doi.org/10.36721/PJPS.2025.38.2.REG.13358.1

Nanotechnology, nano-systems and applications of nanoparticles in novel drug delivery - a comprehensive review

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Abstract: Nanotechnology is one of the most important research fields and is widely being used in various subareas of medicine like prevention, mitigation and therapy. It has enabled novel drug applications with particle dimensions ranging from 1 to 100 nm. The physical, biological, and chemical properties of various active pharmaceutical ingredients could be improved. Nanoparticles provide a greater advantage over conventional drug delivery systems and enhance drug performance by enhancing solubility, bioavailability, surface area, and dissolution rate, and by reducing dose, inter-patient variability and fed or fasted state variability. Nanosystems have various types, such as carbon nanotubes, dendrimers, liposomes, metallic nanoparticles, nanocrystal quantum dots, polymeric micelles, and polymeric nanoparticles. Nanomedicine serves various benefits in the prevention of premature drug degradation, improvement of drug intracellular permeability, enhancement of tissue absorption, and interaction with the organic and biological environment. The current review provides updated advances in the field of nanomedicine, promising aspects of nanotechnology in drug delivery, and types of nanoparticles that can serve in the treatment of diseases as novel carriers.

Keywords: Nanotechnology, Nanosystems, Metallic Nanoparticles, lipid-based nanoparticles, protein nanoparticles, nanomedicines, regulatory guidelines

Submitted on 06-09-2024 – Revised on 25-11-2024 – Accepted on 12-12-2024

INTRODUCTION

Nanotechnology is widely used for numerous applications in agriculture, fiber and textiles, space forensic science, and medical therapeutics (Haleem *et al*., 2023). Nanotechnology is widely used in various subareas of medicine, like prevention, mitigation and therapy. It has enabled novel drug applications with particle dimensions ranging from 1 to 100 nm (Shrestha *et al*., 2020). The physical, biological and chemical properties of various active pharmaceutical ingredients have been improved using nanotechnology (Abid *et al*., 2022).

However, both biodegradable and non-biodegradable systems can be manufactured, but biodegradable is used most frequently to enhance the therapeutic efficacy of various aqueous, soluble, insoluble, and bioactive drugs by improving solubility, bioavailability, and retention time. Besides its beneficial effects, it also comes with safety and toxicity concerns as it has the potential to provoke strong immune responses, enhanced production of reactive oxygen species, disturbances of cellular components, highly stable systems that hinder drug distribution to desired sites and mecha nism of interaction of these systems to cellular level isn't clearly understood yet. (Zhang *et al*., 2020)

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History

The first drug delivery system based on nanotechnology was lipid vesicles, which were then named liposomes in the 1960s (Park *et al*., 2022). Subsequently, several other inorganic and organic methods for the delivery of drugs were developed. For the delivery of macromolecules, the first polymer system for controlled release was described in 1976 (Zhang *et al*., 2019). In 1980, the first complex system for drug delivery capable of cell-specific targeting and responding to pH changes for drug release was developed (Aghdam *et al*., 2019). The concept of stealth liposomes (long-circulating liposomes) was explained in 1987 (Sharma *et al*., 2021). Then the role of PEG in increasing the circulation time of liposomes and their use in polymeric nanoparticles was established in 1990 and 1994 (Ibrahim *et al.*, 2020). These discoveries paved the way for the development of doxorubicin liposomes and the approval of Doxil® for the treatment of AIDS in 1995. Doxorubicin was encapsulated in PEGylated liposomes to reduce its toxicity by making it site specific, enhanced efficacy by enhancing drug stability, and enhanced its circulatory time by reducing its uptake by phagocyte system (Chowdhury *et al*., 2022). Another liposome based nano-formulation approved by FDA is Daunoxome® which contains daunorubicin for the treatment of karposi's carcinoma. However PEGylated liposomes were highly stable which reduces the release of drugs in tumor cells thus reducing its cytotoxic potential.

