**Nanotechnology In Novel Drug Delivery System**

Pooja Birade1, Yogini Shete, Lata Potey, Shilpa Mahajan, Ashwini Armarkar

Shree Sainath College of Pharmacy, Nagpur, Maharashtra, India- 440023

Corresponding Author E-mail- poojabirade276@gmail.com

**ABSTRACT:**

The breadth of development in our contemporary society has expanded thanks to nanotechnology, which has given hope and fresh life to numerous fields. Two of the many applications of nanotechnology in modern life are in nanomedicine and Nanobiotechnology. Nanotechnology is the study of incredibly small structures with sizes between 0.1 and 100 nm. Modern nanotechnology has a wide range of possible applications in healthcare for people. Recent research indicates that nanotechnology will significantly affect illness prevention, diagnosis, and therapy. Nanotechnology is transforming surgery and the early diagnosis of diseases like cancer. Nanotechnology has made tremendous strides in recent years, and this multidisciplinary scientific field is quickly growing. Drug research, water filtration, and the creation of stronger, lighter materials are just a few of the ways that nanoscience and nanotechnologies may enhance human health care. By today's standards, nanotechnology makes it possible to create a wide variety of items that are tremendously powerful. Nanomaterials’ physicochemical properties can be changed to improve properties like extended blood circulation and increased functional surface area to speed up drug breakdown, protection, biological barrier crossing, and site-specific targeting has helped to address some of the challenges encountered and continues to do so. In order for a targeting system to be effective, it must circulate over an extended period of time, be present at the target site in the right concentrations, and maintain its therapeutic efficacy. This chapter shows the various drug delivery systems and prospective applications of nanotechnology is our goal. In addition, we are discussing the potential applications of nanotechnology in human health.

**KEYWORDS:** Nanotechnology; Novel Drug Delivery System; Nanomedicines; Prospective Applications; Nanobiotechnology;

1. **INTRODUCTION:**

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometres scale. Nanoparticles are spheres of very small size that are composed of materials designed at the atomic or molecular level. Due to the small size of nanoparticles these function at the molecular level. [13] Hence, they can move more freely in the human body as compared to bigger materials. Nanoscale-sized particles exhibit unique structural, chemical, mechanical, magnetic, electrical, and biological properties. Nanotechnology is shown to bridge the barrier between biological and physical sciences by applying nanostructures and nanophases in various fields of science. [6] In the past few years, nanotechnology has grown by leaps and bounds, and this multidisciplinary scientific field is undergoing explosive development. It can prove to be a boon for human health care because nanoscience and nanotechnologies have a huge potential to bring benefits in areas as diverse as drug development, water decontamination, and the production of stronger, lighter materials. Human healthcare nanotechnology research can definitely result in immense health benefits. The genesis of nanotechnology can be traced to the promise of revolutionary advances across medicine. A complete list of the potential applications of nanotechnology is too vast and inverse, but without doubt, one of the greatest values of nanotechnology will be in the development of a new and effective medical novel drug delivery system. [1]

Nanotechnology is a very shady multidisciplinary area invented to engineer biological matters such as atoms, molecules, and supramolecular at the nanoscale range approx. 1–100 nm to hold promise against existing challenges by creating new devices and characterization of material structure technologies with unique properties to study and understand the lethal biological problems followed by diagnosis and cure of disease.[2] Due to their small size, these novel DDS offer superior advantages, such as altered pharmacokinetic behavior and improved payload, over traditional large-scale systems. [14] Nanotechnology in novel drug delivery have been popularized a lot in today’s time because the nanoparticles can be utilized as delivery agents by encapsulating drugs or attaching therapeutic drugs and delivering them to target tissues in a precise and controlled manner with the help of these small molecules. [13]

Nano in novel drug delivery systems allows therapeutic agents to reach their site of action selectively without affecting the non-target cells, organs or tissues. This system is responsible for determining the rate of drug release in the body and also the site where the drug has to be released. The various ways of intake medicines can be through inhalation, skin absorption, and intravenous injections or by swallowing them. For every medication different methods of intake can be used as each intake method has its own merit and demerit. In order to improve the usage of prevailing medications there is a need for more efficient and effective drug delivery methods either by improvising the existing ones or by discovering new ones. [13]

The use of nanotechnology in medicine has the potential to have a significant impact on human health by improving the diagnosis, prevention and treatment of diseases. [3] The novel carriers should ideally fulfill prerequisites. Deliver the drug at a rate directed by the needs of the body, over the period of treatment. [4] Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side-effects, and to increase drug bioavailability and the fraction of the drug accumulated in the required zone. [5] Nanotechnology-based delivery systems can also protect drugs from degradation. These properties can help reduce the number of doses required, make treatment a better experience, and reduce treatment expenses. A number of nano-based systems allow the delivery of insoluble drugs, allowing the use of previously rejected drugs or drugs which are difficult to administer e.g. paclitaxel. [8] Pharmaceutical nanotechnology embraces applications of nanoscience to pharmacy as nanomaterials, and as devices like drug delivery, diagnostic, imaging, and biosensor materials. Pharmaceutical nanotechnology has provided more fine-tuned diagnosis and focused treatment of disease at a molecular level. It helps in detecting the antigen associated with diseases such as cancer, diabetes mellitus, and neurodegenerative diseases, as well as detecting the microorganisms and viruses associated with infections. In pharmacy size reduction has an important application as drugs in the nanometer size range enhance performance in a variety of dosage forms.[16] Recently, there have been enormous developments in the field of delivery systems to provide therapeutic agents with natural-based active compounds to their target location for the treatment of various ailments.[7] There are a number of drug delivery systems successfully employed in recent times, however, there are still certain challenges that need to be addressed and advanced technology needs to be developed for successful delivery of drugs to its target sites. Hence nano-based drug delivery systems are currently being studied that will facilitate the advanced system of drug delivery. [6]

Nanotechnology can play an important role in the development of proper formulations that address the drug delivery issues related to New molecular entities (NMEs) with poor biopharmaceutical properties, such as poor solubility, poor permeability across the intestinal epithelium, enzymatic or no enzymatic degradation/metabolism, complexation with chelating ligands or metal cations, intestinal efflux, and poor transport properties. Additionally, nanotechnology can also achieve desirable pharmacokinetic and toxicological properties that aid in the accelerated development of the NMEs. Nano particulate drug delivery systems are being used to alter the drug’s biopharmaceutics and pharmacokinetics such as drug absorption, distribution, metabolism, and elimination. [11,12]

1. **NANOTECHNOLOGY PROVIDES A NUMBER OF ADVANTAGES IN PHARMA:**
2. Increased surface area
3. Increased rate of dissolution
4. Less amount of dose required & reduces the number of doses
5. Protection of drug from degradation
6. More rapid onset of therapeutic action
7. Achievement of drug targeting
8. Passive targeting of drugs to the macrophages present in the liver and spleen [10]
9. Quantum dots that identify the location of cancer cells in the body.
10. Nanoparticles that deliver chemotherapy drugs directly to cancer cells to minimize damage to healthy cells. [1]
11. Improving the stability and solubility of drugs
12. Controlling their release
13. Minimizing their toxicity
14. Depositing the active agent in the morbid region only with an accurate dose leads to fewer plasma fluctuations and minimized side effects. [15]

**Table No.- 1 List of some patents [108]**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sr. No. | Patent No. | Brief Description | Applicant | Title |
| 1. | WO2015123654A1 | This invention describes a method of preparation of gold nanoparticles passivated with amines and their utility for cancer imaging and treatment. | Shunji Egusa, Yogen Sauntharajah | “Carbon Quantum Dots Based Patternable Material System For Fabricating Fluorescent Nanostructures With Subwavelength Resolution” |
| 2. | US20160287723A1 | This invention deals with method of preparation of doxorubicin conjugated gold nanoparticles and evaluation their biocompatibility and tumor accumulation capacity | Chun-Chia Cheng, Tsai-Yueh Luo | Method of fabricating anticancer drug having doxorubicin bonded with gold nanoparticles. |
| 3. | US2014008628A1 | The invention describes the utility of gold nanoparticles containing microRNAs for treatment of cancer | Aaron E. Foster, Laura B. Carprin, Adham S. Bear, Rebekah Drezek, Adam Yuh Lin | Modified gold nanoparticles for therapy |
| 4. | US20100034735A1 | This patent provides information about method of development of gold nanoparticles for cancer treatment and imaging by acting positron emission tomography tracer | Jien Chen, Wilson Roa | Targeted nanoparticles for cancer diagnosis and treatment |
| 5. | US20070031337A1 | This invention describe development method of ligand (Anti-VEGF antibody) conjugated gold nanoparticles of size 20nm and their biological evaluation. | Dean P. Hainsworth, Raghuramn Kannan, Kattesh V Katti, Ravi Shukla | Anti-VEGF anti-body conjugated gold nanoparticles and fabrication and therapeutic methods |

