DOI: 10.55522/jmpas.V13I5.6514 ISSN NO. 2320 – 7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Research and development of nano-particles in drug delivery

Suraj Choudhary*[1], Garima Verma[2], Depika Rani[1], Ashu devi[3]

[1] Department of pharmaceutics, Aadarsh Vijender institute of pharmaceutical sciences, Shobhit University, Gangoh, Saharanpur, Uttar Pradesh, India

[2] School of Bio-logical Engineering and Sciences, Shobhit University, Gangoh, Saharanpur, Uttar Pradesh, India

[3] Department of pharmaceutics, SGRR University, Dehradun, Uttrakhand, India

Corresponding author: Suraj Choudhary, ✉ omji5235@gmail.com, **Orcid Id**: https://orcid.org/ 0000-0001-8022-1257

Department of pharmaceutics, Aadarsh Vijender institute of pharmaceutical sciences, Shobhit University, Gangoh, Saharanpur, Uttar Pradesh, India

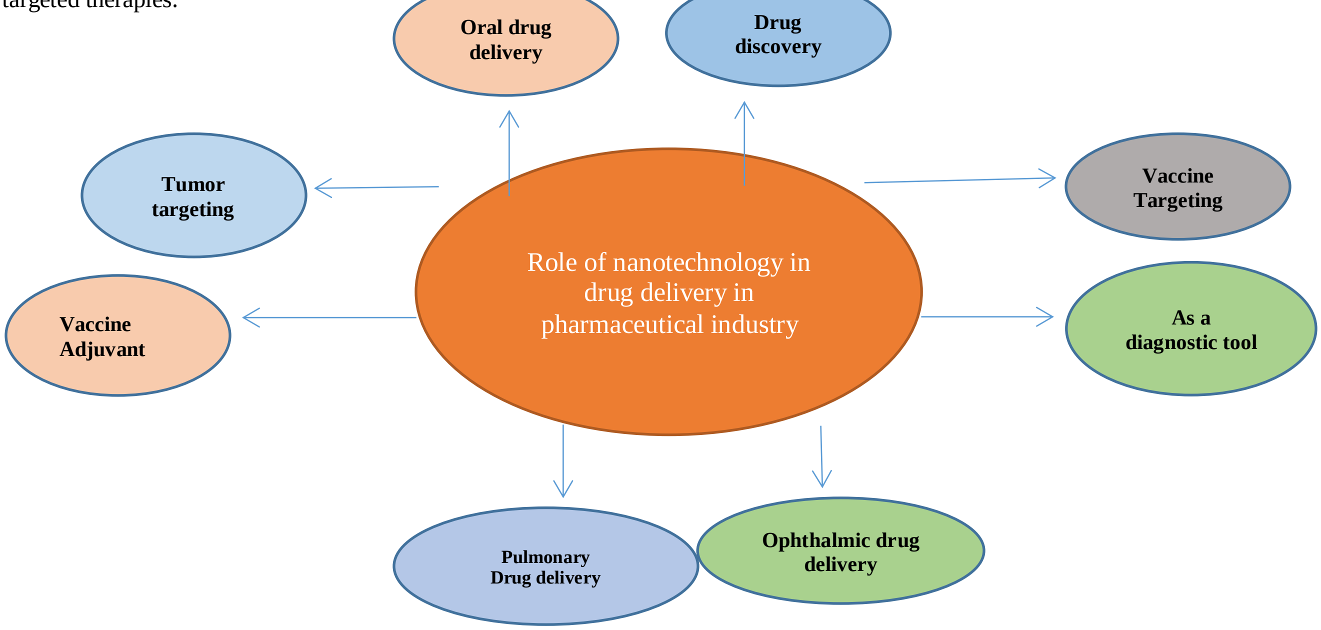
Received - 09-05-2024**, Revised** - 07-10-2024, **Accepted** - 12-10-2024 **(DD-MM-YYYY)**

Refer This Article

Suraj Choudhary, Garima Verma, Depika Rani, Ashu devi, 2024. Research and development of nano-particles in drug delivery**.** Journal of medical pharmaceutical and allied sciences, V 13 - I 5, Pages - 6802 – 6810. Doi: https://doi.org/10.55522/jmpas.V13I5.6514.

ABSTRACT

Nano-technology has revolutionized the pharmaceutical industry, offering a plethora of tools and strategies for drug discovery and development. This review paper delves into the transformative role of nano-materials, particularly nano-particles, in enhancing therapeutic efficacy and overcoming limitations associated with conventional drug delivery systems. We explore how nano-technology facilitates targeted drug delivery, improving drug bio-availability and reducing undesirable side effects. Additionally, the review sheds light on the application of nano-technology in diagnostics and disease imaging, enabling earlier and more accurate disease detection. Furthermore, the paper discusses the ongoing research efforts in utilizing nano-particles for gene therapy and personalized medicine. We address the challenges and considerations surrounding the implementation of nano-technology in pharmaceuticals, including potential safety concerns and regulatory hurdles. Finally, the review concludes by emphasizing the immense potential of nano-technology in shaping the future of pharmaceutical research and development, paving the way for more effective and targeted therapies.



Keywords: Nano-technology, Pharmaceutical industry, Nano- diagnosis, Nano- particles, Targeted drug delivery.

INTRODUCTION

The future is upon us, and it has brought us the gift of nano-technology. In the metric system, a nano-meter (nm) is one billionth of a meter (m). Though this scale is too small for the naked eye, this is the realm of the bio-logical cell and its organelles. Truly speaking, all the real action happens at the molecular or cellular level. The manipulation of technical apparatus at the atomic scale is known as nano-technology. For comparison, the diameter of a ribosome is 20 nm, the length of a single DNA strand is 2 nm, and the size of a nucleus is around 6 µm. A person is made up of 100 trillion cells on average. Novel gadgets for the treatment of several neurological illnesses have been made possible using nano-technology. The development of novel nano-materials, chip-based technologies, and the decrease of equipment size are all significantly lowering morbidity. Innovations in nano-technology have raised human interest and enthusiasm to unprecedented levels. It is reasonable to predict that therapeutic neurology and nano-technology will eventually be integrated given the rate of advancement and study in this field [1, 2].

