

NANOTECHNOLOGY IN NOVEL DRUG DELIVERY SYSTEM

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 nanomedicine and Nanobiotechnology. Nanotechnology is the study of extremely minor structures with 0.1 and 100 nm in size. Modern nanotechnology has an extensive variety of possible uses in healthcare meant for people. Recent investigation 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; also this multidisciplinary systematic field is quickly growing. Drug research, water filtration, also the creation of tougher, lighter constituents is 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 a prolonged period of time, be present by the target site now the right concentrations, and maintain its therapeutic efficacy. This chapter shows the various drug delivery systems and prospective applications of nanotechnology are our goal. In addition, we are discussing the potential applications of nanotechnology in social health.

Keywords: Nanotechnology; Novel Drug Delivery System; Nanomedicines; Prospective Applications; Nanobiotechnology;

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I. INTRODUCTION

The research and development behind the creation of devices and materials with the greatest functioning structure occurring in at least one dimension on a nanometre scale is known as nanotechnology. Nanoparticles are tiny spheres made from substances with atomic or molecular arrangements. The molecular scale is where nanoparticles work because of their small dimension. [13] As a result, they can travel within the human body with greater freedom than bulkier materials. The structural, chemical, mechanical, magnetic, electrical, and biological characteristics of nanoscale-sized entities are distinctive. Through the use of nanostructures and nanophases, nanotechnology is able to bridge the gap between biological and physical sciences in a number of scientific domains. [6] The diverse scientific subject of nanotechnology has expanded dramatically in recent years and is currently experiencing rapid growth. Nanoscience and nanotechnologies have an enormous chance to help improve the health of people in a variety of ways, including medicine discovery, water purification, or the creation of more powerful lighter substances. Nanotechnology studies regarding healthcare for humans can undoubtedly have a significant positive impact on health. The potential of dramatic developments in medicines is where nanotechnology first emerged. Although it would be impossible to identify all possible uses for nanotechnology, among of its biggest benefits will undoubtedly be the creation of a cutting-edge medication way of administration for use in medicine. [1]

Nanotechnology is a murky multidisciplinary field that was developed to manipulate biological components like atoms, molecules, and supramolecular particles at the nanoscale, or between 1 and 100 nm, in order to examine and learn about deadly biological issues, leading to medical diagnosis and therapy, and keep potential toward current challenges.[2] These innovative DDS are much more advantageous than conventional systems on a massive scale because of their compact size, including altered pharmacokinetic behavior and improved dosage.[14] Since medications are able to be attached to nanoparticles as well as delivered to target tissues in a precise and controlled manner by encasing those in these tiny particles, nanotechnology in new methods for drug delivery has gained a lot of popularity in recent years. [13]

Therapeutic substances can be precisely transported to the area of action with nano in innovative drug transport systems while harming non-target tissue, organs, or tissues. This mechanism is in charge of choosing both the spot and the pace at which a medicine should be introduced into the body. Inhalation, skin being absorbed, parenteral injections, and oral ingestion are some of the different ways that medications can be consumed. Each prescription drug can be taken in a variety of ways because every approach has benefits and drawbacks of its own. There is a need for more efficient and effective drug delivery techniques, either through upgrading the current ones or by inventing novel approaches in order to optimize the usage of current therapies. [13]

By enhancing illness diagnosis, prevention, and treatment, the use of nanotechnology in medicine has the potential to have a substantial effect on people's health. The innovative carriers must preferably meet the requirements. Administer the medication over the course of treatment at a rate determined by the body's demands. [4] Different drug delivery and drug targeting methods are now being developed to reduce drug degradation and loss, avoid negative side effects, boost drug bioavailability, and raise the proportion of the medication

accumulating in the necessary zone. [5] Drugs can be safeguarded against deterioration using methods of administration that use nanotechnology. Those features can lessen the number of dosages needed; improve therapeutic knowledge, and lower treatment costs. A variety of Nano-based technologies enable the delivery of hydrophobic medications, allowing the use of previously rejected drugs or drugs that are difficult to administer e.g. paclitaxel. [8] Pharmaceutical nanotechnology includes the use of nanomaterials and equipment for medication delivery, diagnostic, imaging, and biosensor purposes. Pharmaceutical nanotechnology has made it possible to diagnose diseases more precisely and treat them with greater molecular precision. It aids in the detection of germs and viruses linked to infections as well as antigens linked to diseases like cancer, diabetes mellitus, and neurological disorders. Since medications within the nanoscale vary in size to improve performance in a variety of dose forms, size reduction has vital applications in the field of pharmacy.[16] Additionally, there have been significant advancements in the field of delivery systems that allow medicinal products containing active ingredients derived from natural sources to be delivered to the desired site for the treatment of various diseases.[7] While many drug delivery systems have been successfully used in recent decades, there are still some issues that need to be resolved and cutting-edge technology needs to be created in order to effectively transport medications to their target sites. As a result, researchers are currently looking into enhanced ways to deliver drugs based on nanotechnology. [6]

