IMMENSE ROLE OF NANOPARTICLES IN DRUG DELIVERY

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**ABSTRACT**

Nanotechnology is the study of molecules also called Nanoparticles. The field of nanotechnology has grabbed attention due to its uses in various fields like Oncology, Data mining, Quantitative Structure-Activity Relationship (QSAR), Drug Delivery, etc. Nowadays Nanotechnology is vastly used in the medical field in the drug delivery system. Nanoparticles such as Metal Nanoparticles, Polymeric micelle, Stimuli-responsive micelle, Polymeric nanoparticles, Dendrimers, and carbon Nanotubes are used in drug delivery. In this review, we will briefly overlook the types of nanoparticles and the Use of Polymeric Nanoparticles in Cancer treatment.

**KEYWORDS**

 Metal Nanoparticles, Mesoporous Silica System, Polymeric Micelle, Polymeric Nanoparticles, Dendrimers, Carbon Nanotubes.

**INTRODUCTION**

 Nanotechnology is the study of structures and molecules on the scale of a nanometer ranging in between 1-100 nm and technology that utilizes in practical applications such as devices, etc is called Nanotechnology. Nano is the Greek prefix meaning 'dwarf'. Nanotechnology was a concept introduced by Richard Feynman in his lecture 'There is Plenty of Room at the Bottom' in 1959[23]. Nanotechnology is applied in areas like bioimaging, bio-detection, and drug delivery. Nanoparticles that are used as drug delivery vehicles are very low in dimension. The dimension of the nanoparticle should be <100 nanometers in one dimension. For example, Nano molecules used in anticancer drug molecules including Doxorubicin, and CPG oligonucleotide have been successfully loaded on DNA nanostructure. To achieve drug delivery, it is important to understand the interaction of nanomaterial with the biological environment targeting cell surface receptors, drug release, multiple drug administration, stability of therapeutic agent, and molecular mechanism of signaling involved in the pathology of disease under consideration [1]. Various nanoparticles such as paclitaxel, doxorubicin, 5-fluorouracil, and dexamethasone have been successfully formulated. Drug efficacy of nanoparticles is reduced due to various factors like instability of the drug inside the cell, unavailability due to multiple targeting or chemical properties of delivering molecule, damage in the signaling pathway, or drug degradation. The efficacy of therapeutic treatment can be maximized in numerous ways because nanoscale intelligent systems can rapidly detect and respond to disease states. Nanotechnology has been developed in the field of medicine, engineering, physics, and medicine. The drug loaded in the nanoparticle formulation releases a high dose for a prolonged period and the proliferation of vascular smooth muscles is completely inhibited.[2][3][5]

* Key properties of nanoparticles are:
1. Nanoparticles should have at least one dimension of about 1-100 nm.
2. Nanoparticles are designed through methodologies that exhibit fundamental control over physical and chemical attributes.
3. Nanoparticles can be combined to form a larger structure.[2]
* Advantages of nanotechnology in the field of pharmacy:
1. Increase surface area.
2. Enhance solubility.
3. Increase rate of dissolution.
4. Increase in oral bioavailability.
5. Less amount of doses are required and reduce the number of doses.
6. Protection of drug from degradation.
7. More rapid onset of therapeutic action.
8. Achievement of drug targeting.
9. Passive targeting of drugs to the macrophages present in the liver and spleen.[3]

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| Period | Before Nanotechnology (Past) | Transition Period (Present) | Mature Nanotechnology (Future) |
| Technology | Emulsion-based preparation of nano/microparticles | Nano/microfabrication | Nano/micro manufacturing |
| Examples | * Liposomes
* Polymer micelles
* Dendrimers
* Nanoparticles
* Nanocrystals
* Microparticles
 | * Microchip systems Microneedle transdermal delivery systems
* Layer-by-layer assembled systems
* Micro dispersed particles
 | * Nano/micro machines for scale-up production
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Table 1. Examples of drug delivery technologies in relation to the current nanotechnology. [4]

**DISCOVERY AND FURTHER STUDIES**

 Nanoparticles were first used in the 4th century A.D. The best example is the Lycurgus Cup from British Museum, which represents the achievement glass industry. In 1857, Michael Faraday studied 'Ruby gold' and concluded that ruby gold can make the most interesting nanoparticles. In 1986, Binning and Rohrer received the Noble Prize for their design of a Scanning Tunneling Microscope (STM).