As Figure 1 illustrates, nano-bio-technology may serve as a barrier for a variety of bio-medical applications, which is highly beneficial for protecting living things from illnesses like cancer and tumours [3]. Many illnesses or syndromes can be treated by the controlled application of desired medications via the use of different bio--nano-particles and nano-materials for targeted drug delivery. The nano-materials' bio-compatibility and bio-adaptability are crucial because they open the door to more accurate medical research employing bio-technology and nano-technology [4, 5].

We give a broad summary of the characteristics of nano-particles, which are a crucial part of nano-technology, in this review article. Future applications of nano-bio-technology to target desired or specified areas are covered, including the use of medication delivery methods, nano-materials, and bio-structures to target tumours.

Development of Nano-technology

On December 29, 1959 the famous physicist Richard Feynman delivered a lecture on quantum mechanics at the California Institute of Technology. Little did he know that this talk would become the cornerstone for technological revolution in the field of nano-technology. Feynman proposed writing the entire 24 volumes of Encyclopedia Britannica on the head of a mere pin.

Another radical idea suggested by his friend Albert Hibbs was that of micromachines, dubbed as the "swallowable surgeon," that could be controlled from the outside to perform surgery at the cellular level. This device could be used to eliminate malignant neoplasms at their inception or repair defective heart valves. Among the boons of working at the nano- level are the minimal friction and mechanical wear and tear. Furthermore, because the device's mass is so little, the effects of gravity also become insignificant. [6]

Nano-materials

The physical and chemical properties of nano-materials are determined by their particular composition, shape and size. The effects of nano-materials on health and the environment also depend on their size, shape, etc. It is difficult to find a single, universally accepted definition of nano-particles, and the scientific community is currently debating a strict definition of nano-materials. According to the EU Commission's definition, a nano-material is "a man-made or natural material containing unbound, aggregated or agglomerated particles with an external diameter between 1 and 100 nm". There are four types of nano-materials: (1) carbon-based nano-material's, (2) organic based nano-material's, (3) composite-based nano-materials and (4) inorganic-based nano-material's. Different metal and metal oxide nano-particles are examples of inorganic-based nano-material's [7].

The synthesis of inorganic nano-materials such as metals and metal oxides using the "green synthesis technique" has gained popularity due to its sustainability, reliability, low cost, simple procedure, large-scale production and harmlessness. By employing a plant or plant extract as a reducing agent to decrease the metal precursor to its elemental form at the nano-scale, inorganic nano-material's can be created utilizing this technique [8-14].

Inorganic nano-particles include metals and metal oxides. Metal oxide-based inorganic nano-material include zinc oxide (ZnO), copper oxide (CuO), magnesium aluminium oxide ($MgAl_2O_4$), titanium dioxide (TiO_2), cerium oxide (CeO_2), iron oxide (Fe_2O_3), silicon dioxide (SiO_2), iron (Fe_3O_4), etc. Carbon-based nano-materials include graphene, fullerene, and carbon nano-tubes with one or more walls, carbon fibres, activated carbon, and carbon black [15].

Among the organic nano-materials without carbon are liposomes, cyclodextrin, dendrimers, and micelles [16]. Any combination of metal, metal oxide, carbon, and/or organic nano-materials can be considered a composite nano-material. These nano-particles feature intricate architectures, like an organic–metal framework.

The materials are ground or milled in the top-down approach (Figure 2). Due to the high energy required for the creation of minuscule particles, this approach is not appropriate for the synthesis of symmetrically organised nano-materials. This method's primary drawback is its imperfect surface structure, which has an immediate impact on the physical and surface characteristics of the materials that are generated. Numerous physical procedures are used in this method, including as atomization, pyrolysis, laser ablation, electro-spinning, lithography, sputtering, radiation-induced chemical etching, and lithography [17-18].

Figure 1: Nano-technology and bio-technology synergize with structural and genetic engineering, driving widespread applications. They enable nano- bio-sensors, precise drug delivery, and tumor/disease-specific target identification.