**III. VARIOUS MEDICATION DELIVERY SYSTEM-BASED NANOTECHNOLOGY:**

There has recently been tremendous progress in the field of delivery systems to transfer therapeutic agents or natural-based active chemicals to their target region for the treatment of various illnesses. [38,39] There have been a lot of successful drug delivery systems in recent years; however, there are still some obstacles that must be addressed, and improved technology must be created for successful drug delivery to its target sites. As a result, Nano-based drug delivery systems are currently being researched in order to assist the enhanced drug delivery system. [6]

The following are some major drug delivery systems developed using nanotechnology principles:

1. Magnetic nanoparticle
2. Ceramic nanoparticle
3. Niosomes
4. Liposomes
5. Dendrimers
6. Carbone nanotube
7. Nanoemulsion
8. Nanopores
9. Nano suspension
10. Nanocrystals
11. Micelles
12. Gold nanoparticles
13. **Nanoparticles with magnetic properties:**

Magnetic nanoparticles are nanoparticles that can be controlled by magnetic fields. Such particles usually consist of two parts: a magnetic material, which is usually iron, nickel, or cobalt, and a chemical component with functionality. Microbeads have a diameter of 0.5-500 micrometers, whereas nanoparticles have a diameter of less than one micrometer (typically 1-100 nanometers). Magnetic Nano beads with a diameter of 50-200 nanometers are magnetic nanoparticle clusters formed of a number of individual magnetic nanoparticles. [40,41] Magnetic nanoparticles (MNPs) in particular have sparked great interest in recent years due to their applications in specialized fields such as medicine, cancer theranostics, bio-sensing, catalysis, agriculture, and the environment. [42] Magnetic nanoparticles (MNPs), a nanoscale substance with unique magnetic properties, have found widespread application in healthcare, energy, engineering, and environmental domains. Because of their unique and distinguishing features, MNPs have recently become a focus of intense research due to their potential applications in biology, catalysis, agriculture, and the environment. [43] MNPs' physicochemical properties differ from those of their parent bulky substance in terms of large specific surface area, making them more superparamagnetic. [44]

**Primary Synthesis Approaches for MNPs:**

Over the past decade, there has been intensive research into the development of several methods for the synthesis of MNPs. To produce MNPs with the required size, shape, stability, and biocompatibility, a variety of synthetic approaches are used. The most widely used techniques include ball milling, co-precipitation, thermal decomposition, hydrothermal, microemulsion, sol-gel method, and biological method.

**Physical Techniques:**

The two categories of physical approaches are "top-down" and "bottom-up" strategies. Using the top-down method, high-intensity ball milling reduces the bulk materials into nanoparticle size. It is difficult to obtain NPs with the desired form and size due to mechanical crushing. [45] Bottom-up methods can result in finer, more evenly scattered nanoscale tiny particles than top-down methods. An illustration of a bottom-up approach is laser evaporation. [46] MNPs are also prepared using additional physical procedures such as wire explosion and inert gas condensation. Three physical processes—ball milling, laser evaporation, and wire explosion—will be discussed in this paper.

1. **Method of Ball Milling/Mechanical Method**

A top-down technique for producing MNPs from bulk material is ball milling. It is simple and practical to mechanically crush coarse-textured particles into fine-textured particles. [47] This strategy was developed by Benjamin in 1970. [48] The principle of operation is simple: the raw materials are placed in a tiny hollow cylindrical jar with a lot of steel balls inside as the grinding medium. Steel balls constantly colliding with solid objects cause the solid object to gain kinetic energy, which turns the solid object into Nano- or micro-sized powder. The ratio of balls to powder, ball size, vibration speed, and milling duration are the main variables affecting the production of Nano/micro-size crystals. Contamination of the product is this strategy's principal drawback. [49] The particles have a wide size distribution as compared to chemically produced particles.

1. **Laser Evaporation:**

By condensation from a liquid or gaseous phase, laser evaporation is a bottom-up method that creates nanoparticles [46]. Using a powerful laser, laser evaporation, often referred to as laser ablation, is a straightforward method for creating MNPs. Iron oxide MNPs can also be produced using this method. Iron oxide MNPs can also be produced using this method. [50] This process involves choosing coarse-textured particles (in the m or mm size ranges) as raw materials and evaporating them under a laser's intense intensity. A concentrated laser beam is directed toward the object, which is positioned at the bottom of a liquid-filled compartment. The material in a solution is irradiated using a laser beam. Cooling the material's vapors in a gas phase causes quick condensation and nucleation, which produces nanoparticles. [51] Due to the lack of expensive chemicals or the production of hazardous waste, this approach is less expensive than wet chemistry procedures. [52]

1. **Method of Wire Explosion**

The wire explosion method is a novel clean and safe physiochemical method for the synthesis of MNPs. This method is a one-step, extremely productive technique that doesn't need any further steps like by-product re-treatment or NP separation from solution. This method was previously used to create iron oxide MNPs for the removal of arsenic from water. [53] It produces less contaminated Nanopowders with low energy use and no harm to the environment. [54] Monodispersed nanoparticles are not produced using this method. [55]

**Chemical Procedures**

In chemical synthesis, various bottom-up techniques are employed. Below is a thorough explanation of several popular techniques for creating MNPs.

1. **Method of Co-Precipitation**

The most popular method for creating MNPs with controlled size and magnetic properties is co-precipitation. [56] It is widely utilized in biological applications and calls for the use of less dangerous materials and procedures. [57] Co-precipitation is a very practical and straightforward method for synthesizing MNPs when large quantities of nanocrystals are needed. This method is frequently used to produce NPs with controlled sizes and desirable magnetic characteristics. Different metal ions are dissolved in a solvent to create MNPs. The metal ions ferric chloride (FeCl3), manganese(II) chloride (MnCl2), and sodium hydroxide (NaOH) salts were used to create manganese ferrite (MnFe2O4) nanoparticles. [58] Fe3+ and Mg2+ ions can be combined and co-precipitated with NaOH to form MgFe2SO4 nanocrystals. [57] In a related study, Fe2+ and Fe3+ ions were co-precipitated to create Fe3O4 nanoparticles. [59] This method is also suggested due to its simplicity, however, sometimes it can be difficult to manage the shape of MNPs by co-precipitation

1. **Thermal Decomposition:**

This method yields MNPs with excellent crystallinity, controlled size, and precise form. Organometallic precursors are broken down in the presence of organic surfactants to create MNPs of the proper size and shape. [60] Oleic acid, hexadecylamine, and fatty acids are a few of the stabilizing ingredients used in the creation of MNPs. Inhibiting the nucleation of NPs, which regulates the growth of MNPS and helps to produce a spherical shape with a desirable size of less than 30 nm, is a capability of stabilizers used in the breakdown process. It has been reported that using this technique, magnetically active iron composites and Fe3O4 nanocrystals can be produced. [61] Metal NPs are created through the thermal breakdown of the zero-valent metal precursor Fe (CO)5, although high-quality iron oxide MNPs can also be created during oxidation. On the other hand, precursor breakdown with cationic metal centers may result in the immediate production of metal oxide NPs [62]. Previously, monodispersed iron oxide MNPs with sizes ranging from 6 to 20 nm were produced by the breakdown of Fe(CO)5 in the presence of polymers [63]. The type of precursor used affects the required temperature. To obtain the proper form and size, several factors including temperature, reaction time, surfactant and solvent type, and aging period are altered. [64]

1. **Microemulsion synthesis method:**

Surfactants and, occasionally, co-surfactants, as well as lipophilic and hydrophilic phases, are all components of microemulsion, which are turbid systems. This is an isotropic transparent liquid system composed of water, oil, and amphiphilic. Oil and a surfactant are mixed with water that has been magnetically swirled at room temperature. There are three categories for microemulsion: There are three types of mixtures: 1) oil in water (O/W), which is the aqueous phase with some oil droplets, 2) water in oil (W/O), which is oil as the dominant phase with some water droplets, and 3) mixtures in which the proportions of oil and water are equal. As an illustration, in a w/o microemulsion, MNPs were made smaller by coating droplets of water in an organic solvent with a surfactant. [65] The surfactant used in this method determines the shape and size of MNPs produced.