Table 1.1: Nanosystem features and functions

Types	Size (nm)	Features	Medicinal agents	Function	References
Carbon Nanotubes	Diameter (0.5-3) Length (20-1000)	Single walled or multiple walled nanotube are formed from crystalline carbon sheets. These crystals have unique electrical properties and remarkable strength.	Anthracycline anticancers i.e. dauxorubicin	Enhanced solubility and permeability across cell, used as carrier for peptide and gene delivery.	(Law Simon *et al* 2024) (Yaghoubi & Ramazani, 2020)
Dendrimers	<10	Comprises of three parts core, branch, surface, monodisperse system highly branched produced by process of controlled polymerization.	Chemotherapeutic agents i.e. Bortezomib, docetexal, trastuzumab	Controlled delivery, long circulatory, targeted delivery to liver and macrophages	(Kharwade *et al*., 2024) (Kumar, Khan, & Gupta, 2020)
Liposomes	50-100	Phospholipid vesicles, enhanced entrapment efficiency, biocompatible.	Anti-diabetic i.e. glibenclamide (Maritim, Boulas, & Lin, 2021) Anti-cancers i.e. Nitroimadazole	Active and passive gene, peptide, protein delivery, long circulatory,	(Yan *et al*., 2023) (Li *et al*., 2019)
Quantum dots	2-9.5	Semi-conducting material size ranging from 10-100Å, high UV excitation and photo stability, bright flourence.	Biomedical imaging and drug delivery i.e. iron and doxorubicin quantum dots	Color imaging of hepatic cells for long term, immunoassay, breast cancer cell surface labeling, and receptor-mediated endocytosis.	(Joshi *et al*., 2019) (Nasrollahi *et al*., 2020)
Metallic nanoparticles	<100	Colloids of gold/silver, small size with remarkably high surface area, stable	Gold plated metallic nanoparticles of doxorubicin to reduce cardiotoxic effects of doxorubicin	Diagnostic assay, drug or gene delivery, enhancement of radiotherapy, reduction of toxicity	(Khurshid *et al*., 2024) (Du *et al*., 2018)
Polymeric miscells	10-100	High efficiency of drug entrapment, biostability, payload.	Anticancer drug docetaxel	Active and passive targeted drug delivery, long circulatory, diagnostic value.	(Cheng *et al*., 2023) (Kotta *et al*., 2022) (Atanase, 2021)
Polymeric nanoparticles	10-1000	Biocompatible, biodegradable, Drug protection.	Analgesics i.e. morphiceptic, kyotorphin Nerve growth factors for alzeimer's and parkinson's disease	Sustained and controlled drug delivery, surface modified and stealth nanoparticle for active/passive delivery of drugs.	(Begines *et al*., 2020) (Hartl, Adams, & Merkel, 2021)

Table 1.2: Classification of nanoparticles

Types	Characteristic	Applications	References
Carbon-based	Carbon nanotube are included in this class. Fullerenes has nanomaterial of globular shape i.e. carbon's allotropic forms.	Support medium for catalyst, for environmental remediation as gas adsorbents. Anticancer drugs i.e. paclitaxel, docetaxel	(Cabaleiro *et al*., 2020) (Raj *et al*., 2021)
Metal	Made up of metal precursors having unique optoelectrical properties e.g. Ag, Cu	Gold nanoparticles are used for high resonance SEM imaging,	(Jamkhande *et al*., 2019) (Sharma *et al*., 2021)
Ceramics	Non-metallic inorganic solids can be found forms as porous, dense, amorphous, hollow forms, polycrystalline.	Imaging, photocatalysis, photodegradation of dyes, catalysis. Iron oxide based nanoparticles with ceramic materials are used to protect from pH and temperature effects.	(Paul & Sharma, 2020) (Chan, Li, Chang, & Hsiao, 2022)
Semiconductor	Possess properties of metals/non-metals. With bandgap tuning alteration exist in their properties.	Copper sulphide nanoparticles for transdermal drug delivery	(Hossain, *et al*., 2023) (Hany, 2020)
Polymeric micelle	Organic nanoparicles, mostly nanospheres, they are matrix particles solid in nature other molecules being adsorbed at surface.	Used for anticancers, nutraceuticals, antimicrobials, genetic drugs i.e. FDA approved drug onpattro® (patisiran) for amylpidosis	(Begines *et al*., 2020) (Dilliard & Siegwart, 2023)
Lipid based	Spherical in diameter ranging from 10-1000nm, matrix of lipophillic molecules and solid core of lipids.	Used s drug carrier and for drug deliver, release of RNA in cancer treatment. For transdermal drug delivery of diclofenac sodium	(Kumar, 2019) (Hany, 2020)
Nano vaccines	Diameter ranging from 1-30nm, types of nanovaccine includes inorganic, polymeric, liposomal, and virus like nanoparticles	Used for enhanced immunogenicity, safety and scalability. iron oxide nanoparticle are used for delivery of vaccine because of its better immune status, increased cellular uptake, efficient traceability and low cost	(Gheibi Hayat & Darroudi, 2019)