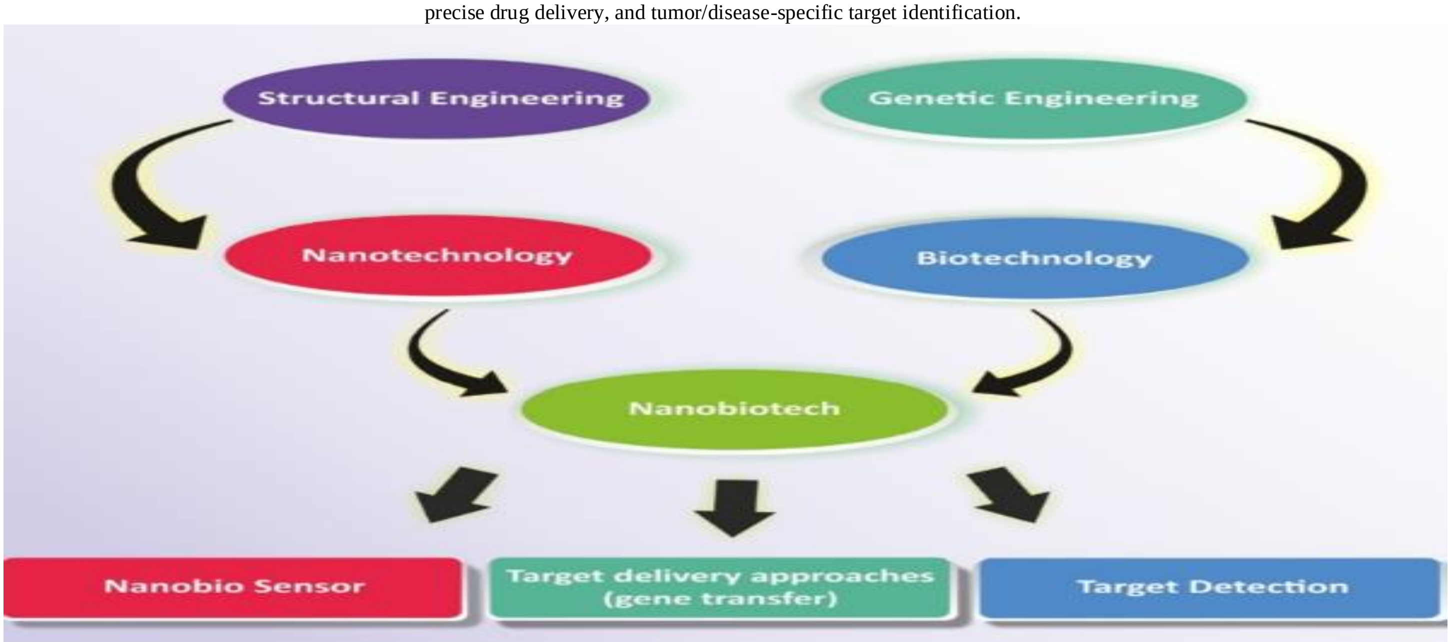
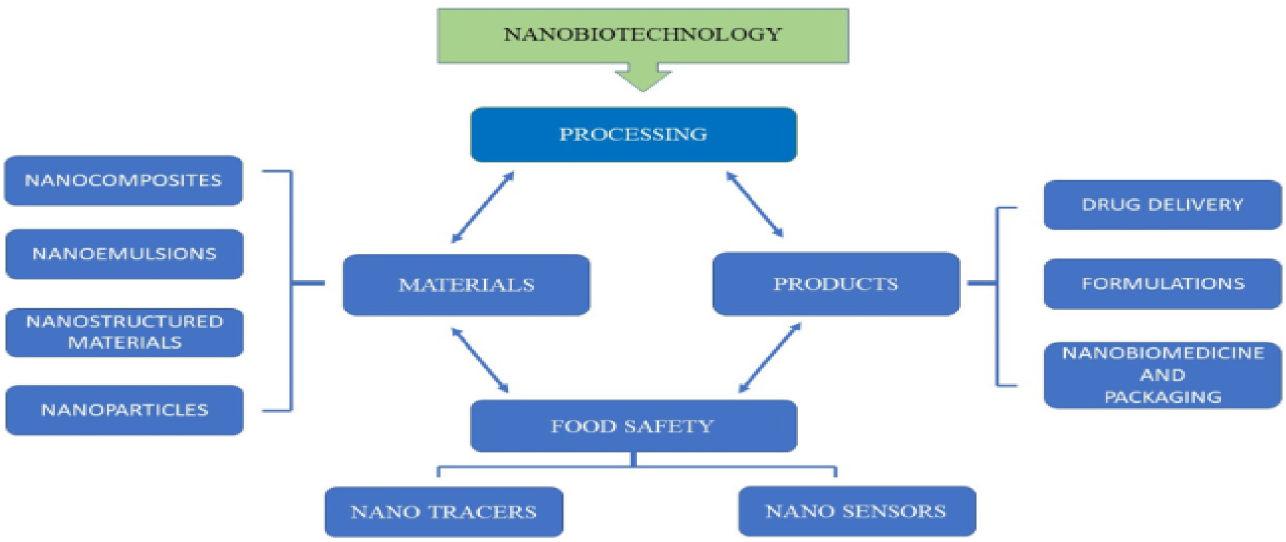


Figure 2: Nano-bio-technology's interdisciplinary nature offers potential for advancing drug formulation, packaging systems, and delivery crucial across various human-centric fields.



Nano- Technology and Drug Discovery and Development

Zinc Oxide Nano-particles: Cancer Cell Apoptosis via ROS

The potential use of zinc oxide nano-particles (ZnO NPs) in cancer treatment have drawn a lot of interest. ZnO NPs have been shown to cause cancer cells to die selectively. Nevertheless, it is still unknown what molecular processes underlie ZnO NPs' anticancer effect. By killing all three types of cancer cells while having no effect on normal rat astrocytes or hepatocytes, Akhtar et al.'s investigation into the cytotoxicity of ZnO NPs against two primary rat cells (astrocytes and hepatocytes) and three cancer cell types revealed that ZnO NPs exert distinct effects on mammalian cell viability. [19]

Nano-particles in Sunscreens

One of the ingredients that has lately been seen in cosmetics is nano-particles. In sunscreens nowadays, for instance, TiO2 and ZnO2 in nano-form are widely used because of their strong photostability and minimal propensity for photoallergic reactions [20-21]. These NPs filter UV radiation more effectively than microparticles, in addition to being colourless. TiO2 NPs typically have primary sizes between 10 and 100 nm, however when applied to skin, aggregates of primary particles with sizes between 30 and 150 nm form [22]. It is generally believed that smaller particles do more damage [23]. Toxicology, however, is a topic of some debate, and our understanding of possible dangers at diameters less than 100 nm is still lacking [24-25]. According to some studies, once applied to the skin, these NPs aggregates retain their form invariably, preventing the release of primary particles and, as a result, posing little hazards to people. On the other hand, reasonable viewpoints said that the hazardous effects of NPs on humans are dependent on factors such as particle size, composition, and dosage [26].

Polysaccharide-based Nano-materials for Specific Delivery of Anti-cancer Medications

An essential family of bio-logical polymers, polysaccharides exhibit a great deal of structural and property variety and are hydrophilic, bio-degradable, nontoxic, and bio-active. These are readily bio-chemically and chemically modifiable to improve stability, increase bio-adhesion with bio-logical tissues, and increase medication bio-availability. The majority of chemotherapeutic medications are sluggish to act, have a limited therapeutic index, and are poorly soluble in water, all of which make them harmful to human health. These bio-polymers' innate bio-compatibility has been demonstrated to improve the solubility of several chemotherapeutic medications, which has also prompted the development of nano-materials for the many routes of administration of antibio-tics, anticancer agents, proteins, peptides, and nucleic acids. Synthesis and study of nano-materials based on polysaccharides have attracted a lot of interest lately as one of the most useful resources in the field of nano-medicine.