1. **Hydrothermal Synthesis Method:**

This method, which uses high pressure and temperature to create nanoparticles in an aqueous solution, is utilized. [66] Hydrothermal, also known as solvothermal, is one of the effective reaction-based solutions for manufacturing MNPs at high pressure and temperature. The hydrothermal method produces MNPs through oxidation and hydrolysis processes. [67] The degree to which minerals are soluble in water affects how crystals form. This method resulted in magnetic nanomaterial particles of various sizes. [68] Fe3O4 NPs, for instance, were produced and employed in tumor MRI with dimensions of 15 nm and a spherical form. [69] Similar to this, 25 nm Fe3O4 NPs coated with Chitosan were made and employed for enzyme immobilization. [70] The proper solvent mixture, duration, pressure, and temperature will determine the shape and crystallinity of MNPs produced through synthetic processes. This technique has a higher potential for NP production than the microemulsion technique. However, because this technique calls for high pressure and temperatures, it is carried out carefully and with specialist tools. Because it yields NPs with suitable shapes, sizes, high crystallinity, and constant composition, the hydrothermal method is preferred over sol-gel and other techniques. [71]

1. **Sol-gel method:**

The entire chemistry of this technique consists of hydrolysis and metal alkoxide poly-condensation reactions that generate gels at normal temperatures. Metallic salts are dissolved in water or other solvents and uniformly dispersed to create a sol or colloidal solution. [72] There are van der Waals forces between particles, and as the temperature rises, the interaction between the particles gets stronger. The mixture is dried, and the removal of the solvent from the mixture produces gel. [73] Both silica-coated and iron-oxide MNPs can be created using this method.

**c] Biological Method**

Utilizing living things like plants and microbes (fungi, viruses, bacteria, and actinomycetes) is a well-known technique for producing MNPs. [74] The MNPs created by this method are biocompatible and may be used in the biomedical industry. The efficacy, environmental friendliness, and cleanliness of this technology are its benefits. The low dispersion of the NPs is a drawback. [75] Researchers are interested in the creation of NPs using plant tissue, extracts, exudates, and other plant parts. [76] For instance, it has been claimed that ferromagnetic magnetite particles with an average size of 60 nm can be manufactured organically. [77] The manufacture of NP via microbes and plants is currently being explored, despite the fact that biological synthesis is a promising technology that has recently emerged. [75]

1. **Ceramic Nanoparticles:**

Ceramic nanoparticles are formed of components including titanium, alumina, silica, and others. One benefit of these particles is how easy it is to prepare them. Changes in pH or temperature have no effect on them. Numerous characteristics of these nanoparticles, including size, shape, porosity, inertness, and others, may be changed, and they are simple to work with when attaching different biomolecules. They are roughly 50 nm in size on average. Serratiopeptidase, an acid-labile model enzyme, and hydrophobic drug molecules have all been enclosed in ceramic nanoparticles, which have also been used to boost DNA transfection efficiency when paired with a DNA-dendrimer conjugate. Ceramics have been used in bone tissue engineering because of their osteoinductive and biocompatible properties. [78] The use of medical technology is made. Nanoparticles made of ceramic for bone repair. It has been suggested that it be used in industries like communication, building, energy generation and storage, transportation, and medical technology. Due to their electrical properties, energy transmission efficiency may be close to 100%. The usage of Nano trusses as building materials could eventually replace the need for steel or concrete. [79]

1. **Niosomes:**

In order to achieve the intended therapeutic effects, medicines are delivered to precise locations using Niosomes. [80] Similar to liposomes, Niosomes are composed of non-ionic surfactant-based vesicles that include cholesterol as an excipient in addition to non-ionic surfactant, which may enhance medication absorption [81, 82] In that, they both contain a lipid bilayer, Niosomes, and liposomes are structurally identical. However, during the manufacturing and storage processes, Niosomes are more stable than liposomes. [83] Both lipophilic and hydrophilic pharmaceuticals can be captured by them, either in an aqueous layer for lipophilic drugs or in a lipid-based vesicular membrane for hydrophilic ones. Niosomes are non-ionic surfactant vesicles that resemble liposomes in form. They can serve as medication carriers and encapsulate aqueous solutes. Non-ionic amphiphilic are self-assembled to create Niosomes in watery media. Applying heat or agitating the process physically aids in creating a closed bilayer structure. Niosomes are ideal as drug delivery systems in conditions affecting these organs since they are taken up by tissues like the liver and spleen. Additionally, they are utilized to target cancer cells. Niosomes antigens can be used as adjuvants in the delivery of vaccines because they are effective stimulators of the cellular and humoral immune responses. When using Niosomes as opposed to traditional modes of administration, high levels of medicines were discovered in the target area. They have also been utilized in conjunction with anti-inflammatory and anti-infective medications. Oligonucleotide delivery to cells has been accomplished using PEGylated Cationic Niosomes. Niosomes are non-toxic and aid in the percutaneous transit of 5-fluorouracil (5-FU) through the human stratum corneum and epidermis. According to reports, furosemide Niosomes increased skin permeability and maintained medication levels. [84,1]

1. **Liposomes:**

An amphiphilic lipid molecule in solution, such as phospholipids, self-assembles to create a colloidal spherical structure known as a liposome. [85] An internal aqueous core is surrounded by one or more lipid bilayers (also known as lamellas), with the polar head groups facing the inner and outer aqueous phases, respectively. [86] Liposomes have the unique capacity to load and distribute compounds with various solubilities to this well-organized structure. Amphiphilic molecules are at the water/lipid bilayer interface, hydrophilic molecules are in the interior aqueous core, and hydrophobic molecules are in the lipid bilayer. [87] The first examples of nanoscale drug delivery systems were liposomes, which were found in the middle of the 1960s. They can be unilamellar, with a single lamella of membrane, or multilamellar, with many membranes. They are spherical nanoparticles constructed of lipid bilayer membranes with an aqueous interior. They are useful as systems for delivering medications. When utilized as liposomal medications, cancer chemotherapy agents and other hazardous pharmaceuticals like amphotericin and hamycin produce significantly greater efficacy and safety when compared to conventional preparations. Either the lipid membrane or the aqueous compartment of these liposomes can be filled with medicines. Water-soluble medications are often placed in the aqueous compartment, while lipid-soluble medications are included in the liposomal membrane, where they undergo rapid breakdown and removal by the liver macrophages [88], shortening the duration of the medication's activity. The insertion of substances such as cholesterol [89], polyvinylpyrrolidone polyacrylamide lipids [89], and high transition temperature phospholipids stearoyl phosphatidylcholine are other methods of extending the duration of liposome circulation. [90] Orienting liposomal medications: Both passive and active techniques can be used to direct liposomes to a particular organ or tissue. Liposomal medicine has a superior safety profile than non-liposomal drugs since it has a negligible effect on other tissues. There is substantial blood vessel leakage from the poorly structured vascularity in the tumor tissue. The liposomal medications passively aggregate in the tumor tissue and have stronger effects. Using immunoliposomes and ligand-directed liposomes, active medication targeting can be accomplished.

1. **Dendrimers:**

A monodisperse macromolecule with a perfectly branching regular structure and at least one branched junction at each repeat unit is a dendrimer, according to the widely used definition. For a number of uses, including the treatment of cancer and other disorders, dendrimers are a form of nanostructure that can be precisely created and engineered. At the same time, dendrimers carrying various materials and their branches can identify unhealthy cells, diagnose pathological states (including cell death), distribute drugs, report locations, and report treatment results. The dendrimers molecule has been employed as a contrast agent and diagnostic reagent for tumor imaging by magnetic resonance imaging; these compounds can be used for a variety of specialized imaging purposes by altering their size and hydrophilicity as well as by combining with tumor-targeting antibodies. [91] The most common route of administration for treating a variety of ocular illnesses is to apply active medications topically to the eye. For the delivery of ophthalmic drugs, dendrimers offer special answers to challenging delivery issues. It should not irritate the eye, be biocompatible, sterile, isotonic, or biodegrade. [92]

1. **Carbon Nanotube:**

One of the distinctive and sought-after advancements in nanotechnology is the carbon nanotube (CNT). Because of their small size, lightweight, strong tensile strength, and superior conductivity, CNTs have drawn significant interest in various pharmacological and engineering disciplines since they were first developed by researcher Iijima in 1991. CNTs are the most durable material used by any human researcher up to this point; they are naturally occurring graphite with sp2 hybridization. SWCNTs, DWCNTs, and MWCNTs are the three classes that they fall under according to their distinctive structure. There are numerous ways to make CNTs, including chemical vapor deposition, laser ablation, and arc discharge. Because of their distinctive mechanical, thermal, electrical, and optical capabilities, CNTs are used in a variety of applications. They are utilized in fields such as biomedicine, drug delivery systems, sensors, implants, tissue engineering, and cancer prevention. [93] Proteins, nucleotides, and medicinal molecules can all be transported using CNTs. Carbon nanotubes can infiltrate living cells due to their size and form without resulting in cell death or visible harm. Covalent or non-covalent attachments of molecules to the surface are both possible. Although CNTs' hollow nature allows for the encapsulation of molecules, there are currently very few examples of this being used for medication delivery. Covalent or non-covalent CNTs are required for biological applications. [94] fictionalization in order to enhance their solubility and prevent agglomeration. Amphotericin B, [95] which is typically insoluble and poisonous due to its propensity to agglomerate, is one of the medications that has been successfully given. improved solubility, minimal aggregation (and hence lower toxicity), and improved anti-fungal efficacy were all seen when CNTs were used for delivery. CNTs have been used for a variety of medicinal purposes, including gene and siRNA transfer, boron neutron capture treatment (BNCT), and generating an immune response. [96]