Recent molecular compounds (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 cations of metals, low gastrointestinal efflux, and inadequate transport properties, can cause problems with drug delivery. Nanotechnology can play a significant role in the development of proper formulations that address these problems. The rapid development of the NMEs is facilitated by the favorable physicochemical and toxicological features that nanomaterials can also attain. To change the properties of biopharmaceuticals and pharmacokinetics, such as absorption, distribution, metabolism, and waste elimination, drug delivery methods are currently utilized. [11, 12]

II. NANOTECHNOLOGY BRINGS MANY BENEFITS TO PHARMACY

1. A larger surface area
2. Faster disintegration rate
3. Less dose is needed and there are fewer doses.
4. Protection against drug deterioration
5. A faster start to the therapeutic activity
6. Successful medication targeting
7. Drugs can be passively targeted to liver and spleen macrophages. [10]
8. The quantum dots that show where tumor cells are located in the human body.
9. Nanomaterials that limit harm to healthy cells by directly delivering chemotherapeutic medications to malignant cells. [1]
10. Improving drug stability and solvability
11. Controlling their release
12. Minimizing their toxicity
13. Only placing the active agent in the diseased area with an accurate dose leads to fewer plasma fluctuations and minimized side effects. [15]

Table 1: List of Some Patents [108]

Sr. No.	Patent No.	Brief Description	Applicant	Title
1.	WO2015123654A1	This development explains a method of creating tiny gold particles that have been passivated with amines and its use in both the identification and therapy of cancer.	Shunji Egusa, Yogen Sauntharajah	“Carbon Quantum Dots Based Patternable Material System For Fabricating Fluorescent Nanostructures With Subwavelength Resolution”
2.	US20160287723A1	This invention deals with the method of preparation of doxorubicin conjugated gold nanoparticles and the evaluation of their biocompatibility and tumor accumulation capacity	Tsai-Yueh Luo and Chun-Chia Cheng	Process of manufacturing anticancer drug having doxorubicin attached through gold nanoparticles.
3.	US2014008628A1	The invention describes the utility of gold nanoparticles containing microRNAs for the treatment of cancer	Foster, Laura B. Carprin, Rebekah Drezek, Adam Yuh Lin, Aaron E. Laura B. Adham S. Bear,	Modified gold nanoparticles for therapy
4.	US20100034735A1	This patent provides information about the method of development of gold nanoparticles for cancer treatment and imaging by acting as a positron	Wilson Roa, Jien Chen	nanoparticles for targeted cancer diagnosis also treatment

		emission tomography tracer		
5.	US20070031337A1	This invention describes the development method of ligand (Anti-VEGF antibody) conjugated gold nanoparticles of size 20nm and their biological evaluation.	Dean P. Hainsworth, Raghuram Kannan, Kattesh V Katti, Ravi Shukla	Anti-VEGF antibody conjugated gold nanoparticles and fabrication and therapeutic methods

III. VARIOUS MEDICATION DELIVERY SYSTEM-BASED NANOTECHNOLOGY

There has recently been tremendous progress in the arena of drug transport systems to transfer therapeutic agents or natural-based vital chemicals to their target region intended for the treatment of several disorders. [38,39] Here have been a lot of successful Nano-delivery systems in past years; Although, here are still some obstacles that must be addressed, along with improved innovation must be created for effective drug transfer to its target sites. As a result, drug delivery-based Nano-systems are currently being researched in order to assist the enhanced delivery system of drugs. [6]