Quantum Dots as Drug Delivery System

Fluorescence nano-crystals or quantum dots (QDs) are engineered nano-particles (NP) that have shown great promise with potential for many bio-logical and bio-medical applications, especially in drug delivery/activation and cellular imaging. The use of nano-technology in medicine directed to drug delivery is set to expand in the coming years. However, it is unclear whether QDs, which are defined as NPs rather than small molecules, can specifically and effectively deliver drugs to molecular targets at subcellular levels. When QDs are linked to suitable ligands that are site specific, it has been shown to be brighter and photostable when compared with organic dyes. Interestingly, pharmaceutical sciences are exploiting NPs to minimize toxicity and undesirable side effects of drugs. The unforeseen hazardous properties of the carrier NPs themselves have given rise to some concern in a clinical setting. The kind of hazards encountered with this new nano-technology materials are complex compared with conventional limitations created by traditional delivery systems. The development of cadmium-derived QDs shows great potential for treatment and diagnosis of cancer and site-directed delivery by virtue of their size-tunable fluorescence and with highly customizable surface for directing their bio-activity and targeting. However, data regarding the pharmacokinetic and toxicology studies require further investigation and development, and it poses great difficulties to ascertain the risks associated with this new technology. Furthermore, toxic cadmium presents yet another intrinsic danger associated with nano-technology, which will emerge as a new type of hazard in the bio-medical industry. [27]

Advantages of Nano-particles

Nano-particles, being minute materials, offer numerous advantages across various applications. They notably enhance the bio-availability and effectiveness of bio-active compounds, ensuring better absorption and utilization within the body. Additionally, they enable dose proportionality and reduce variability in drug absorption between fed and fasted states. Their smaller size allows for more compact dosage forms, like smaller tablets, facilitating easier administration. Compared to non-nano-particle formulations, drugs encapsulated within nano-particles exhibit enhanced stability and bio-availability. Moreover, the increased surface area of active agents in nano-particle formulations promotes faster dissolution in aqueous environments, such as the human body, leading to improved bio-availability, lower required drug doses, and decreased toxicity levels. All of these features highlight how important nano-particles are to improving treatment outcomes and drug delivery methods [28].

Science and Technology of Nano- Carriers

Encapsulation of therapeutic agents in bio-degradable and bio-compatible carriers has been considered a safe way of delivering anticancer drugs. Unprotected drugs, when introduced into the body, exhibit a short in vivo half-life and deficient antitumor properties. Consequently, the effective delivery of anticancer drugs necessitates protection from the hostile immunological and enzymatic environments of the body. Microencapsulation systems and microcarriers have been extensively utilized for the protection and delivery of bio-active agents, including drugs, vaccines, nutrients, and cosmetics, both in the research and development as well as manufacturing of various products. However, using nano-carrier technology can deliver targeted controlled release considerably more effectively [29].

Novel nano-carrier systems can make it possible to use certain drugs that were previously impractical to prescribe due to toxicities, high cost of manufacture, or because they were impossible to administer. Nano-carriers have a larger surface area than micronsized carriers and can potentially improve controlled release, increase solubility, improve bio-availability, and allow for more precise targeting of the entrapped pharmaceuticals. [30]

As a consequence of improved stability and targeting, the amount of drug required to exert a specific effect when encapsulated or incorporated to a nano-carrier is much less than the amount of drug administered in the free form. A timely, targeted release improves the effectiveness of therapeutics, broadens their application range, and ensures optimal dosage, thereby improving cost-effectiveness of the product. Reactive or sensitive materials, such as polynucleotides and polypeptides, can be turned into stable ingredients through encapsulation or entrapment by nano-carrier systems. Injectable emulsions for parenteral and enteric administration, intravascular infusion preparations, and vaccine dosage forms for subcutaneous or intramuscular injections are among the uses for nano-particles and other nano-carriers [31-33].

Applications of Nano-technology

Application of nano-technology in research and development in the field of pharmaceutical industry include formulation development, Nano-diagnosis, Nano- therapy (controlling drug delivery), and Remedial (renovated) medicine.

Nano- Diagnosis

A heart transplant is the ultimate treatment for chronic heart illnesses, particularly myocardial infarction. However, this may not be possible due to autoimmune disorders, organ rejection risks, and donor shortage. Recently, the creation of scaffolds has focused more emphasis on bio-mimetic materials based on nano-technology [34]. These scaffolds are made of nano-materials that aid in tissue regeneration and repair mechanically, electro-magnetically, and physically. To help tissue function and mend, they can seed cells at the location of an injury or deteriorating tissue [35].

The problems with the currently used conventional stents are being investigated in relation to nano-polymeric-coated bio-degradable stents. These new stents have the potential to lower the rate of platelet adhesion while simultaneously improving medication release characteristics. Blood-compatible and anti-thrombogenic stents are being made with nano-composite polymers, such as polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA), and polyhedral oligomeric silsesquioxane poly-(carbonate-urea) (POSS-PCU) [36-38]. There is a lot of research being done on nano-medicines with various properties and compositions to cure CVDs. According to Figure 3, these include metallic nano-particles, niosomes, liposomes, surface-modified nano-structures, exosomes, nano-tubes, nano-fibers, dendrimers, metallic nano-particles, poly (ethylene glycol)-ated (PEGylated) nano-spheres, hybrid nano-systems, and immunomodified nano-shells [39-43].

Nano- Bio-technology

Nano-bio-technology", an extended term, can be defined as the Science and Engineering involved in the design, synthesis and characterization of non-toxic bio-active nano-materials and devices which interact with cells and tissues at a molecular level with a high degree of specificity. These engineered materials and devices at the nano-meter scale are constituted by molecules and atoms that were manipulated for specific and controlled physico-chemical properties. The different synthetic methods of nano-engineered materials and devices, employing precursors from any of the three states of matter viz., solid, liquid and gas, have been broadly classified under "Top down" or "Bottom up" approaches. The photolithography process, which the semiconductor industry uses to create integrated circuits, is the best example of the "top down" technique, which is the process of integrating smaller-scale features into macroscopic material [44].