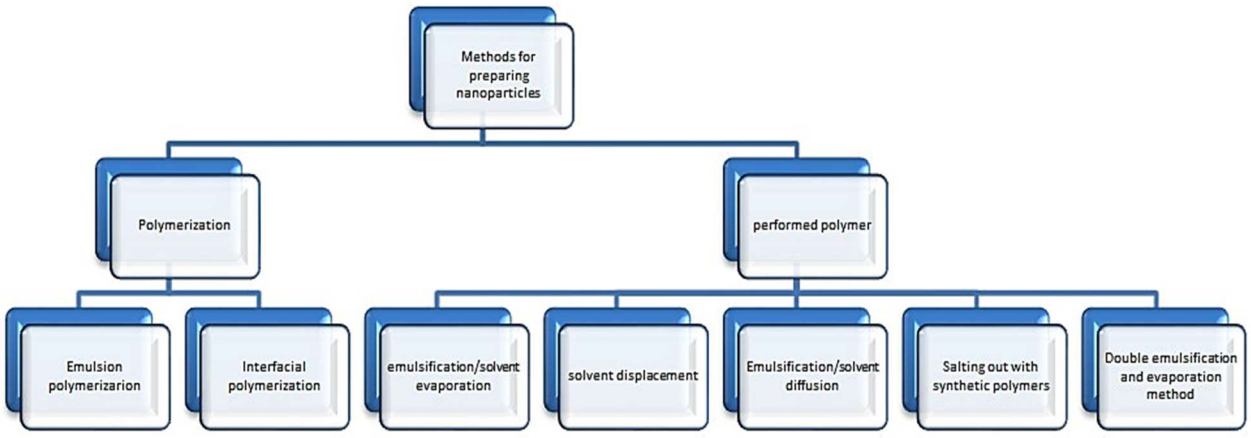

Fig. 1.1: Method of nanoparticle preparation

There are various types of nanosystems which holds significant potential (Zhang *et al*., 2020). More than two dozen therapeutic products based have been approved for clinical use to date. The dominant classes among first-generation products are polymer-drug conjugates and liposomal drugs with improved therapeutic efficacy (Haleem *et al*., 2023).

Emerging nanosystems

Different emerging nanosystems have been designed and are being used to overcome the potential drawbacks associated with various drug delivery techniques. Representative systems are carbon nanotubes, dendrimers, liposomes; quantum dots and metallic nanoparticles (Seaberg *et al*., 2021). Nanosystems serve as potential carriers for anticancer drugs i.e. dauxorubicin, methrotrexate, anti-inflammatory drugs and steroidal drugs i.e. dexamethasone and also have potential in reversing the multidrug resistance in chemotherapy (Faheem *et al*., 2020).

There are various types of nanosystems has been developed, their features and functions described in the table 1.1

Nanoparticles

Various materials at the nanoscale level have been produced, which include materials of size less than 100 nm called nanoparticles (Joseph *et al*., 2023). Core-shell nanoparticles are made up of three layers: one is an outer layer called a surface layer, the other is a shell layer, and the third is a nanoparticle called a core, which carries drug substances for their delivery at target site, for sequence controlled delivery and protection of sensitive drugs i.e. peptides and hormones. (Khan, Saeed, and Khan, 2019) Polymeric nanoparticles are one of the innovative delivery systems for the delivery of medicinal plants. They are colloidal systems that serve the function of controlled delivery at the target site of drug action (Kianfar, 2021). There are two approaches to forming: top-down or bottom-up. The dispersion of polymers forms polymeric nanoparticles and the polymerization of monomers, respectively (Abid *et al*., 2022). The drug formulation depends on the suitable polymeric system chosen, which has higher encapsulation efficiency and enhanced bioavailability. The desired nanoparticle-based formulations are achieved through computational modeling. The encapsulation efficiency of polymeric nanoparticles is higher than that of other nano-formulation systems. Such systems are superior to traditional drug delivery in terms of therapeutic impact, targeted delivery, and controlled drug release (Dang and Guan 2020). To make drug delivery targeted, they must be persistently circulated in blood circulation; thus, the surface is modified by the coating with hydrophilic polymers to repel plasma proteins and protect them from opsonization and macrophages of MPS (mononuclear phagocytic system) organs (Fang *et al*., 2023). Protein-based nanoparticles can be used for targeted therapies for various organs such as the lungs (Carrasco-Esteban *et al*., 2021), cardiovascular system (Banik *et al*., 2019), boosting the immune system via vaccination (Kheirollahpour *et al*., 2020), liver (Böttger *et al*., 2020), breast (Kunde and Wairkar, 2022), heart (Banik *et al*., 2019), kidneys (Huang *et al*., 2021) and spleen (Afshari-Kaveh *et al*., 2021). Careful designing of these systems is required concerning the site of target, nature of the concerned drug and route of administration. Biological barriers are dependent on the target site, tissue, and circulation. Surface charge plays an important role when it comes to the internalization at the cellular level; it determines whether they will cluster with or adhere to red blood cells or interact with other charged membranes *in vivo.* Cationic charge on the surface is most favorable as it enhances the interaction between biological surfaces with these systems, and hence they internalize at a greater rate and extent (Kianfar, 2021).

