advances. 2015;5(119):98222-30.
76. Qi L, Gao X. Emerging application of quantum dots for drug delivery and therapy. Expert Opinion on Drug Delivery. 2008;5(3):263-7.
77. Karimi M, Solati N, Ghasemi A, Estiar MA, Hashemkhani M, Kiani P, et al. Carbon nanotubes part II: a remarkable carrier for drug and gene delivery. Expert Opinion on Drug Delivery. 2015;12(7):1089-105.
78. Mohajeri M, Behnam B, Sahebkar A. Biomedical applications of carbon nanomaterials: Drug and gene delivery potentials. Journal of Cellular Physiology. 2019;234(1):298-319.
79. Chen Z, Zhang A, Wang X, Zhu J, Fan Y, Yu H, et al. The Advances of Carbon Nanotubes in Cancer Diagnostics and Therapeutics. Journal of Nanomaterials. 2017;2017:3418932.
80. Simon J, Flahaut E, Golzio M. Overview of Carbon Nanotubes for Biomedical Applications. Materials. 2019;12(4):624.
81. Le NTT, Nguyen TNQ, Cao VD, Hoang DT, Ngo VC, Hoang Thi TT. Recent Progress and Advances of Multi-Stimuli-Responsive Dendrimers in Drug Delivery for Cancer Treatment. Pharmaceutics. 2019;11(11).
82. Somani S, Blatchford DR, Millington O, Stevenson ML, Dufès C. Transferrin-bearing polypropylenimine dendrimer for targeted gene delivery to the brain. Journal of Controlled Release. 2014;188:78-86.
83. Mhlwatika Z, Aderibigbe BA. Application of Dendrimers for the Treatment of Infectious Diseases. Molecules. 2018;23(9):2205.
84. Dayem AA, Choi HY, Yang GM, Kim K, Saha SK, Kim JH, et al. The potential of nanoparticles in stem cell differentiation and further therapeutic applications. Biotechnology journal. 2016;11(12):1550-60.
85. Carradori D, Eyer J, Saulnier P, Préat V, des Rieux A. The therapeutic contribution of nanomedicine to treat neurodegenerative diseases via neural stem cell differentiation. Biomaterials. 2017;123:77-91.
86. Pinho S, Macedo MH, Rebelo C, Sarmento B, Ferreira L. Stem cells as vehicles and targets of nanoparticles. Drug Discovery Today. 2018;23(5):1071-8.
87. Sun Y, Lu Y, Yin L, Liu Z. The Roles of Nanoparticles in Stem Cell-Based Therapy for Cardiovascular Disease. Frontiers in Bioengineering and Biotechnology. 2020;8(947).

88. Masoudi Asil S, Ahlawat J, Guillama Barroso G, Narayan M. Application of Nanotechnology in Stem-Cell-Based Therapy of Neurodegenerative Diseases. Applied Sciences. 2020;10(14):4852.