1. **Nanoemulsion:**

A nanoemulsion is a dispersed Nano-system with droplet sizes as small as submicron. Nanoemulsions are liquid mixtures of oil, water, surfactant, and co-surfactant that are clear, isotropic, and thermodynamically stable. Droplet diameters in nanoemulsions typically range from 20 to 200 nanometers. The main differences between an emulsion and a nanoemulsion are the size and makeup of the scattered particles in a continuous phase. This strategy aims to address some of the problems that low bioavailability and noncompliance, two problems with conventional drug delivery systems, raise. Today, a variety of administration routes can use nanoemulsion. A pharmaceutical delivery strategy that is efficient, secure, and acceptable to patients is a nanoemulsion formulation. Nowadays, pharmacology, dosage form design, and research have all shown a great deal of interest in nanoemulsions. [97] The latter are opaque combinations of two immiscible liquids, thermodynamically unstable, and typically need the application of high torque mechanical mixing or homogenization to produce scattered droplets in the range of 0.2–25 mm. This is where Nanoemulsions vary from microemulsions. Oil-in-water (o/w) or water-in-oil (w/o) versions of both types are available. Based on the model drug's hydrophilicity, the dispersed and continuous phases of microemulsion formulations are chosen. Additionally, surfactants with hydrophilic-lipophilic balances (HLB) of 3-6 tend to encourage the formation of o/w microemulsion, whereas those with HLB values of 8–10 prefer to do the opposite. [1]

1. **Nano suspension:**

Colloidal dispersions of nanoparticles of an insoluble chemical that are stabilized by surfactants are known as Nano suspensions. These medications can be kept in their desired crystalline state using Nano suspensions, which are tiny enough for intravenous administration. They share many Nanoemulsion advantages. Due to the drug's solid nature, it can also reach even higher levels of drug loading. Numerous studies have shown that Nano suspensions can deliver drugs more effectively and quickly. [98]

1. **Nanopores:**

Desai and Ferrari (1997) created Nanopores, which are made of wafers with many tiny pores (20 nm in diameter). Oxygen, glucose, and other substances like insulin can flow through the pores. However, it prevents cells and immunoglobulin from passing through them. Utilizing the advantages of transplantation, Nanopores can be employed as devices to shield transplanted tissues from the host immune system. Pancreatic b cells may be contained inside the Nanopores device and inserted into the recipient's body. This tissue sample absorbs nutrients from the surrounding tissues while avoiding detection by the immune system, preventing rejection. [99] This might be a more recent method of treating insulin-dependent diabetes [100]. DNA sequencing can also make use of Nanopores. Harvard University's Branton team [101] has developed customized Nanopores that can distinguish between distinct DNA strands based on variations in base pair sequences. Nanopores that can distinguish between purines and pyrimidines are also currently being developed. Incorporating electricity-conducting electrodes is also intended to enhance base pair identification's longitudinal resolution. [102] A thousand bases per second might potentially be read with this technique. These can be employed for high-throughput genome sequencing at a cheap cost [103], which would be very advantageous for pharmacogenomics applications in the drug development process.

1. **Nanocrystals:**

A "cluster" of several hundred to tens of thousands of atoms is what constitutes a nanocrystal. These aggregates typically range in size from 10 to 400 nm, and their physical and chemical characteristics fall between those of bulk solids and molecules. Other characteristics, like the bandgap, charge conductivity, crystalline structure, and melting temperature, can be changed by adjusting the size and surface area. In order to prevent larger aggregates from developing, the crystals must be stabilized. Nano sonication creates nanocrystals. High-speed stirring first creates a Nano suspension, which is then transformed into Nano-sized crystals using wet milling, high-pressure homogenization, Nano crystallization, and spray drying. High bioavailability, a significant reduction in dosage volume, and an increase in tolerable dose are all benefits of Nano crystallization. [104] It also has the ability to make medications that are poorly soluble.

1. **Micelles:**

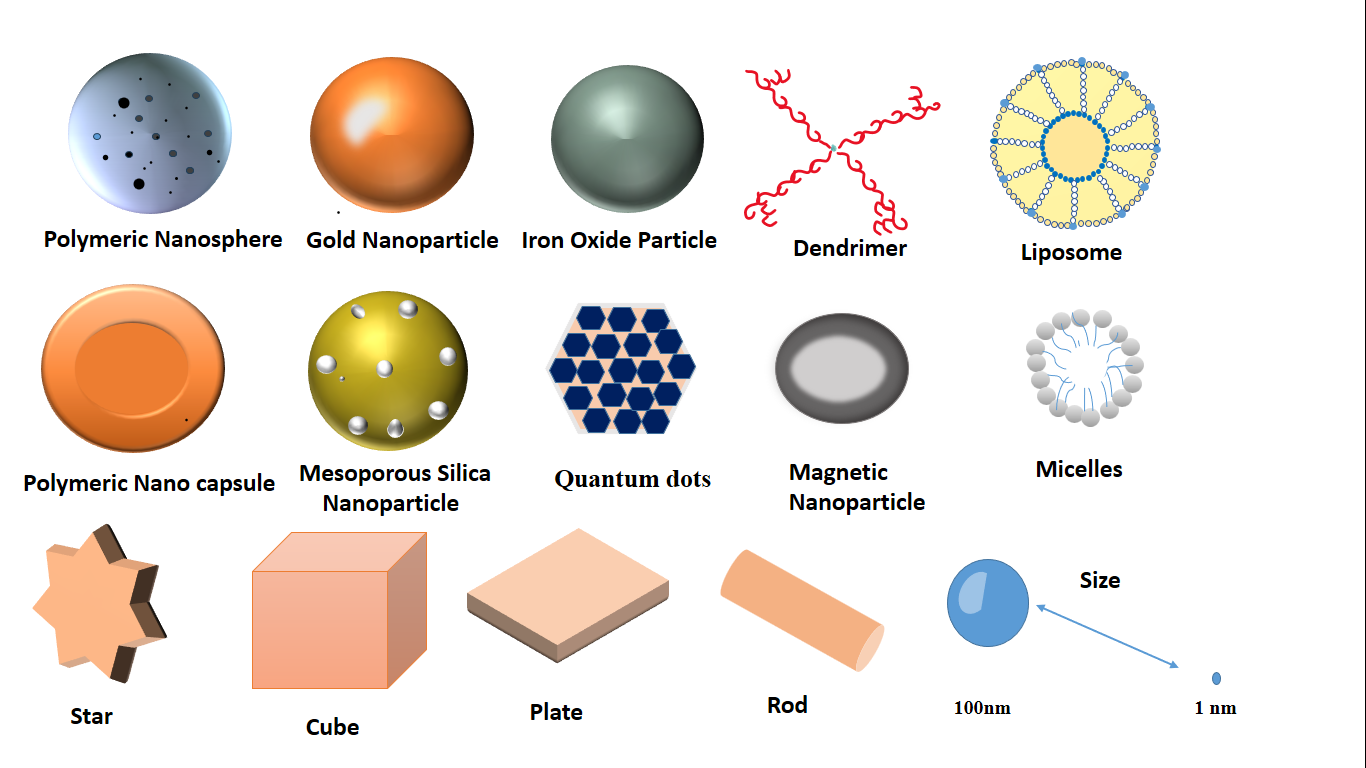
Micelles are spherical lipid nanostructures as well, although they lack an inner cavity or bilayer. The hydrophobic and hydrophilic ends of the phospholipids point inside and outward, respectively, to produce a spherical structure. The polarity of reverse micelles is in the opposite direction. Micelles used in pharmaceutical applications typically range in size from 10 to 80 nm. Because they are smaller than liposomes, micelles circulate through the body more quickly. Due to the EPR effect, they do have the benefit of being able to infiltrate tumor cells more quickly. Polymers can also be used to create micelles. Block-copolymers made of hydrophilic (like PEG) and hydrophobic monomer units with longer hydrophilic blocks and shorter hydrophobic blocks are what create polymeric micelles. They are composed of hydrophilic components that stabilize a hydrophobic core. Because of their superior biodistribution and longer circulation times than traditional micelles, these micelles are more stable than those in use today and are favored for drug delivery applications. Micelles consisting of lipids and polymers can also be produced. They are capable of transporting a variety of substances, including camptothecin, diazepam, and paclitaxel. They also have good stability and lifespan. PEG-phosphatidylethanolamine (PEG-PE) conjugates have been used to create micelles with enhanced solubility and intracellular delivery. Micelles that have been coupled with transferrin can carry DNA to cancer cells. Adriamycin has also been delivered to cancer cells via folate residues bound to micelles. Due to their reduced size and ease of transportation to the target area, these agents have an advantage in that they penetrate targets more effectively. [105, 1]