The neuron-astrocyte communication experiments [45] give the quintessential bio-logical illustration of the lithographic approach. In this study, neuron and astrocyte cell cultures were placed in adjacent wells in agar that were connected by a channel made of poly dimethyl siloxane, allowing the diffusion of soluble factors. "Bottom-up" approaches, on the contrary, begin by designing and synthesizing custom-made molecules that have the inherent ability to self-assemble into structures of higher order. The key to this strategy is designing molecules that, in response to physical or chemical stimuli (such as changes in pH, a particular solute's concentration, non-covalent interactions, the application of an electric field, etc.), self-assemble into macroscopic structures with desirable and distinctive physico-chemical properties that the constituents do not exhibit [46].

Nano- Medicine

Additionally important roles for nano-materials are played in the treatment of CVDs [47]. Applications of nano-materials are strongly tied to medical research and offer potent remedies for CVDs. Numerous novel approaches might improve these medicines' effectiveness. The use of nano-technology and nano-materials for CVDs has advanced during the previous few decades [48-58]. For certain medications whose clinical utility is restricted because of their toxicity or undesirable pharmacokinetic characteristics, NPs are thought to be safe and effective platforms. Common nano-materials and their shared characteristics utilised in CVD applications are shown in Table 1 [59-65].

Figure 3: Application of nano-theranostics for cardiovascular diseases.

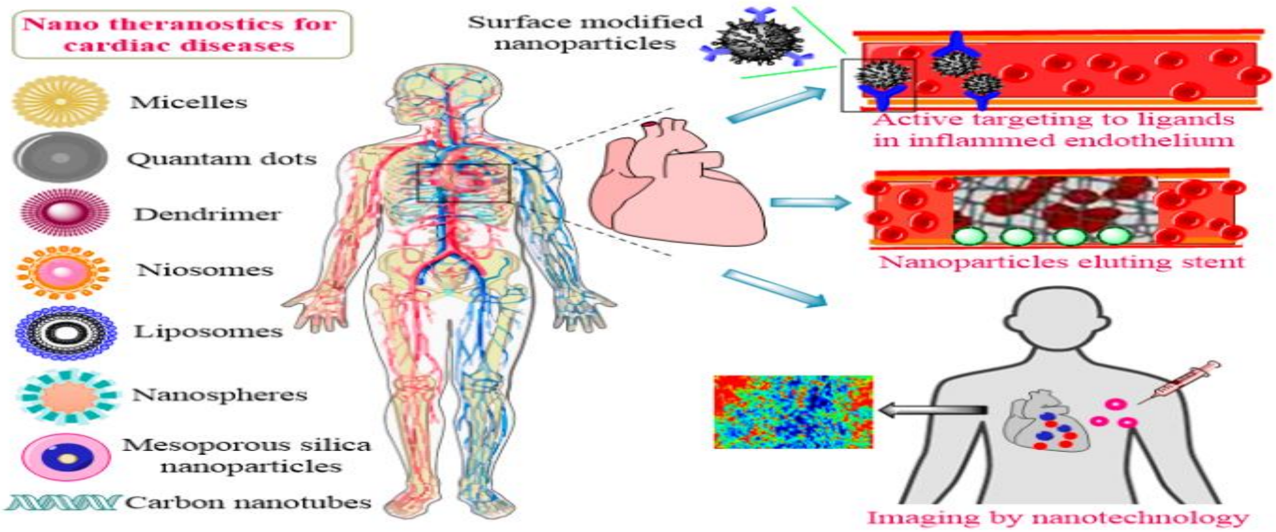


Table 1: Type and characteristics of nano-drug delivery systems for CVD therapy

Type	Structures	Drug loading techniques	Pros	Cons	References
Polymeric NPs	Nano-capsules and nano-spheres with lipophilic core	Physical/chemical encapsulation	Stability without leakage	Systemic toxicity	[60-61]
Liposomes	Bilayers of lipid	Physical/chemical encapsulation	Nontoxic and non-immunologic bio-compatibility	Leakage with less stability	[62-63]
Metal nano-materials	Nano-rods, nano-wires and nano-particles	Encapsulation (physical)	Magneto-optical response characteristic and antibacterial property	Toxicity, hard to degrade	[64]
Inorganic non-metallic nano-materials	Adjustable pore size with same measurement	Encapsulation (physical)	stable size, Large surface area, high drug loading	Low rate of bio-degradation	[65-66]
Polymeric micelles	Structure of core shell formulated by self-assembly	Physical/chemical encapsulation	High stability with easy preparation	Less stability, DE polymerization after dilution	[67]

Nano- therapy

Renovated medicine uses nano-technology materials to repair or replicate damaged tissues and organs, while nano-therapy assigns effective nano--systems to execute a more successful therapy while minimizing negative effects.

CONCLUSION

In conclusion, the integration of nano-technology into the pharmaceutical industry represents a paradigm shift, offering innovative solutions to longstanding challenges in drug discovery, development, and delivery. Nano-materials, particularly nano-particles, have emerged as powerful tools, enabling targeted drug delivery, enhanced therapeutic efficacy, and precise disease diagnosis. The multifaceted applications of nano-technology span across various domains, from cancer therapy utilizing zinc oxide nano-particles to the formulation of nano-medicines for cardiovascular diseases. Moreover, the versatility of Nano-carrier systems facilitates controlled release of therapeutic agents, minimizing toxicity and maximizing therapeutic outcomes. The development of nano-bio-technology further augments these advancements, offering tailored solutions for tissue repair and regeneration, as well as facilitating interactions at the molecular level with high specificity. Despite the immense potential, challenges such as safety concerns and regulatory complexities necessitate careful consideration and ongoing research. However, the transformative impact of nano-technology on pharmaceutical research and development cannot be overstated. Looking ahead, nano-technology holds the promise of revolutionizing personalized medicine through targeted therapies and precise diagnostics. As we continue to unlock the potential of nano-materials and refine nano-carrier technologies, we move closer to realizing the vision of more effective, targeted, and safer pharmaceutical interventions. In essence, the future of pharmaceutical research and development is intricately intertwined with the boundless possibilities offered by nano-technology, paving the way for a new era of healthcare innovation and improved patient outcomes.