 The American physicist and Nobel prize laureate Richard Feynman introduced the concept of nanotechnology in 1959, during the annual meeting of the America Physical Society, Feynman presented a lecture entitled "There's Plenty of Room at the Bottom" at the California Institute of Technology (Caltech). After the lecture of Richard Feynman in 1959 the new idea came into existence after fifteen years by Japanese scientist Nori Taniguchi. Nori Taniguchi define the term nanotechnology in 1974. Nori Taniguchi defined nanotechnology as 'Nanotechnology mainly consists of the processing of separation, consolidation, and deformation of material by one atom or one molecule. In 2006, Paul Rothmund developed the ‘Scaffolded DNA origami' by enhancing the complexity and size of self-assembled DNA nanostructure in a 'one-pot reaction.'

 Hence, nowadays nanotechnology is used in various fields like Oncology, Data mining, Quantitative Structure-Property Relationships (QSPR), Quantitative Structure-Activity Relationships (QSAR), Absorption Distribution Metabolism, Excretion, and Toxicity (ADMET).[6]

**TYPES OF NANOPARTICLES**



Fig. 1. Types Of Nanomaterials.[22]

**1. Inorganic Nanoparticles**

 They are the particles obtained from metal oxide or metallic composition ranging in nanometer scale. The traditional preparation method of inorganic nanoparticle synthesis is the sol-gel route. Inorganic molecules such as metal salt, metal halide, or inorganic alkaloid are synthesized by condensation and hydrolysis reaction into relevant metal oxide species. The method of preparation of inorganic nanoparticles is microemulsion processing. Inorganic nanoparticles consist of quantum dots and metal nanoparticles. Metal nanoparticles are obtained from gold and silver, and also from metal oxide based on iron, titanium, cerium, and alumina. [2][7]

There are two types of inorganic nanoparticles:

1. Metal Nanoparticles.
2. Mesoporous Silica System
3. **Metal Nanoparticles**

 Metal Nanoparticles were started in 1971. Metal Nanoparticles were used in various biochemical applications such as DNA detection, Vehicle for delivering drugs, visualizing the cellular component, probes for electric microscopes, etc. Metallic nanoparticles like gold and silver show many optical and electronic properties. The gold nanoparticles are conjugated with specific oligonucleotides it can sense the complementary DNA strands by the change in the color. Silver works as an antimicrobial agent. Silver nanoparticles are used to prevent the attack of broad-spectrum antibiotics. Silver catheters and vascular grafts are also used to reduce infection in burn treatment. Nowadays magnetic nanoparticles are used as a contrast media for Magnetic Resonance Imaging (MRI).[2][24]

1. **Mesoporous Silica System**

 Mesoporous materials are used for the encapsulation of drugs and biogenic materials. Mesoporous materials such as Santa Barbara Amorphous (SBA), Mesoporous Silica Nanoparticle (MSN), and Hollow Mesoporous Sphere (HMS) were used for drug delivery. The group mesoporous material with longer pore size such as Santa Barbara Amorphous including SBA-15, SBAH-6, SBA-1, SBA-3, MSU, and HMS. Hollow Mesoporous Sphere (HMS) are another group of important mesostructured that are used in drug delivery. In a research, researchers found that HMS exhibited much more storage capacity than MCM-41. MCM-48, MCM-41, and SBA-51 are bioactive materials for drug delivery systems. Mesoporous Silica Nanoparticles (MSN) have unique properties like:

1. The particle size of MSN can be from 50-300nm allowing facile endocytosis by living animal and plant cells without any significant cytotoxicity.
2. MSN is more stable to heat, pH, mechanical stress and hydrolysis induce degradation, compared to other based drug carriers.
3. The uniform pore size distribution of MSN is very narrow, and the pore diameter can be turned between 2-6nm.
4. High surface area and large pore volume MSN allow high loading of drug molecules.[2]

**2. Organic Nanoparticles**

 Organic nanoparticles are assemblies of organic molecules of which there are virtually endless numbers of unique structures. Organic nanoparticles are also formed by non-covalent intermolecular interaction. Organic nanoparticles are more labile in nature. Organic nanoparticles are important for application that requires the detection of physiochemical changes, molecular binding interaction, and stimuli-driven effects. Organic nanoparticles have attracted widespread attention for various applications like disease diagnosis and cancer therapy.[2]

1. **Polymer in Drug Delivery.**

 Advantages in polymer science have led to the development of several Novel Drug Delivery systems. Polymers used in drug delivery must be biocompatible. Biocompatibility is the ability of the material to act on the host at specific sites and specific applications. Biodegradable polymers must have specific requirements such as:

1. Mechanical strength has to meet the need of specific applications.
2. Processibility using available equipment.
3. Solubility in various solvents.
4. Chemical, Structural, and application versatility.
5. Economically acceptable shelf life.[2][17]

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| Synthetic biodegradable polymers | Natural biodegradable polymers |
| Polyesters | Poly oxalates | Starch | Albumin |
| Poly orthoesters | Poly imino carbonates | Hyaluronic acid | Dextran |
| Polyanhydrides | Polyurethanes | Heparin | Chitosan |
| Polydioxanones | Poly phosphazenes | Gelatin | – |
| Poly(a-cyanoacrylates) | – |  |  |

Table 2. Classification of biodegradable polymers used in drug delivery system.[2]

The polymers used in the drug delivery system are:

1. Polymeric Micelles
2. Stimuli-Responsive Micelle
3. Polymeric Nanoparticles
4. Dendrimers
5. **Polymeric Micelle**

 A polymeric micelle is an amphiphilic block copolymer. They have a core-shell structure. These amphiphilic co-polymers are in dynamic equilibrium. Polymeric micelles are the self-assembly of amphiphilic polymer with hydrophilic and hydrophobic units. The micelle size ranges from 10 to 100 nm. When Poly micelle is combined with metal nanoparticles it can be used in various biocompatibility, pharmacokinetics, adhesion, targetability, and longevity.[22][9]



Fig 2. Structure of Polymeric micelle.[22]

1. **Stimuli-Responsive Micelle**

 Stimuli-responsive micelle has unique intelligent properties as a potential drug delivery system. Stimuli-responsive micelle has an amphiphilic structure. Stimuli-responsive micelle is recently used in sensing and biosensing. They can also be used for the preparation of photonic crystals. Stimuli-responsive micelle act as building blocks in photonic crystals.[10]



Fig. 3. Stimuli Responsive Micelle.[2]

1. **Polymeric Nanoparticles**

 Polymeric Nanoparticles consist of hydrophobic and hydrophilic blocks on polymer chains. Hydrophilic polymers consist of PEG, PVP, or polysaccharides. They are colloidal solid particles with a size range from 10-100 nm. Polymeric nanoparticles can be branched, spherical, or shell structures made up of biodegradable and non-biodegradable polymers. In polymeric nanoparticles drug molecules can be encapsulated within particles, physically adsorbed on the surface, or chemically linked to the surface of particles.[3][11]



Fig.4. Polymeric Nanoparticle.[22]

1. **Dendrimers**

 Dendrimers are nanosized, radially symmetric molecules with well-defined, homogenous, and monodisperse structures that have typically symmetric cores, inner shells, or outer shells. A scientist named Tomalia first coined the term dendrimer in 1985. A dendrimer structure consists of the focal core, building blocks, and multiple peripheral functional groups. Dendrimer can be used in drug delivery in two ways:

1. Molecules can be physically entrapped inside the dendrimer.
2. Drug molecules can be covalently attached to the surface.

Dendrimer has biological properties like solubility, low cytotoxicity, electrostatic interaction, polyvalency, self-assembling, and chemical stability.[12][3]



Fig. 5. Structure of Dendrimer.[2]

**3.Carbon Nanotubes**

 Carbon nanotubes have a unique tubular structure. The carbon network of shells in nanotubes is closely related to honeycomb arrangement. Nanotubes have high Young's modulus and tensile strength due to the graphite-like arrangement of carbon atoms in the shell. At specific heat carbon nanotube systems are determined primarily by phonons. Carbon nanotubes are highly sensitive, so they are suitable for the preparation of semiconductors.[2][3][13]

Properties of Carbon Nanotubes:

1. Carbon Nanotubes have high thermal conductivity.
2. Carbon Nanotubes have high electric conductivity
3. Carbon Nanotubes must be elastic.
4. Carbon Nanotubes should have high tensile strength.
5. Carbon Nanotubes should be highly flexible.
6. They should have a low expansion coefficient.
7. Carbon Nanotubes are good electron field emitters.
8. Carbon Nanotubes should have high axial strength due to the presence of carbon-carbon sp2 bonding.[25]



Fig.6. Functionalization of Carbon Nanotubes through Oxidation.[2]

**USE OF POLYMERIC NANOPARTICLES IN CANCER TREATMENT**

Cancer is nothing but the abnormal growth of body cells. Cancer is treated by mainly four methods that are Surgery, Radiation, Chemotherapy, and immunotherapy. Mainly drug delivery system that targeted drug delivery system is used to treat cancer patients. The targeted drug delivery system is based on Polymeric Nanoparticles. Polymeric Nanoparticles act as a drug carriers. Anticancer agents are encapsulated either within or on the surface of polymeric nanoparticles.[14][15][18][20][21] Nanoparticle act in cancer patients by targeting the cancerous cell. Targeting is done by 2 processes:

1. Active Targeting.
2. Passive Targeting.

**A) Active Targeting**

 In active targeting the chemotherapeutic agents directly interact with defective cells. Nanoparticles are designed in such a manner that nanoparticles target cancerous cells. Target drug delivery system work on three components that is Anticancer drug, Targeting moiety penetration enhancer, and carrier. Nanoparticles in active targeting are commonly made up of metals, lipids, and polymers. When the nanoparticle binds to the receptor, the cell undergoes receptor phagocytosis.

1. **Specific Receptor Targeting**

 Folate Receptor:

 Researchers found in the study that the patient suffering from cancer has overexpressed the number of folate receptors. The folate receptor provides a target for many anticancer drugs. Scientists have developed a nanoparticle-mediated with folic acid. The doxorubicin-polyethylene glycol folate conjugate micelle was prepared. It was targeting the folate receptor and the result was it causes tumor suspension.

 Luteinizing Releasing Hormone Receptor:

 Luteinizing Release Hormone Receptors are overexpression in breast cancer, ovarian cancer, and prostate cancer. The nanoparticles are combined with the drug Docetaxel. Aptamers in nanoparticles detect cancerous cells. Aptamers are the targeting molecule present outside the nanoparticle.

1. **Antibody-Mediated Targeting**

 Nanoparticles are conjugated with antibodies to show action against specific tumor antigens. Antibodies are used in their original form for cancer treatment. Malignant cells need iron in very high amounts. Iron acts as a cofactor for DNA synthesis. Nanoparticles act as drug carriers and transferrin receptors provide a binding site to antibodies. Antibody-mediated targeting improves anticancer activity and reduces exposure of cancerous cells to healthy cells.

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| Type of nanoparticle | Anticancer drug | Targeting agent | Name of the polymers used | Outcome |  |
| Polymeric nanoparticle | Paclitaxel | Folic acid | Polylactic acid and polyethylene glycol | Enhanced drug accumulation in tumor |  |
| Dendrimer | — | Folic acid | Poly amidoamine | Increased cellular uptake |  |
| Nano shell | Docetaxel | Folic acid | Biodegradable polymer | Sustainable, controlled, and targeted delivery |  |
| Dendrimer | Small interfering RNA (siRNA) | Luteinizing hormone-releasing hormone (LHRH) peptide | Poly(propylene imine) and polyethylene glycol | High specificity |  |
| Nanoparticle | Paclitaxel | Folic acid | Poly(D, L-lactide glycolide) | Inhibition of P-glycoprotein |  |
| Polymer micelle | Doxorubicin | Folic acid | PEG-co-poly(lactic-co-glycolic acid) | increased cellular uptake and cytotoxicity |  |
| Polymer micelle | Doxorubicin | Folic acid | PEG-poly(aspartate hydrazone doxorubicin) | Increased endocytotic cellular uptake |  |

Table 3. Formulation of Nanoparticle Used in Cancer Therapy.[15]

**B) Passive Transport**

 Cancerous cells do not perform apoptosis. Nutritional agents get continuously sucked by the cancerous cell. Hence the size of the tumor is increased. The size of the pores of cancerous cells is between 100- 780nm. So, the nanoparticles below 100-780nm can pass the pore, and efflux of the nanoparticle occurs. Nanoparticles accumulate by enhanced permeability and retention effect and diffuse into the cell[15 ]



Fig. 7 Active and Passive Targeting.[15]

**CONCLUSION**

In this review, the development of nanoparticles in drug delivery is reviewed. The Nanoparticles work as a drug carrier in the drug delivery system. Polymeric Nanoparticles play an important role in the treatment of cancer. Nanotechnology is an emerging and advanced technology for drug delivery.