1. **Gold Nanoparticles:**

For the treatment of illnesses like cancer, rheumatoid arthritis, multiple sclerosis, and neurological ailments like Alzheimer's disease, colloidal gold nanoparticles have been around for a while. Gold nanoparticles are advantageous because they are simple to prepare, come in a variety of sizes, are well-biocompatible, can be easily functionalized, and can conjugate with other biomolecules without changing their biological properties. It has been demonstrated that gold nanoparticles smaller than 50 nm can traverse the BBB. TNF (tumor necrosis factor)-conjugated PEGylated gold nanoparticles can infiltrate tumor cells through their leaky vasculature. [106] The primary attribute of nanoparticles is multi-functionality. For precise medication delivery and cellular uptake, nanoparticles can be combined with ligands, imaging labels, therapeutic compounds, and other capabilities. [1]

**Table 2: Particle size distribution for several nanotechnology methods: [107]**

|  |  |  |
| --- | --- | --- |
| **Sr. No.** | **Techniques** | **Particle size** |
| 1. | Nanoparticles | 10-1000nm |
| 2. | Gold Nanoparticles | 5-50nm |
| 3. | Magnetic Nanoparticles | 5-500nm |
| 4. | Liposomes | 15nm to several nm |
| 5. | Niosomes | 20nm to several |
| 6. | Dendrimers | 1.5-10nm |
| 7. | Carbon Nano Tubes | Less than 100nm |
| 8. | Nanoemulsion | 50-1000nm |
| 9. | Nano suspension | 10-1000nm |
| 10. | Nanocrystals | 10-400nm |
| 11. | Micelles | 10-80nm |



**Fig No 1:Different types of nanoparticles**

**Table 3: List of some drugs as Nano drug delivery system nanoparticles.**

|  |  |  |
| --- | --- | --- |
| Sl. No. | Name of the drug | Purpose |
| NANOPARTICLES | | |
| 1. | Dexamethasone | To increase the amount of drug release with respect to pure drug [17] |
| 2. | Praziquantel | To study the effect of formulation variables on size distribution [18] |
| 3. | Salbutamol sulphate | To achieved the size and shape of spray dried nanosized particles is suitable for the respiratory deposition in lungs. [19] |
| 4. | Amphotericin B | To improve oral bioavailability and to show reduced nephrotoxicity compared to intravenous fungizone.[20] |
| 5. | Naringenin | To enhance hepatoprotective effect in-vivo.[21] |
| SOLID LIPID NANOPARTICLES | | |
| 6. | Vinpocetine | To improve oral bioavailability of poorly soluble drug & in treatment of various types of cerebrovascular circular disorders.(oral)[22] |
| 7. | Oridonin | Antitumour effect, anti-inflammatory anti-bacterial especially esophageal carcinoma & prostate carcinoma.[23] |
| 8. | Itraconazole | Used to improve the therapeutic efficiency and reduction of toxicity and improve antifungal activity.[24] |
| F | Lovastatin | To improve bioavaibility of lovastatin. (Duodenal) |
| 10. | Ubidecarenone | Immobilization of drug molecules by the triglycerides lattice allow sustain release.[25] |
| NANOSUSPENSIONS | | |
| 11. | Itraconazole | To increase aqueous solubility & dissolution and hence to increase the oral bioavaibility. (Aerosols)[26] |
| 12. | Diclofenac | To enhance the solubility of drug. (intramuscular)[27] |
| 13. | Hesperetin | To enhance the effect of drug through dermal delivery. [28] |
| 14. | Retinoic acid | To attain controlled release and high saturation solubility of the drug.[29] |
| 15 | Famotidine | To improve dissolution rate of the drug. (Mucoadhesive)[30] |
| NANOEMULSION | | |
| 16. | Aceclofenac | To increase the anti-inflammatory effect compared with aceclofenac gel.[31] |
| 17. | Glycyrrhetinic acid | Used in cosmetic as lenitive & anti-redding agent.[32] |
| 18. | B-carotene | To prepare protein-stabilized B carotene nano dispersion by emulsification evaporation method[33] |
| NANOGOLD PARTICLE | | |
| 19. | Insulin | To improve the surface properties for binding of biomolecules which improve pharmacodynamic activity[34] |
| 20. | Lecodopa,6-mercaptopurine | To prevent uptake by the mononuclear phagocyte system and to allow penetration through the smallest pores of membrane.[35] |
| NANOSPONGES | | |
| 21. | Paclitaxel | To enhance oral bioavalibility of paclitaxel.[36] |
| 22. | Itraconazole | To increase the solubility of drug many folds compared to plain drug.[37] |

1. **CHALLENGES:**

Although nanotechnology in drug delivery has been successful, as evidenced by some Nano drug products in the market, not all approaches have met with the same success. New nanomaterials being developed come with challenges that have to be surmounted. However, some of the challenges encountered have been and are still being tackled by modification of the physicochemical characteristics of the nanomaterials to improve on properties such as long circulation in the blood, increased functional surface area, protection of the incorporated drug from degradation, the crossing of biological barriers and site-specific targeting. Another challenge of research and development (R&D) of nanomaterials for drug delivery is large-scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. A number of Nano drug delivery technologies may not be scalable due to the method and process of production and the high cost of materials employed. The challenges of scaling up include a low concentration of nanomaterials, agglomeration, and the chemistry process – it is easier to modify nanomaterials at a laboratory scale for improved performance than at a large scale. Maintaining the size and composition of nanomaterials at a large scale is also a challenge. [9]

**V. CONCLUSION:**

The experimental development of nanotechnology is continually progressing at a fast pace; however, significant challenges still exist in promoting these platforms into clinically feasible therapies. Therefore, continued translational success will require communication and collaboration between experts involved in all stages of pharmaceutical development of nanotechnologies including pharmaceutical design and manufacturing, cellular interactions and toxicology, as well as preclinical and clinical evaluation. Extensive research is going on in the area of novel drug delivery and targeting. However, research in this area is still at the exploratory stage. Many problems in research, production, and application need to be solved. In addition, more attention should be paid to the research on the carrier materials in order to develop more suitable carriers which can reduce the toxicity of drugs, enhance their activity and improve the overall quality of the agents. Novel drug delivery systems not only reduce the repeated administration to overcome non-compliance, but also help to increase the therapeutic value by reducing toxicity and increasing bioavailability and, so on. Hence there is great potential in the development of novel drug delivery systems for distinct dosage forms. Nanotechnology is disturbing the world, reinventing “old” technologies and creating new solutions. We will have the opportunity to see an interesting concern regarding how the nanoworld is supporting research on drug delivery systems and being applied in medicine. Nanotechnology is disrupting the world, reinventing "old" technologies and creating new solutions. we will have the opportunity to see an interesting concern regarding how the nanoworld is supporting research in Drug Delivery systems and being applied in medicine.

**VI. REFERENCES:**

[1] Kapil, Aruna, G. Aggarwal, and S. L. Harikumar, "Nanotechnology in novel drug delivery system," *Journal of Drug Delivery and Therapeutics,* vol 4, no.5, pp. 21-28, 2014.

[2] Sahu, Tarun, Y. K. Ratre, S. Chauhan, L. V. K. S. Bhaskar, M. P. Nair, and H. Kumar Verma. "Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science," *Journal of Drug Delivery Science and Technology*, vol. 63, pp. 102487, 2021.

[3] Hua, Susan, and Sherry Y. Wu. "Advances and challenges in nanomedicine," *Frontiers in pharmacology*, vol 9, pp 1397, 2018.

[4] Saraf, S. "Applications of novel drug delivery system for herbal formulations." *Fitoterapia* 81, no. 7 (2010): 680-689.

[5] Devi, V. Kusum, Nimisha Jain, and Kusum S. Valli. "Importance of novel drug delivery systems in herbal medicines." *Pharmacognosy reviews* 4, no. 7,pp 27, 2010.

[6] Patra, Jayanta Kumar, Gitishree Das, Leonardo Fernandes Fraceto, Estefania Vangelie Ramos Campos, Maria del Pilar Rodriguez-Torres, Laura Susana Acosta-Torres and Luis Armando Diaz-Torres, "Nano based drug delivery systems: recent developments and future prospects," *Journal of nanobiotechnology, vol* 16, no. 1, pp1-33, 2018.

[7] Obeid, Mohammad A., Mohammed M. Al Qaraghuli, Manal Alsaadi, Abdullah R. Alzahrani, Kanidta Niwasabutra, and Valerie A. Ferro, "Delivering natural products and biotherapeutics to improve drug efficacy," *Therapeutic delivery*, vol 8, no. 11, pp 947-956, 2017.

[8] Duncan, R. "Polymer therapeutics: Nanomedicines in routine clinical use." *Proceedings of Euronanoforum* 2005.

[9] Wagner, Volker, Anwyn Dullaart, Anne-Katrin Bock, and Axel Zweck, "The emerging nanomedicine landscape," *Nature biotechnology*, vol 24, no. 10, pp1211-1217, 2006.