REFERENCES

1. Haglund E, Seale-Goldsmith MM, Leary JF, 2009. Design of multifunctional nano-medical systems. Ann Bio-med Eng. 37, Pages 2048-2063. Doi: 10.1007/s10462-009-9241-2.

2. Seale-Goldsmith MM, Leary JF. 2009. Nano-bio-systems. Wiley Interdiscip Rev Nano-med Nano-bio-technol. 1, Pages 553-567. Doi: 10.1002/wnan.42.

3. Goldberg MS, 2019. Improving cancer immunotherapy through nano-technology. Nat Rev Cancer. 19(10), Pages 587-602. Doi: 10.1038/s41571-019-0217-5.

4. Wang Y, 2016. Bio-adaptability: an innovative concept for bio-materials. J Mater Sci Technol. 32(9), Pages 801-809. Doi: 10.1016/j.jmst.2016.06.001.

5. Raghavendra GM, Varaprasad K, Jayaramudu T, 2015. Bio-materials: design, development and bio-medical applications. Elsevier. Pages 21-44. Doi: http://dx.doi.org/10.1016/B978-0-323-32889-0.00002-9.

6. Feynman R, 1960. There's plenty of room at the bottom. Eng Sci. 23, Pages 22-36. Doi: https://doi.org/ 10.1515/9783839438039-022.

7. Mech A, Wohlleben W, Ghanem A, et al, 2020. Nano- or not nano-: A structured approach for identifying nano-materials according to the European Commission's definition. Small. 16(36), Pages 2002228. Doi: 10.1002/smll.202002228.

8. Anjum S, Abbasi BH, Shinwari ZK, 2016. Plant-mediated green synthesis of silver nano-particles for bio-medical applications: challenges and opportunities. Pak J Bot. 48(4), Pages 1731-1760.

9. Bhattacharjee R, Kumar L, Mukerjee N, et al, 2022. The emergence of metal oxide nano-particles (NPs) as a phytomedicine: A two-facet role in plant growth, nano--toxicity and anti-phyto-microbial activity. Bio-med Pharmacother. 155, Pages 113658. Doi: 10.1016/j.bio-pha.2022.113658.

10. Zulfiqar H, Amjad MS, Mehmood A, et al, 2022. Antibacterial, antioxidant, and phytotoxic potential of Phytosynthesized silver nano-particles using Elaeagnus umbellata fruit extract. Molecules. 27(18), Pages 5847. Doi: 10.3390/ molecules27185847.

11. Ehsan M, Raja NI, Mashwani ZUR, et al, 2022. Effects of Phytogenically synthesized bimetallic Ag/ZnO nano-materials and nitrogen-based fertilizers on bio-chemical and yield attributes of two wheat varieties. Nano-materials. 12(17), Pages 2894. Doi: 10.3390/nano-12172894.

12. Sarwer Q, Amjad MS, Mehmood A, et al, 2022. Green synthesis and characterization of silver nano-particles using Myrsine africana leaf extract for their antibacterial, antioxidant and phytotoxic activities. Molecules. 27(21), Pages 7612. Doi: 10.3390/molecules27217612.

13. Bandopadhyay S, Anand U, Gadekar VS, et al, 2022. Dioscin: A review on pharmacological properties and therapeutic values. Bio-factors. 48(1), Pages 22-55. Doi: 10.1002/bio-f.1815.

14. Anand U, Nandy S, Mundhra A, et al, 2022. A review on antimicrobial botanicals, phytochemicals and natural resistance modifying agents from Apocynaceae family: possible therapeutic approaches against multidrug resistance in pathogenic microorganisms. Drug Resist Updat. 51, Pages 100695. Doi: 10.1016/j.drup.2022.100695.

15. Gupta TK, Budarapu PR, Chappidi SR, et al, 2019. Advances in carbon based nano-materials for bio-medical applications. Curr Med Chem. 26(38), Pages 6851-6877. Doi: 10.2174/0929867326666181107111155.

16. Cy W, Makvandi P, Zare EN, et al, 2020. Advances in antimicrobial organic and inorganic nano-compounds in bio-medicine. Adv Therapeut. 3(8), Pages 2000024. Doi: 10.1002/adtp.202000024.

17. Biswas A, Bayer IS, Biris AS, et al, 2012. Advances in top–down and bottom–up surface nano-fabrication: techniques, applications & future prospects. Adv Colloid Interface Sci. 170(1–2), Pages 2-27. Doi: 10.1016/j.cis.2011.09.001.

18. Fu X, Cai J, Zhang X, et al, 2018. Top-down fabrication of shape-controlled, monodisperse nano-particles for bio-medical applications. Adv Drug Deliv Rev. 132, Pages 169-187. Doi: 10.1016/j.addr.2018.07.004.

19. Akhtar MJ, Ahamed M, Kumar S, et al, 2012. Zinc oxide nano-particles selectively induce apoptosis in human cancer cells through reactive oxygen species. Int J Nano-medicine. 7, Pages 845-57. Doi: 10.2147/IJN.S29642.

20. Burnett ME, Wang SQ, 2011. Current sunscreen controversies: a critical review. Photodermatol Photoimmunol Photomed. Pages 58–67. Doi: 10.1111/j.1600-0781.2011.00557.x.

21. Gelabert Y, Sivry R, Ferrari A, et al, 2014. Uncoated and coated ZnO nano-particle life cycle in synthetic seawater. Environ Toxicol Chem. Pages 341–349. Doi: 10.1002/etc.2447.

22. Contado, 2015. Nano-materials in consumer products: a challenging analytical problem. Front Chem. Doi: 10.3389/fchem.2015.00048.

23. Shi H, Magaye R, Castranova V, et al, 2013. Titanium dioxide nano-particles: a review of current toxicological data. Part Fibre Toxicol. Doi: 10.1186/1743-8977-10-15.