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

- 1. Nanoparticles with Magnetic Properties:** Particles that can be manipulated by magnetic waves are called nanoparticles of magnetic material. Such molecules typically include two different elements: a material with magnetic properties that is typically a nickel, iron, or cobalt, and an essential organic element. While the dimension of microbeads ranges from 0.5 to 500 micrometers that of nanoparticles is typically between 1 and 100 nanometers. Magnetic nanoparticle clusters made up of several separate magnetic nanoparticles possess a length of 50–200 nanometers and are known as magnetic Nano beads. [40,41] Recent years have seen a surge in interest in magnetic nanoparticles (MNPs) especially because of their potential in specialized domains like medicine, cancer theranostics, bio-sensing, catalysis, agriculture, and environmental protection. [42] The use of magnetic nanoparticles (MNPs), a nanoscale substance with distinctive magnetic characteristics, is common in the fields of technology, energy, and the environment. Due to their potential applications in biological processes, catalytic processes, the farming industry, and surroundings, MNPs have most recently been the subject of significant investigation because of their distinctive and distinguishing characteristics. [43] Because MNPs have a greater amount of specific surface area than their parent heavy material, they have different physical characteristics that make things extra superparamagnetic. [44]

- **Primary Synthesis Approaches for MNPs:** The previous ten years have seen intensive investigation into the creation of various techniques for the production of MNPs. In order to create MNPs that possess the necessary dimensions, forms, stability, and biocompatibility, a variety of artificial approaches are used. The most widely used techniques include the physiological technique, ball milling, co-precipitation, thermal decomposition, hydrothermal, microemulsion, and sol-gel.
- **Physical Techniques:** The two categories of physical approaches are "Bottom-up" and "top-down" strategies. Using High-intensity ball milling, which is a top-down technique, lowers bulk substances to tiny particles. It is tough to acquire NPs with the preferred form and dimensions due to manual crushing. [45] Bottom-up methods can result in finer, more evenly scattered nanoscale tiny particles than top-down methods. Laser evaporation provides a prime example of a based-on-bottom- strategy. [46] MNPs are also prepared by means of additional physical actions such as inert gas condensation and wire explosion. Three physical processes—laser evaporation, ball milling, and wire eruption—will be discussed in this paper.
 - **Method of Ball Milling/Automatic Technique:** A top-down technique for producing MNPs from bulk substantial is ball grinding. 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 minute-deepcylinder-shaped jar with a lot of steel balls inside as the crushing medium. Steel balls constantly colliding with solid objects cause the solid object to gain kinetic energy, which turns the solid object into Micron- or Nano 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] Compared to biologically generated parts, the dimension distribution of the particles is very broad.
 - **Laser Evaporation:** By condensation from a gaseous orliquid phase, laser evaporation is a 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 similarly be produced by means of this method. [50] The process involves choosing coarse-textured particles (size ranges from m or mm) as raw materials and evaporating them under a laser's intense intensity. A concentrated laser beam is directed toward the object, which is situated at the lowest of a liquid-filled compartment. The solid in a solution is irradiated using a laser ray.Cooling the matter'sgasses in a vapor phase causes nucleation and quick condensation, which yields 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]
 - **Method of Wire Eruption:** The wire eruption method is a novel clean and safe physiochemical method for the production of MNPs. This technique is a one-step, extremely creative technique that doesn't need any additional steps like by-product re-treatment or NP parting from the solution. This method was previously used to generate iron oxide MNPs for the elimination 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.
 - **Method of Co-Precipitation:** The widely held method for generating MNPs with controlled dimensions and magnetic properties is co-precipitation. [56] This one is widely utilized in organic applications and calls for the usage of fewer 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 process is widely used to create NPs having desired magnetic properties and regulated sizes. MNPs are formed by dissolving various metal ions in an organic solvent. Manganese ferrite ($MnFe_2O_4$) nanostructures were produced using the metal ions ferric chloride ($FeCl_3$), manganese (II) chloride ($MnCl_2$), and sodium hydroxide ($NaOH$) salts. [58] Fe^{3+} and Mg^{2+} ions can be combined and co-precipitated with $NaOH$ to form $MgFe_2SO_4$ nanocrystals. [57] In a related study, Fe^{2+} and Fe^{3+} ions were co-precipitated to create Fe_3O_4 nanoparticles. [59] This method is also suggested due to its easiness, though; sometimes it can be difficult to achieve the shape of MNPs by co-precipitation
 - **Thermal Decomposition:** With this approach, MNPs are produced that have superior crystallinity, regulated size, as well as exact form. In the presence of organic surfactants, the organometallic precursors are decomposed to produce MNPs with the right dimension and form. [60] Oleic acid, fatty acids, and hexadecylamine are a few of the stabilizing ingredients employed in the creation of MNPs. Inhibiting the nucleation of NPs, which regulates the development of MNPs and helps to produce a spherical shape with a required size of not as much as 30 nm, is a capability of stabilizers used in the breakdown process. It has been reported that using this technique, it is possible to create Fe_3O_4 nanocrystals and magnetically active iron composites. [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 gain the proper form and size, several factors including temperature, reaction time, surfactant and solvent type, and aging period are altered. [64]
 - **Microemulsion Synthesis Method:** Co-surfactants and surfactants, as well as lipophilic and hydrophilic phases, are all components of microemulsion, which are turbid systems. A system of translucent, isotropic in nature liquids contains amphiphilic, oil, and water. Water that has been magnetically rotated at room