Advantages over conventional DDS

Nanoparticles provide a greater advantage over conventional drug delivery systems and enhance drug performance by enhancing solubility, bioavailability, surface area and dissolution rate and by reducing dose, inter-patient variability and fed or fasted state variability (Sultana *et al*., 2022). The actual target in drug delivery systems other than ordinary DDS is to improve and enhance the release of active ingredients in drugs at specific sites at the required rate and dose. Poorly soluble substances that have a short half-life show better solubility and an enhanced half-life. This is actually due to the sustained release of the drug at the target site, which in turn reduces the number of doses needed to attain maximum concentration (Hami 2021). Another advantage is for patients, as they feel ease and comfort as therapeutic performance is better maintained through this than with conventional DDS. It also has the advantage of having a having a first-pass effect on ordinary DDS, specifically in the metabolism of water-insoluble drugs (Duan *et al*., 2020). Another unique technical aspect in the DDS is its targeting capability to only affected tissue which enhances the therapeutic effect. These unique points make nanotechnology as a DDS more superior in the research and drug development processes (Yusuf *et al*., 2023). The degradation of a drug (either through enzymes or chemicals) can be prevented in which drugs are absorbed or encapsulated (Moller *et al*., 2019). These particles can act as drug carriers or adjuvants in vaccines by entrapping or dissolving active ingredients in them. In comparison with ordinary drug delivery systems, nanomaterials have the advantage of being very small with greater surface area, due to which they can make entry into cells easily. It also enhances many factors of drug delivery, including absorption and stability, making it superior to common drug delivery systems (Macedo *et al*., 2020). Instead of common drug delivery systems, the well-controlled and

steady release of drugs for longer periods happens both during transportation and at the target site. It also improves distribution as well as clearance from the targeted site of the drug, making it more efficacious with a reduction in side effects (Li *et al*., 2020).

Classification of nanoparticles

Nanoparticles are simple molecules whose sizes range from 1-100 nm in size. There are various subtypes depending on their nature and size. With the advancement of techniques of electron microscopy, nano- and micro fever swept across the world of science (Modena *et al*., 2019). Interest has been developed in the preparation of particles having variable properties depending on the size, shape, and structure of these particles. They are different types: particles having a uniform structure and comprised of various elements (solid-lipid), particles with chemical and physical properties (Janus particles), empty interior particles (hollow particles), coated outer layer and solid inner particles (core-shell particles), reverse bumpy balls (encapsulated cores with shells), and nanorattle type (yolk-shell) (Mourdikoudis *et al*., 2021). They are classified based on size, morphology, and chemical properties. They can be widely classified as one-dimension (chemical/biological sensors), two-dimension (carbon nanotubes), and three-dimension (dendrimers and quantum dots). They can also be classified based on their chemical characteristics. Some well-known classes on the basis of chemical and physical characteristics mentioned in table 2.2.

Methods for preparation

Methods used for the preparation of nanoparticles can be classified into two main categories based on the use of monomers or polymers. One of them is polymerization (emulsion and interfacial), while the other is polymerization (emulsification, solvent displacement, solvent diffusion, salting out, and double emulsification) (Jamkhande *et al*., 2019). They can be formed by various methods, including solvent displacement or precipitation, coacervation or ionic gelations, the polymerization method, solvent evaporation, spontaneous emulsification, and solvent diffusion (fig 1.1). The solvent displacement or precipitation method is the most appropriate method used for poorly soluble drugs. By optimizing various formulation parameters, one can effectively control the size of the nanosystem and the release profile of the drug (Herdiana *et al*., 2022).

Nanomedicine

Since 1965, more than 50 nanomedicines had approved by FDA and are used clinically. They are available for intravenous or oral administration (Germain *et al*., 2020). FDA approved nanomedicines include protein, liposomes, micelle, polymer and inorganic nanoparticles (Abdel-Mageed *et al*., 2021). Application of nanoscience to prevent, diagnose and treat diseases has progressed remarkably. The process of development evokes greater challenges than any other nano-system (Zhang *et al*., 2020). Nano-drug delivery reduces the cost and toxicity of various therapeutic formulations (Vega-Vásquez *et al*., 2020).