[10] Jain, Nilesh, Ruchi Jain, Navneet Thakur, Brham Prakash Gupta, Deepak Kumar Jain, Jeetendra Banveer, and Surendra Jain, "Nanotechnology: a safe and effective drug delivery system," *Asian Journal of Pharmaceutical and Clinical Research* , vol 3, no. 3, pp 159-165, 2010.

[11] Devalapally, Harikrishna, Ananthsrinivas Chakilam, and Mansoor M. Amiji, "Role of nanotechnology in pharmaceutical product development," *Journal of pharmaceutical sciences,* vol 96, no. 10, pp 2547-2565, 2007.

[12] Schek, Rachel Maddox, Scott J. Hollister, and Paul H. Krebsbach, "Delivery and protection of adenoviruses using biocompatible hydrogels for localized gene therapy," *Molecular Therapy*, vol 9, no. 1, pp 130-138, 2004.

[13] Tiwari, Shashank, and Shreya Talreja, "Nanotube: A New Approach to Novel Drug Delivery System," *Journal of Pharmaceutical Sciences and Research*, vol 12, no. 8, pp 1024-1028, 2020.

[14] Jiang, Wen, Betty YS Kim, James T. Rutka, and Warren CW Chan, "Advances and challenges of nanotechnology-based drug delivery systems," *Expert opinion on drug delivery,* vol4, no. 6, pp 621-633, 2007.

[15] Rahman, Heshu Sulaiman, Hemn Hassan Othman, Nahidah Ibrahim Hammadi, Swee Keong Yeap, Kawa Mohammad Amin, Nozlena Abdul Samad, and Noorjahan Banu Alitheen, "Novel drug delivery systems for loading of natural plant extracts and their biomedical applications," *International journal of nanomedicine*, pp 2439-2483,2020.

[16] Jain, N. K. "Pharmaceutical nanotechnology." 2008.

[17] Cascone, Maria Grazia, Paola Maron Pot, Luigi Lazzeri, and Zhouhai Zhu, "Release of dexamethasone from PLGA nanoparticles entrapped into dextran/poly (vinyl alcohol) hydrogels," *Journal of Materials Science: Materials in Medicine, vol* 13, pp265-269, 2002.

[18] Mainardes, Rubiana M., and Raul C. Evangelista, "PLGA nanoparticles containing praziquantel: effect of formulation variables on size distribution." *International journal of pharmaceutics*, vol 290, no. 1-2, pp 137-144, 2005.

[19] Bhavna, F. J. Ahmad, R. K. Khar, S. Sultana, and A. Bhatnagar, "Techniques to develop and characterize nanosized formulation for salbutamol sulfate," *Journal of Materials Science: Materials in Medicine*, vol 20, no. Suppl 1, pp 71-76, 2009.

[20] Italia, J. L., M. M. Yahya, D. Singh, and M. N. V. Ravi Kumar, "Biodegradable nanoparticles improve oral bioavailability of amphotericin B and show reduced nephrotoxicity compared to intravenous Fungizone®," *Pharmaceutical research*, vol 26, pp 1324-1331, 2009.

[21] Yen, Feng-Lin, Tzu-Hui Wu, Liang-Tzung Lin, Thau-Ming Cham, and Chun-Ching Lin, "Naringenin-loaded nanoparticles improve the physicochemical properties and the hepatoprotective effects of naringenin in orally-administered rats with CCl 4-induced acute liver failure," *Pharmaceutical research*, vol 26, pp 893-902, 2009.

[22] Luo, YiFan, DaWei Chen, LiXiang Ren, XiuLi Zhao, and Jing Qin, "Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability," *Journal of controlled release*, vol 114, no. 1, pp 53-59, 2009.

[23] Maravajhala, Vidyavathi, Sandya Papishetty, and Sarika Bandlapalli, "Nanotechnology in development of drug delivery system," *International journal of pharmaceutical sciences and research, vol* 3, no. 1, pp 84, 2012.

[24] Maravajhala, Vidyavathi, Sandya Papishetty, and Sarika Bandlapalli, "Nanotechnology in development of drug delivery system," *International journal of pharmaceutical sciences and research,vol* 3, no. 1, pp 84, 2012.

[25] Bunjes, Heike, Markus Drechsler, Michel HJ Koch, and Kirsten Westesen, "Incorporation of the model drug ubidecarenone into solid lipid nanoparticles," *Pharmaceutical research, vol* 18, pp 287-293, 2001.

[26] Shah, Dhiren P., Bhavesh Patel, and Chainesh Shah, "Nanosuspension technology: A innovative slant for drug delivery system and permeability enhancer for poorly water soluble drugs," *Journal of Drug Delivery and Therapeutics*, vol 5, no. 1, pp 10-23, 2015.

[27] Maravajhala, Vidyavathi, Sandya Papishetty, and Sarika Bandlapalli, "Nanotechnology in development of drug delivery system," *International journal of pharmaceutical sciences and research, vol* 3, no. 1, pp 84, 2012.

[28] Mishra, Prabhat R., Loaye Al Shaal, Rainer H. Müller, and Cornelia M. Keck, "Production and characterization of Hesperetin nanosuspensions for dermal delivery," *International journal of pharmaceutics, vol* 371, no. 1-2, pp 182-189, 2009.

[29] Zhang, X., Q. Xia, and N. Gu., "Preparation of all-trans retinoic acid nanosuspensions using a modified precipitation method," *Drug development and industrial pharmacy* , vol 32, no. 7, pp 857-863, 2006.

[30] Patel, Dhaval J., and Jayvadan K. Patel, "Mucoadhesive effect of polyethyleneoxide on famotidine nanosuspension prepared by solvent evaporation method," *Int J Pharm Pharm Sci*, vol 2, no. 2, pp 122-7, 2010.

[31] Shakeel, Faiyaz, Sanjula Baboota, Alka Ahuja, Javed Ali, Mohammed Aqil, and Sheikh Shafiq, "Nanoemulsions as vehicles for transdermal delivery of aceclofenac," *Aaps Pharmscitech*, vol 8, pp 191-199, 2007.

[32] Puglia, Carmelo, Manuela Liotta, Markus Drechsler, Luisa Rizza, and Francesco Bonina, "EVALUATION OF IN VITRO PERCUTANEOUS ABSORPTION OF GLYCYRRHETINIC ACID FROM NANOEMULSIONS OBTAINED BY THE PHASE INVERSION TEMPERATURE (PIT) METHOD," In *Proc. 5th World meeting on Pharmaceutics, Biopharmaceutics and Pharm. Tech, Geneva*. 2006.

[33] Chu, Boon-Seang, Sosaku Ichikawa, Sumiyo Kanafusa, and Mitsutoshi Nakajima, "Preparation of protein-stabilized β-carotene nanodispersions by emulsification–evaporation method," *Journal of the American Oil Chemists' Society*, vol 84, pp 1053-1062, 2007.

[34] Bhumkar, Devika R., Hrushikesh M. Joshi, Murali Sastry, and Varsha B. Pokharkar, "Chitosan reduced gold nanoparticles as novel carriers for transmucosal delivery of insulin," *Pharmaceutical research*, vol 24, pp 1415-1426, 2007.

[35] Kaur, Harsimran, Archana Chaudhary, Inderpreet Kaur, Kashmir Singh, and Lalit M. Bharadwaj, "Transportation of drug–gold nanocomposites by actinomyosin motor system," *Journal of Nanoparticle Research*, vol 13, pp 2295-2303, 2011.

[36] Swaminathan, Shankar, P. R. Vavia, Francesco Trotta, and Satyen Torne, "Formulation of betacyclodextrin based nanosponges of itraconazole," *Journal of inclusion phenomena and macrocyclic chemistry, vol*  57, pp 89-94, 2007.

[37] Torne, Satyen J., Khalid A. Ansari, Pradeep R. Vavia, Francesco Trotta, and Roberta Cavalli, "Enhanced oral paclitaxel bioavailability after administration of paclitaxel-loaded nanosponges," *Drug delivery*, vol 17, no. 6, pp 419-425, 2010.

[38] Miele, Evelina, Gian Paolo Spinelli, Ermanno Miele, Enzo Di Fabrizio, Elisabetta Ferretti, Silverio Tomao, and Alberto Gulino, "Nanoparticle-based delivery of small interfering RNA: challenges for cancer therapy," *International journal of nanomedicine,* pp 3637-3657, 2012.

[39] McNamara, Karrina, and Syed AM Tofail, "Nanosystems: the use of nanoalloys, metallic, bimetallic, and magnetic nanoparticles in biomedical applications," *Physical chemistry chemical physics*, vol 17, no. 42, pp 27981-27995, 2015.

[40] Sachin, J., and N. Vishal Gupta, "Solid lipid nanoparticles–preparation, applications, characterization, uses in various cancer therapies: a review," *Research Journal of Pharmacy and Technology*, vol 6, no. 8, pp 825-837, 2013.