temperature is combined with oil and a surfactant. There are three categories for microemulsion: Here are three categories of mixtures: 1) mixtures where the ratios of oil and water are equal; 2) mixtures where the ratios of oil and water are dominant; and 3) mixtures where the ratios of oil and water are not dominating. As an illustration, in a w/o microemulsion, MNPs were made smaller by coating drops of water in a biological solvent with a surface active agent. [65] The surfactant used in this method determines the dimensions of MNPs produced.

- **Hydrothermal Synthesis Method:** This method, which uses high pressure and temperature to create nanoparticles in an aqueous solution, is utilized. [66] One of the efficient reaction-based methods for producing MNPs at high pressure and temperature is hydrothermal, also known as solvothermal. 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] Alike to this, 25 nm Fe₃O₄ NPs layered with Chitosan were made also 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. The hydrothermal approach is preferred over other methods like sol-gel because it produces NPs with appropriate sizes, morphologies, high crystallinity, and constant composition. [71]
- **Sol-gel Method:** The entire interaction of this technique consists of metal alkoxide poly-condensation reactions and hydrolysis that generate gels at normal temperatures. To make a sol or colloidal solution, metallic salts are uniformly dissolved in water or other solvents and distributed. [72] There are van der Waals forces between particles, also as the temperature rises, the interface 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.
- **Biological Method:** A well-known method for creating MNPs involves using living objects like plants and microbes (fungi, viruses, bacteria, and actinomycetes). [74] The magnetic nanoparticles produced with this technique are still biocompatible and can be applied to the biomedical sector. The efficacy, environmental friendliness, and cleanliness of this technology are its benefits. One disadvantage of the NPs is their low dispersion. [75] Researchers are interested in the creation of NPs using plant tissue, extracts, exudates, and other plant parts. [76] For instance, it has been asserted that it is possible to produce organically ferromagnetic magnetite particles with an average size of 60 nm. [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]

- 2. 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' dimensions, shapes, porosities, inertness, and other characteristics can be altered., 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. Because of their osteoinductive and biocompatible qualities, ceramics have been used in bone tissue engineering. [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]
- 3. Niosomes:** To get the desired therapeutic results, medicines are delivered to precise locations using Niosomes. [80] Like liposomes, Niosomes remain 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, more stable than liposomes are Niosomes. [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 are similar to 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 additionally 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]
- 4. Liposomes:** A lipid amphiphilic molecule like phospholipids, which are in solution, self-assembles to create a colloidal spherical structure known as a liposome. [85] One or more lipid bilayers (also known as lamellas) surround an internal aqueous core, using the polar head groups directed toward the inner and outer aqueous phases, respectively. [86] The ability to load and distribute substances with a variety of solubilities to this well-organized structure is unique to liposomes. Hydrophilic molecules are in the aqueous core's interior, hydrophilic molecules are in the lipid bilayer, and amphiphilic molecules are at the water/lipid bilayer contact. [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. Aqueous compartments are frequently used for water-soluble drugs, while liposomal membranes are used for lipid-soluble pharmaceuticals, which are quickly broken down and eliminated by the liver macrophages. [88] Shortening the duration of the medication's activity. The insertion of substances such for example cholesterol [89], polyvinylpyrrolidone polyacrylamide lipids [89], and high transition temperature phospholipids stearyl 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 special effects. Using immunoliposomes and ligand-directed liposomes, active medication targeting can be accomplished.