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**REFERENCES**

1. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology. 2007 Dec;2:1-6.
2. Safari J, Zarnegar Z. Advanced drug delivery systems: Nanotechnology of health design A review. Journal of Saudi Chemical Society. 2014 Apr 1;18(2):85-99.
3. Maravajhala V, Papishetty S, Bandlapalli S. Nanotechnology in development of drug delivery system. International journal of pharmaceutical sciences and research. 2012 Jan 1;3(1):84.
4. Park K. Nanotechnology: What it can do for drug delivery. Journal of controlled release: official journal of the Controlled Release Society. 2007 Jul 7;120(1-2):1.
5. Sahu T, Ratre YK, Chauhan S, Bhaskar LV, Nair MP, Verma HK. Nanotechnology-based drug delivery system: Current strategies and emerging therapeutic potential for medical science. Journal of Drug Delivery Science and Technology. 2021 Jun 1;63:102487.
6. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical–physical applications to nanomedicine. Molecules. 2019 Dec 27;25(1):112.
7. Stevanović M, Lukić MJ, Stanković A, Filipović N, Kuzmanović M, Janićijević Ž. Biomedical inorganic nanoparticles: preparation, properties, and perspectives. InMaterials for Biomedical Engineering 2019 Jan 1 (pp. 1-46). Elsevier.
8. Lemarchand C, Gref R, Couvreur P. Polysaccharide-decorated nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics. 2004 Sep 1;58(2):327-41.
9. Perumal S, Atchudan R, Lee W. A review of polymeric micelles and their applications. Polymers. 2022 Jun 20;14(12):2510.
10. Wei M, Gao Y, Li X, Serpe MJ. Stimuli-responsive polymers and their applications. Polymer Chemistry. 2017;8(1):127-43.
11. Prabhakar C, Krishna KB. A review on polymeric nanoparticles. Research Journal of Pharmacy and Technology. 2011;4(4):496-8.
12. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, Hanifehpour Y, Nejati-Koshki K, Pashaei-Asl R. Dendrimers: synthesis, applications, and properties. Nanoscale research letters. 2014 Dec;9:1-0.
13. Ajayan PM, Zhou OZ. Applications of carbon nanotubes. Carbon nanotubes: synthesis, structure, properties, and applications. 2001 Mar 9:391-425.
14. Tabatabaei Mirakabad FS, Nejati-Koshki K, Akbarzadeh A, Yamchi MR, Milani M, Zarghami N, Zeighamian V, Rahimzadeh A, Alimohammadi S, Hanifehpour Y, Joo SW. PLGA-based nanoparticles as cancer drug delivery systems. Asian Pacific Journal of Cancer Prevention. 2014;15(2):517-35.
15. Sutradhar KB, Amin ML. Nanotechnology in cancer drug delivery and selective targeting. International scholarly research notices. 2014;2014.
16. Ng KK, Zheng G. Molecular interactions in organic nanoparticles for phototheranostic applications. Chemical Reviews. 2015 Oct 14;115(19):11012-42.
17. Pillai O, Panchagnula R. Polymers in drug delivery. Current opinion in chemical biology. 2001 Aug 1;5(4):447-51.
18. Zhang G, Zeng X, Li P. Nanomaterials in cancer-therapy drug delivery system. Journal of biomedical nanotechnology. 2013 May 1;9(5):741-50.
19. Rajabi M, Srinivasan M, Mousa SA. Nanobiomaterials in drug delivery. InNanobiomaterials in Drug Delivery 2016 Jan 1 (pp. 1-37). William Andrew Publishing.
20. Tang M, Lei L, Guo S, Huang W. Recent progress in nanotechnology for cancer therapy. Chin J Cancer. 2010 Sep 1;29(9):775-80.
21. Masood F. Polymeric nanoparticles for targeted drug delivery system for cancer therapy. Materials Science and Engineering: C. 2016 Mar 1;60:569-78.
22. <https://en.wikipedia.org/wiki/Nanoparticle#:~:text=A%20nanoparticle%20or%20ultrafine%20particle,nm%20in%20only%20two%20directions>.
23. Hu Q, Li H, Wang L, Gu H, Fan C. DNA nanotechnology-enabled drug delivery systems. Chemical reviews. 2018 Feb 21;119(10):6459-506.
24. Jamkhande PG, Ghule NW, Bamer AH, Kalaskar MG. Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. Journal of drug delivery science and technology. 2019 Oct 1;53:101174.
25. [Applications of Carbon Nanotubes - AZoNano.com](https://www.bing.com/ck/a?!&&p=56517f99442e7bb7JmltdHM9MTY5MDQxNjAwMCZpZ3VpZD0zYjlhZGMwZS0yZTQ4LTY3NzctMGRlMy1jZjQyMmZkMzY2YzkmaW5zaWQ9NTIyMg&ptn=3&hsh=3&fclid=3b9adc0e-2e48-6777-0de3-cf422fd366c9&psq=applicatin+of+carbon+nanotubes&u=a1aHR0cHM6Ly93d3cuYXpvbmFuby5jb20vYXJ0aWNsZS5hc3B4P0FydGljbGVJRD00ODQy&ntb=1)

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