24. Gondikas AP, von der Kammer F, Reed RB, et al, 2014. Release of TiO2 nano-particles from sunscreens into surface waters: A one-year survey at the Old Danube recreational lake. Environ Sci Technol. Pages 5415–5422. Doi: 10.1021/es405596y.

25. V.L. Colvin, 2003. The potential environmental impact of engineered nano-materials, Nat. Bio-technol. Pages 1166–1170. Doi: 10.1038/nbt875.

26. C. Contado, A. Pagnoni, 2008. TiO 2 in Commercial Sunscreen Lotion: Flow Field-Flow Fractionation and ICP-AES Together for Size Analysis, Anal. Chem. Pages 7594– 7608. Doi: 10.1021/ac8012626.

27. Ghaderi S, Ramesh B, Seifalian AM, 2011. Fluorescence nano-particles "quantum dots" as drug delivery system and their toxicity: a review. Journal of drug targeting. 19(7), Pages 475-486. Doi: http://dx.doi.org/10.3109/1061186X.2010.526227.

28. Mozafari MR, 2006. Bio-active entrapment and targeting using nano-carrier technologies: an introduction. InNano-carrier technologies: Frontiers of nano-therapy. Dordrecht: Springer Netherlands. Doi: http://dx.doi.org/10.1007/978-1-4020-5041-1_1.

29. Khosravi-Darani K, Pardakhty A, Honarpisheh H, et al, 2007. The role of high-resolution imaging in the evaluation of nano-systems for bio-active encapsulation and targeted nano-therapy. Micron. 8(8), Pages 804-818. https://doi.org/10.1016/j.micron.2007.06.009.

30. Gibaud S, Rousseau C, Weingarten C, et al, 1998. Polyalkylcyanoacrylate nano-particles as carriers for granulocyte-colony stimulating factor (G-CSF). Journal of controlled release. 52(1-2), Pages 131-9. Doi: https://doi.org/10.1016/s0168-3659(97)00194-6.

31. Lemoine D, Préat V, 1998. Polymeric nano-particles as delivery system for influenza virus glycoproteins. Journal of Controlled Release. 54(1), Pages 15-27. Doi: https://doi.org/10.1016/s0168-3659 (97)00241-1.

32. Song CX, Labhasetwar V, Murphy H, et al, 1997. Formulation and characterization of bio-degradable nano-particles for intravascular local drug delivery. Journal of controlled release. 43(2-3), Pages 197-212. Doi: https://doi.org/10.1016/s0168-3659(96)01484-8.

33. Mombini S, Mohammadnejad J, Bakhshandeh, B, et al, 2019. Nourmohammadi, J.; Vahdat, S.; Zirak, S. Chitosan-PVA-CNT nano-fibers as electrically conductive scaffolds for cardiovascular tissue engineering. Int. J. Bio-l. Macromol. 140, Pages 278–287. Doi: https://doi.org/10.1016/ j.ijbio-mac.2019.08.046.

34. Mukhtar M, Ali H, Ahmed N, et al, 2020. Drug delivery to macrophages: A review of nano--therapeutics targeted approach for inflammatory disorders and cancer. Expert Opin. Drug Deliv. 17, Pages 1239–1257. Doi: https://doi.org/10.1080/ 17425247.2020.1783237.

35. Sevostyanov M, Baikin A, Sergienko K et al, 2020. Bio-degradable stent coatings on the basis of PLGA polymers of different molecular mass, sustaining a steady release of the thrombolityc enzyme streptokinase. React. Funct. Polym.150, Pages 104550. Doi:10.1016/j.reactfunctpolym.2020.104550.

36. Sun J, Sun K, Bai K, et al, 2019. A novel braided bio-degradable stent for use in congenital heart disease: Short-term results in porcine iliac artery. J. Bio-med. Mater. Res. 107, Pages 1667–1677. Doi: https://doi.org/10.1002/jbm.a.36682.

37. Maleki B, Alinezhad H, Atharifar H, et al, 2019. One-pot synthesis of polyhydroquinolines catalyzed by ZnCl2 supported on nano- Fe3O4@ SiO2. Organic Preparation Procedures International. 51, Pages 301–309. Doi: http://dx.doi.org/ 10.1080/00304948.2019.1600132.

38. Cervadoro A, Palomba R, Vergaro G, et al, 2018. Targeting inflammation with nano-sized drug delivery platforms in cardiovascular diseases: Immune cell modulation in atherosclerosis. Front. Bio-eng. Bio-technol. 6, Pages 177. Doi: https://doi.org/10.3389/fbio-e.2018.00177.

39. Sandoval-Yañez C, Castro Rodriguez, C. Dendrimers, 2020. Amazing platforms for bio-active molecule delivery systems. Materials j 13, Pages 570. Doi: 10.3390/ma13030570.

40. Dizaj S.M, Rad A.A, Safaei N, et al, 2019. The application of nano-materials in cardiovascular diseases: A review on drugs and devices. J. Pharmaceutical Pharma Sci. 22, Pages 501–515. Doi: http://dx.doi.org/10.18433/jpps30456

41. Thompson LC, Sheehan NL, Walters DM, et al, 2019. Airway exposure to modified multi-walled carbon nano-tubes perturbs cardiovascular adenosinergic signaling in mice. Cardiovasc. Toxicol. 19, Pages 168–177. Doi: https://doi.org/ 10.1007/s12012-018-9487-6.

42. Siegel RW, Hu E, Cox DM, et al, 1999. Research Programs on Nano-technology in the World: Americas, Asia/Pacific, and Europe. Nano-structure Science and Technology: R&D Status and Trends in Nano-particles. Nano-structured Materials, and Nano-devices. Pages 131-49. Doi: 10.3390/ma17071621.

43. Takano H, Sul JY, Mazzanti ML, et al, 2002. Micropatterned substrates: approach to probing intercellular communication pathways. Analytical chemistry. 74(18), Pages 4640-4646. Doi: https://doi.org/10.1021/ac0257400.