Nanomedicine enhances the specificity, efficacy, and therapeutic index of drugs. It serves various benefits in the prevention of premature drug degradation, improvement of drug intracellular permeability, enhancement of tissue absorption, and interaction with the organic/biological environment (Pelaz *et al*., 2017). Using nanotechnology in medicine, one can achieve: (1) enhanced delivery of poorly aqueous soluble drugs i.e. Rapamycin which is an immunosuppressant is formulated in nanocrystals (RUPAMUNE®) (2) intracellular drug delivery of macromolecules to sites of action i.e. Interleukin IL-2 receptor/diphtheria toxin for T-cell lymphoma are protein based nanoparticles (ONTAK®) (3) transcytosis of drug particles across tight barriers of endothelial and epithelial layers i.e. Trastuzumab Emtansine for metstatic breast cancer are protein based nanoparticles (kadcycla®) (4) targeted drug delivery in cells and tissues i.e. paclitaxel in breast cancer are protein based nanoformulation (Abraxane®) (5) combination therapy co-delivery of two or more therapeutic modalities i.e. two antiretroviral medication cabotegravir and rilpivirine (Cabenuva®) (6) visualization of drug delivery sites by combination of therapeutic agents with imaging modalities i.e. iron oxide nanoparticles in anemia in patients with chronic renal disease (feraheme®) (Zhang *et al*., 2020) (7) nanomedicine based controlled and targeted vaccine delivery i.e. SARS-COV-2 vaccine®. Besides the advantages of there are also various challenges and drawbacks associated with its development i.e. lack of safety and efficacy characterization methods, lack of toxicity evaluation data for each type of formulation, lack of regulatory guidelines. The approval process by FDA is same as other drugs. The FDA has issued guidelines to industries regarding nanotechnology use in nanomedicine formulation, which encourages manufacturers to consult with FDA regarding any scientific and regulatory issue. (Thapa and Kim, 2023)

Ethical and regulatory affairs

Regulatory guidelines are crucial in developing nano-drug delivery systems and their applications. FDA regulates these Nanosystems as drugs or devices based on their therapeutic use. EMA (European Medicine Agency) regulations provide guidelines on the safety, efficacy, and quality of the systems. ISO provides standard guidelines on biocompatibility, characterization, and toxicity of nano formulations. GMP (good manufacturing practice) and GLP (good laboratory practice) guidelines by WHO and environmental regulations should be followed while manufacturing these systems. Various other regulatory bodies are there that provide guidelines regarding the safe and effective use of Nano drug delivery systems including

the National Nanotechnology Initiative (NNI), the International Council on Nanotechnology (ICON), and the American Society for Testing and Materials (ASTM). Ethical considerations must be taken into account while using nano drug delivery systems i.e. informed patient consent must be taken briefing them about benefits and potential risks, and ensuring that these systems are accessible and affordable for all patients. (Csóka, Ismail, Jójárt-Laczkovich, and Pallagi, 2021)

CONCLUSION

Nanotechnology has proven various benefits in drug delivery. Nanoparticles can also be employed for targeted drug delivery with slight structural modifications. Nanomedicine serves various benefits in the prevention of premature drug degradation, improvement of drug intracellular permeability, enhancement of tissue absorption, and interaction with the organic and biological environment. This can be achieved by formulating site-specific nanoparticles, releasing drugs on demand, reducing toxicities, and allowing new combinatorial treatments. Hence allowing medicine to be used for therapeutic purposes with precision, it is a promising approach with significant potential in the near future. Despite of its advantages it offer challenges as well in respect of safety, toxicity, immunogenicity, cost effectiveness and oxidative stress induction. It is often associated environmental pollution i.e. Nano air pollution inhaled nanoparticles can cause serious health hazards to human lungs. Therefore researches must be carried to manufacture nanomedicine efficiently and effectively.

Future scope

Nanomedicine's future scope is promising and vast, with potential medicinal applications. Future therapeutic perspectives include gene therapy, infectious disease, cancer chemotherapy, regenerative medicine (neurological and CVS disorder), personalized medicine and diagnostic perspectives include the development of biosensors for disease monitoring, upgraded imaging procedures, and the development of portable devices. However, challenges needed to be addressed and opportunities in this field are significant to realizing its full potential.

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