[41] Tadic, Marin, Slavko Kralj, Marko Jagodic, Darko Hanzel, and Darko Makovec, "Magnetic properties of novel superparamagnetic iron oxide nanoclusters and their peculiarity under annealing treatment," *Applied Surface Science*, vol 322, pp 255-264, 2014.

[42] Rinkevich, Anatoly B., and Dmitry V. Perov. "Advances in Magnetic Nanocomposites: A New Open Special Issue in Materials." *vol*15, pp 6905, 2022.

[43] Ali, Arbab, Tufail Shah, Rehmat Ullah, Pingfan Zhou, Manlin Guo, Muhammad Ovais, Zhiqiang Tan, and YuKui Rui. "Review on recent progress in magnetic nanoparticles: Synthesis, characterization, and diverse applications." *Frontiers in Chemistry*, vol 9, pp 629054, 2021.

[44] Hao, Rui, Ruijun Xing, Zhichuan Xu, Yanglong Hou, Song Gao, and Shouheng Sun. "Synthesis, functionalization, and biomedical applications of multifunctional magnetic nanoparticles." *Advanced materials,* vol 22, no. 25: pp 2729-2742, 2010.

[45] Babes, Lucia, Benoı̂t Denizot, Gisèle Tanguy, Jean Jacques Le Jeune, and Pierre Jallet. "Synthesis of iron oxide nanoparticles used as MRI contrast agents: a parametric study." *Journal of colloid and interface science* vol 212, no. 2, pp 474-482, 1999.

[46] DeCastro, Claudio L., and Brian S. Mitchell. "Nanoparticles from mechanical attrition." *Synthesis, functionalization, and surface treatment of nanoparticles*, vol 5, 2002.

[47] Biehl, Philip, Moritz Von der Lühe, Silvio Dutz, and Felix H. Schacher. "Synthesis, characterization, and applications of magnetic nanoparticles featuring polyzwitterionic coatings." *Polymers*, vol 10, no. 1, pp 91, 2018.

[48] Fecht, H. J., E. Hellstern, Z. Fu, and W. L. Johnson. "Nanocrystalline metals prepared by high-energy ball milling." *Metallurgical Transactions A*, vol 21, pp 2333-2337, 1990.

[49] Benjamin, John S. "Dispersion strengthened superalloys by mechanical alloying." *Metallurgical transactions*, vol 1, pp 2943-2951, 1970.

[50] Mohammed, Leena, Hassan G. Gomaa, Doaa Ragab, and Jesse Zhu. "Magnetic nanoparticles for environmental and biomedical applications: A review." *Particuology, vol* 30, pp1-14, 2014.

[51] Shin, D. N., Y. Matsuda, and E. R. Bernstein. "On the iron oxide neutral cluster distribution in the gas phase. II. Detection through 118 nm single photon ionization", *The Journal of chemical physics,* vol. 120, no. 9, pp.4157-4164, 2004.

[52] Kurland, H. Dieter, J. Grabow, G. Staupendahl, W. Andrä, S. Dutz, and M. E. Bellemann, "Magnetic iron oxide nanopowders produced by CO2 laser evaporation", *Journal of Magnetism and Magnetic Materials,* vol 311, no. 1, pp.73-77, 2007.

[53] Yang, Ziyu, T. Zhao, X.Huang, X. Chu, T. Tang, Y. Ju, Q. Wang, Y.Hou, and S. Gao, "Modulating the phases of iron carbide nanoparticles: from a perspective of interfering with the carbon penetration of Fe@ Fe 3 O 4 by selectively adsorbed halide ions", *Chemical science* 8, vol 1, pp.473-481, 2017.

[54] Song, Kyungsun, W. Kim, C.Y.Suh, D.Shin, K.S. Ko, and K. Ha, "Magnetic iron oxide nanoparticles prepared by electrical wire explosion for arsenic removal", *Powder technology*, vol 246, pp. 572-574, 2013.

[55] Kotov, Yu A, "Electric explosion of wires as a method for preparation of nanopowders", *Journal of nanoparticle research,* vol 5, pp.539-550, 2003.

[56] Kawamura, Go, S.Alvarez, I.E. Stewart, M.Catenacci, Z. Chen, and Y.Ha, "Production of oxidation-resistant Cu-based nanoparticles by wire explosion", *Scientific Reports* 5, vol no. 1, pp,18333, 2015.

[57] S. Kumar, V. "Magnetic nanoparticles-based biomedical and bioanalytical applications," *J Nanomed Nanotechol* 4, vol e130, 2013.

[58] Shalihah, D.Haibatus, N.Nashikudin, M.Munasir, and Y. A. Hariyanto, "Effect of ZnO on the Nanostructure, Magnetic, and Optical Properties of Fe2O3/MWCNT/ZnO Nanocomposites", *Journal of Magnetism and Its Applications* 1, vol no. 2, pp. 40-45, 2021.

[59] S.Kumar, V, "Magnetic nanoparticles-based biomedical and bioanalytical applications", *J Nanomed Nanotechol* 4, vol e130, 2013.

[60] Chen, J. P., C. M. Sorensen, K. J. Klabunde, G. C. Hadjipanayis, E. Devlin, and A. Kostika,"Size-dependent magnetic properties of MnFe 2 O 4 fine particles synthesized by coprecipitation", *Physical review B* 54, vol no. 13, pp. 9288, 1996.

[61] Effenberger, B.Fernando, R. A. Couto, P.K. Kiyohara, G. Machado, S. H. Masunaga, R. F. Jardim, and L.M. Rossi, "Economically attractive route for the preparation of high quality magnetic nanoparticles by the thermal decomposition of iron (III) acetylacetonate", *Nanotechnology* 28, vol no. 11, pp.115603, 2017.

[62] Ren, Baiyu, A. E. Kandjani, M. Chen, M.R. Field, D. K. Oppedisano, S. K. Bhargava, and L. A. Jones, "Preparation of Au nanoparticles on a magnetically responsive support via pyrolysis of a Prussian blue composite", *Journal of colloid and interface science, vol* 540, pp.563-571, 2019.

[63] Frey, A.Natalie, S.Peng, K.Cheng, and S.Sun, "Magnetic nanoparticles: synthesis, functionalization, and applications in bioimaging and magnetic energy storage", *Chemical Society Reviews* 38, vol no. 9, 2532-2542, 2009.

[64] Smith, W.Thomas, and D.Wychick, "Colloidal iron dispersions prepared via the polymer-catalyzed decomposition of iron pentacarbonyl", *The Journal of Physical Chemistry* 84, vol no. 12, pp. 1621-1629, 1980.

[65] Lu, An‐Hui, E. emsp14L Salabas, and F. Schüth, "Magnetic nanoparticles: synthesis, protection, functionalization, and application", *Angewandte Chemie International Edition* 46, vol no. 8,1222-1244, 2007.

[66] Moros, María, J. I.López, L.Asín, E. M.Antolín, L. Beola, V. Grazú, R.M. Fratila, L. Gutiérrez, and J. M. de la Fuente, "Triggering antitumoural drug release and gene expression by magnetic hyperthermia", *Advanced drug delivery reviews*, vol 138,pp.326-343, 2019.

[67] Zhang, Peiming, Y.Zhang, M.Gao, and X.Zhang,"Dendrimer-assisted hydrophilic magnetic nanoparticles as sensitive substrates for rapid recognition and enhanced isolation of target tumor cells", *Talanta*, vol 161, 925-931, 2016.

[68] Reddy, L. Harivardhan, J.L. Arias, J. Nicolas, and P.Couvreur, "Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications", *Chemical reviews* 112, vol no. 11, pp.5818-5878, 2012.

[69] Wang, Z. H., C. J. Choi, B. K. Kim, J. C. Kim, and Z. D. Zhang, "Characterization and magnetic properties of carbon-coated cobalt nanocapsules synthesized by the chemical vapor-condensation process", *Carbon* 41, vol no. 9, pp.1751-1758, 2003.

[70] Li, Jingchao, L.Zheng, H. Cai, W. Sun, M. Shen, G. Zhang, and X. Shi, "Polyethyleneimine-mediated synthesis of folic acid-targeted iron oxide nanoparticles for in vivo tumor MR imaging", *Biomaterials* 34, vol no. 33, pp.8382-8392, 2013.

[71] Li, G.yin, Yu.Jiang, K.l.Huang, P. Ding, and J. Chen,"Preparation and properties of magnetic Fe3O4–chitosan nanoparticles", *Journal of alloys and compounds* 466, vol no. 1-2 pp.451-456, 2008.

[72] Zahid, Muhammad, N.Nadeem, M. A. Hanif, I.A. Bhatti, H.N.Bhatti, and G.Mustafa, "Metal ferrites and their graphene-based nanocomposites: synthesis, characterization, and applications in wastewater treatment", *Magnetic nanostructures: environmental and agricultural applications*, pp.181-212, 2019.