44. Silva GA, 2004. Introduction to nano-technology and its applications to medicine. Surgical neurology. 61(3), Pages 216-20.Doi: https://doi.org/10.1016/j.surneu.2003.09.036.

45. Jiang W, Rutherford D, Vuong T, et al, 2017. Nano-materials for treating cardiovascular diseases: A review. Bio-act. Mater. 2, Pages 185–198. Doi: https://doi.org/10.1016/j.bio-actmat.2017.11.002.

46. Barani M, Bilal M, Rahdar A, et al, 2021. Nano-diagnosis and nano-treatment of colorectal cancer: An overview. J. Nano-part. Res. 23, Pages 18. Doi: https://link.springer.com/article/ 10.1007/s11051-020-05129-6.

47. Barani M, Bilal M, Sabir F, et al, 2020. Nano-technology in ovarian cancer: Diagnosis and treatment. Life Sci. 266, Pages 118914. Doi: https://doi.org/10.1016/j.lfs.2020.118914.

48. Barani M, Mukhtar M, Rahdar A, et al, 2021. Progress in the application of nano-particles and graphene as drug carriers and on the diagnosis of brain infections. Molecules 26, Pages 186. Doi: https://doi.org/10.3390/molecules26010186.

49. Barani M, Mukhtar M., Rahdar A, et al, 2021. Recent advances in nano-technology-based diagnosis and treatments of human osteosarcoma. Bio-sensors.11, Pages 55. Doi: https://doi.org/10.3390/bio-s11020055.

50. Ghazy E, Kumar A, Barani M, et al, 2020. Scrutinizing the therapeutic and diagnostic potential of nano-technology in thyroid cancer: Edifying drug targeting by nano--oncotherapeutics. J. Drug Deliv. Sci. Technol. 61, Pages 102221. Doi: http://dx.doi.org/10.1016/j.jddst.2020.102221.

51. Hasanein P, Rahdar A, Barani M, et al, 2021. Oil-in-water microemulsion encapsulation of antagonist drugs prevents renal ischemia-reperfusion injury in rats. Appl. Sci. 11, Pages 1264. Doi: https://doi.org/10.3390/app11031264.

52. Mukhtar M, Bilal M, Rahdar A, et al, 2020. Nano-materials for diagnosis and treatment of brain cancer: Recent updates. Chemosensors. 8, Pages 117. Doi: https://doi.org/10.3390/chemosensors8040117.

53. Qindeel M, Barani M, Rahdar A, et al, 2021. Nano-materials for the diagnosis and treatment of urinary tract infections. Nano-materials. 11, Pages 546. Doi: https://doi.org/10.3390/nano-11020546.

54. Rahdar A, Hajinezhad MR, Sargazi S, et al, 2021. Bio-chemical effects of deferasirox and deferasirox-loaded nano-micellesin iron-intoxicated rats. Life Sci. 270, Pages 119146. Doi: https://doi.org/10.1016/j.lfs.2021.119146.

55. Rahdar A, Sargazi S, Barani M, et al, 2021. Lignin-stabilized doxorubicin microemulsions: Synthesis, physical characterization, and in vitro assessments. Polymers. 13, Pages 641. Doi: https://doi.org/10.3390/polym13040641.

56. Sabir F, Barani M, Rahdar A, et al, 2021. How to face skin cancer with nano-materials: A review. Bio-interface Res. Appl. Chem. 11, Pages 11931–11955. Doi: http://dx.doi.org/10.33263/BRIAC114.1193111955.

57. Deng Y, Zhang X, Shen H, et al, 2020. Application of the nano--drug delivery system in treatment of cardiovascular diseases. Front. Bio-eng. Bio-technol. 7, Pages 489. DoiL: https://doi.org/10.3389/fbio-e.2019.00489.

58. Wang K, Li Y-F, Lv Q, et al, 2018. Bergenin, acting as an agonist of PPARγ, ameliorates experimental colitis in mice through improving expression of SIRT1, and therefore inhibiting NF-κB-mediated macrophage activation. Front. Pharmacol. 8, Pages 981. https://doi.org/10.3389/fphar.2017.00981.

59. Elsabahy M, Wooley KL, 2012. Design of polymeric nano-particles for bio-medical delivery applications. Chem. Soc. Rev. 41, Pages 2545–2561. Doi: https://doi.org/10.1039/c2cs15327k.

60. Chandarana M, Curtis A, Hoskins C, 2018. The use of nano-technology in cardiovascular disease. Appl. Nano-sci. 8, Pages 1607–1619. Doi: https://doi.org/10.1007/s13204-018-0856-z.

61. Bao L, You B, Shi S, et al, 2018. Metastasis-associated miR-23a from nasopharyngeal carcinoma-derived exosomes mediates angiogenesis by repressing a novel target gene TSGA10. 37, Pages 2873–2889. Doi: https://doi.org/10.7150/ijbs.59688.

62. Vimbela GV, Ngo SM, Fraze C, et al, 2017. Antibacterial properties and toxicity from metallic nano-materials. Int. J. Nano-med. 12, Pages 3941.Doi: https://doi.org/10.2147/IJN.S134526.

63. Wang X.-F, Xiao H, Chen P-Z, et al, 2019. Pure organic room temperature phosphorescence from excited dimers in self-assembled nano-particles under visible and near-infrared irradiation in water. J. Am. Chem. Soc. 141, Pages 5045–5050. Doi: https://doi.org/10.1021/jacs.9b00859.

64. Yu Y, Shi Y, Zhang B, 2018. Synergetic transformation of solid inorganic–organic hybrids into advanced nano-materials for catalytic water splitting. Acc. Chem. Res. 51, Pages 1711–1721. Doi: http://dx.doi.org/10.1021/acs.accounts.8b00193.

65. Cagel M, Tesan FC, Bernabeu E, et al, 2017. Polymeric mixed micelles as nano-medicines: Achievements and perspectives. Eur. J. Pharm. Bio-pharm. 113, Pages 211–228. https://doi.org/10.1016/j.jconrel.2021.02.031.