[73] Ansari, S.A.M. Khawja, E. Ficiarà, F. A.Ruffinatti, I.Stura, M.Argenziano, O.Abollino, R. Cavalli, C. Guiot, and F.D’Agata, "Magnetic iron oxide nanoparticles: synthesis, characterization and functionalization for biomedical applications in the central nervous system", *Materials* 12, vol no. 3, pp. 465, 2019.

[74] Hasany, S. F., I. Ahmed, J. Rajan, and A. Rehman, "Systematic review of the preparation techniques of iron oxide magnetic nanoparticles", *Nanosci. Nanotechnol* 2, vol no. 6, pp.148-158, 2012.

[75] Verma, Rajni, S. Pathak, A. K. Srivastava, S. Prawer, and S.T.Hanic,"ZnO nanomaterials: Green synthesis, toxicity evaluation and new insights in biomedical applications", *Journal of Alloys and Compounds*, vol 876, pp.160175, 2021.

[76] Komeili, Arash, "Molecular mechanisms of compartmentalization and biomineralization in magnetotactic bacteria", *FEMS microbiology reviews* 36, vol no. 1, pp.232-255, 2012.

[77] Gul, Saima, S. B. Khan, I.U. Rehman, M. A. Khan, and M. I. Khan, "A comprehensive review of magnetic nanomaterials modern day theranostics", *Frontiers in Materials,* vol 6, pp.179, 2019.

[78] Lenders, J.JM, C. L. Altan, P. HH Bomans, A. Arakaki, S.Bucak, G. de With, and N.AJM Sommerdijk, "A bioinspired coprecipitation method for the controlled synthesis of magnetite nanoparticles", *Crystal growth & design* 14, vol no. 11, pp.5561-5568, 2014.

[79] Yamashita, Taro, J. Ji, A. Budhu, M.Forgues, W. Yang, H.Y. Wang, H. Jia et al, "EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features", *Gastroenterology* 136, vol no. 3 , pp.1012-1024, 2009.

[80] B.Nissan, B, "Nanoceramics in biomedical applications", *MRS bulletin* 29, vol no. 1,pp. 28-32, 2004.

[81] <http://www.reference.md/files/D016/mD016503.html>

[82] Moghassemi, Saeid, and A. Hadjizadeh, "Nano-niosomes as nanoscale drug delivery systems: an illustrated review", *Journal of controlled release, vol* 185, pp. 22-36, 2014.

[83] Teobaldi, G., Al Ma’Mari, M. Rogers, S. Alghamdi, T. Moorsom, S. Lee, T. Prokscha et al, "Proceedings of the National Academy of Sciences", *Proceedings of the National Academy of Sciences of USA* ,2017.

[84] Ge, Xuemei, M. Wei, S. He, and W.E. Yuan, "Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery", *Pharmaceutics* 11, vol no. 2, pp.55, 2019.

[85] Uchegbu, I. F., and S.P. Vyas,"Non-ionic surfactant based vesicles (niosomes) in drug delivery", *International journal of pharmaceutics* 172, vol no. 1-2, pp. 33-70, 1998.

[86] Sebaaly, Carine, C. Charcosset, S. Stainmesse, H.Fessi, and H. G.Gerges, "Clove essential oil-in-cyclodextrin-in-liposomes in the aqueous and lyophilized states: From laboratory to large scale using a membrane contactor", *Carbohydrate Polymers, vol* 138 , pp. 75-85, 2016.

[87] Nisini, Roberto, N.Poerio, S. Mariotti, F. De Santis, and M.Fraziano, "The multirole of liposomes in therapy and prevention of infectious diseases", *Frontiers in Immunology*, vol 9, pp. 155, 2018.

[88] Guimarães, Diana, A. C.Paulo, and E. Nogueira,"Design of liposomes as drug delivery system for therapeutic applications", *International journal of pharmaceutics*, vol 601, pp.120571, 2021.

[89] Gregoriadis, Gregory, and B. E. Ryman, "Fate of protein‐containing liposomes injected into rats: An approach to the treatment of storage diseases", *European journal of biochemistry* 24, vol no. 3, pp. 485-491, 1972.

[90] Torchilin, Vladimir P., M. I. Shtilman, V. S. Trubetskoy, K. Whiteman, and A.r M. Milstein, "Amphiphilic vinyl polymers effectively prolong liposome circulation time in vivo", *Biochimica et Biophysica Acta (BBA)-Biomembranes* 1195, vol no. 1, pp. 181-184, 1994.

[91] Forssen, Eric A., D. M. Coulter, and R.T. Proffitt, "Selective in vivo localization of daunorubicin small unilamellar vesicles in solid tumors", *Cancer Research* 52, vol no. 12, pp. 3255-3261, 1992.

[92] Kobayashi, Hisataka, and M. W. Brechbiel, "Dendrimer-based macromolecular MRI contrast agents: characteristics and application", *Molecular imaging* 2, vol no. 1, pp. 15353500200303100, 2003.

[93] Tolia, Gaurav, and H.Choi, "The role of dendrimers in topical drug delivery", *Pharmaceutical technology* 32, vol no. 11,2008.

[94] Singh, B. G. P., C. Baburao, V. Pispati, H.Pathipati, N.Muthy, S. R. V. Prassana, and B. G. Rathode, "Carbon nanotubes. A novel drug delivery system", *International Journal of Research in Pharmacy and Chemistry* 2, vol no. 2, pp.523-532, 2012.

[95] Star, Alexander, Y. Liu, K.Grant, L.Ridvan, J. F. Stoddart, D.W. Steuerman, M.R. Diehl, A.Boukai, and J. R. Heath,"Noncovalent side-wall functionalization of single-walled carbon nanotubes", *Macromolecules* 36, vol no. 3,pp.553-560, 2003.

[96] Lin, Yi, A. M. Rao, B. Sadanadan, E. A. Kenik, and Y. P. Sun, "Functionalizing multiple-walled carbon nanotubes with aminopolymers", *The Journal of Physical Chemistry B* 106, vol no. 6, pp. 1294-1298, 2002.

[97] Wu, Wei, S.Wieckowski, G. Pastorin, M.Benincasa, C. Klumpp, J.P.Briand, R. Gennaro, M.Prato, and A. Bianco, "Targeted delivery of amphotericin B to cells by using functionalized carbon nanotubes", *Angewandte Chemie International Edition* 44, vol no. 39, pp. 6358-6362, 2005.

[98] Dhumal, Nikhil, V.Yadav, and S. Borkar, "Nanoemulsion as Novel Drug Delivery System: Development, Characterization and Application", *Asian Journal of Pharmaceutical Research and Development* 10, vol no. 6, pp. 120-127, 2022.

[99] Reddy, K. Rajender, M.W. Modi, and S. Pedder, "Use of peginterferon alfa-2a (40 KD)(Pegasys®) for the treatment of hepatitis C", *Advanced Drug Delivery Reviews* 54, vol no. 4, pp. 571-586, 2002.

[100] Desai, Tejal A., W. H.Chu, Jay K. Tu, G.M. Beattie, A. Hayek, and M.Ferrari, "Microfabricated immunoisolating biocapsules", *Biotechnology and bioengineering* 57, vol no. 1, pp. 1108-120, 1998.

[101] Leoni, Lara, and T.A. Desai, "Nanoporous biocapsules for the encapsulation of insulinoma cells: biotransport and biocompatibility considerations", *IEEE transactions on biomedical engineering* 48, vol no. 11, pp. 1335-1341, 2001.

[102] Freitas, A.Robert , "Current status of nanomedicine and medical nanorobotics", *Journal of computational and theoretical nanoscience* 2, vol no. 1, pp. 1-25, 2005.

[103] Deamer, W.David, and M.Akeson, "Nanopores and nucleic acids: prospects for ultrarapid sequencing" ,*Trends in biotechnology* 18, vol no. 4, pp. 147-151, 2000.

[104] Majuru, Shingai, and M. O. Oyewumi, "Nanotechnology in drug development and life cycle management", *Nanotechnology in drug delivery*, pp. 597-619, 2009.

[105] Tadros, Tharwat, P.Izquierdo, J.Esquena, and C. Solans, "Formation and stability of nano-emulsions", *Advances in colloid and interface science*, vol 108 ,pp. 303-318, 2004.

[106] Krishnadas, Aparna, I.Rubinstein, and H.Önyüksel,"Sterically stabilized phospholipid mixed micelles: in vitro evaluation as a novel carrier for water- insoluble drugs", *Pharmaceutical research*, vol 20 , pp. 297-302, 2003.

[107] Joshi, M.Hrushikesh, D. R. Bhumkar, K.Joshi, V.Pokharkar, and M. Sastry,"Gold nanoparticles as carriers for efficient transmucosal insulin delivery", *Langmuir* 22, vol no. 1, pp. 300-305, 2006.

[108] Verma, Shivani, P.Utreja, M. Rahman, and L. Kumar, "Gold nanoparticles and their applications in cancer treatment", *Current Nanomedicine (Formerly: Recent Patents on Nanomedicine)* 8, vol no. 3, pp. 184-201, 2018.