- 5. Dendrimers:** According to the commonly accepted definition, a dendrimer is a monodisperse macromolecule with a flawlessly branching regular structure and at least one branched junction at each repetition unit. Dendrimers are a type of nanostructure that may be carefully generated and manipulated for a variety of applications, including the treatment of cancer and other illnesses. Dendrimers can identify diseased cells, diagnose pathological conditions (including cell death), distribute medications, report locations, and report treatment outcomes all at the same time. The dendrimers molecule has been employed as a contrast medium and diagnostic reagent used 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 greatest common administration route for treating a variety of optical 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]
- 6. 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. CNTs can be produced using a variety of techniques, 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 used in arenas such as biomedicine, drug delivery systems, sensors, implants, tissue engineering, as well as 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 owing 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 multiple medicinal procedures, including genetic material and siRNA transfer, boron neutron capture treatment (BNCT), and generating an immune response. [96]

- 7. Nanoemulsion:** A dispersed nano-system with droplet sizes as small as a submicron is known as a nanoemulsion. Nanoemulsions are transparent, isotropic, thermodynamically stable liquid combinations of oil, water, surfactant, and co-surfactant. Droplet diameters in nanoemulsions typically range from 20 to 200 nanometers. The size and composition of the scattered particles in a continuous phase are the primary distinctions between an emulsion and a nanoemulsion. Low bioavailability and noncompliance, two issues with traditional drug delivery systems, are the focus of this strategy, which tries to solve some of them. Currently, 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 mixtures of two immiscible liquids that are thermodynamically unstable and often need the use of high torque mechanical mixing or homogenization to create scattered droplets in the 0.2–25 μm size range. This is where Nanoemulsions vary from microemulsions. Water-in-oil (w/o) or oil-in-water (o/w) versions of both types are available. Based on the model drug's hydrophilicity, it is decided to use the continuous and scattered phases of microemulsion formulations. Aside from that, surfactants with hydrophilic-lipophilic balances (HLB) of 3-6 tend to promote the production of o/w microemulsions while those with HLB values of 8–10 prefer to do the opposite. [1]
- 8. Nano suspension:** Nanoparticles of colloidal dispersions of an insoluble chemical that are maintained by surface active agents 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 top levels of drug loading. Numerous studies have shown that Nano suspensions can deliver drugs more effectively and quickly. [98]
- 9. Nanopores:** Desai and Ferrari (1997) created Nanopores, which are made of wafers with many tiny pores (20 nm in diameter). The holes allow for the passage of oxygen, glucose, and other chemicals like insulin. Even so, it prevents cells and immunoglobulin from passing through them. Utilizing the advantages of transplantation, Nanopores can be used

as barriers to prevent the host immune system from attacking transplanted tissues. Pancreatic B cells may be contained inside the Nanopores device and inserted into the customer's body. By absorbing nutrients from the surrounding tissues without being detected by the immune system, this tissue sample avoids 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 based on differences in base pair sequences to create DNA strands. 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.

10. Nanocrystals: A nanocrystal is a "cluster" of several hundred to tens of thousands of atoms. These aggregates typically range in size from 10 to 400 nm, and they have properties that are halfway between molecules and bulk solids. The size and surface area can be altered to alter other properties such as the bandgap, charge conductivity, crystalline structure, and melting temperature. The crystals must be stabilized to stop larger aggregates from forming. Nano sonication creates nanocrystals. High-speed stirring first creates a Nano suspension, which is then transformed into Wet milling, high-pressure homogenization, Nano crystallization, and spray drying is methods used to produce nanoscale crystals. High bioavailability and benefits of Nano crystallization include a considerable decrease in dosage volume and an increase in tolerated dose. [104] It also has the ability to make medications that are poorly soluble.

11. 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 from 10 to 80 nm in size. Because they are smaller than liposomes, micelles circulate through the body more quickly. Due to the EPR effect, they do have the advantage of being able to quicker to penetrate cancerous cells. Polymers can also be used to create micelles. Polymeric micelles are formed by block-copolymers comprising hydrophilic (such as PEG) and hydrophobic monomer units with longer hydrophilic blocks and shorter hydrophobic blocks. 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 produce micelles with improved intracellular transport and solubility. Micelles that have 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]

12. Gold Nanoparticles: For the purpose of ill treatment like rheumatoid arthritis, multiple sclerosis, cancer, and neurological ailments like Alzheimer's disease, Colloidal nanoparticles made of gold have been discovered before. Gold nanoparticles are advantageous because they are simple to prepare, come in a variety of sizes, are well-biocompatible are simple to functionalize, and can combine with other biomolecules without affecting their biological characteristics. 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. Nanoparticles can be coupled with ligands, imaging labels, medicinal chemicals, and other capabilities for precise drug delivery and cellular absorption. [1]

Table 2: Particle Size Distribution for Several Nanotechnology Methods: [107]

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

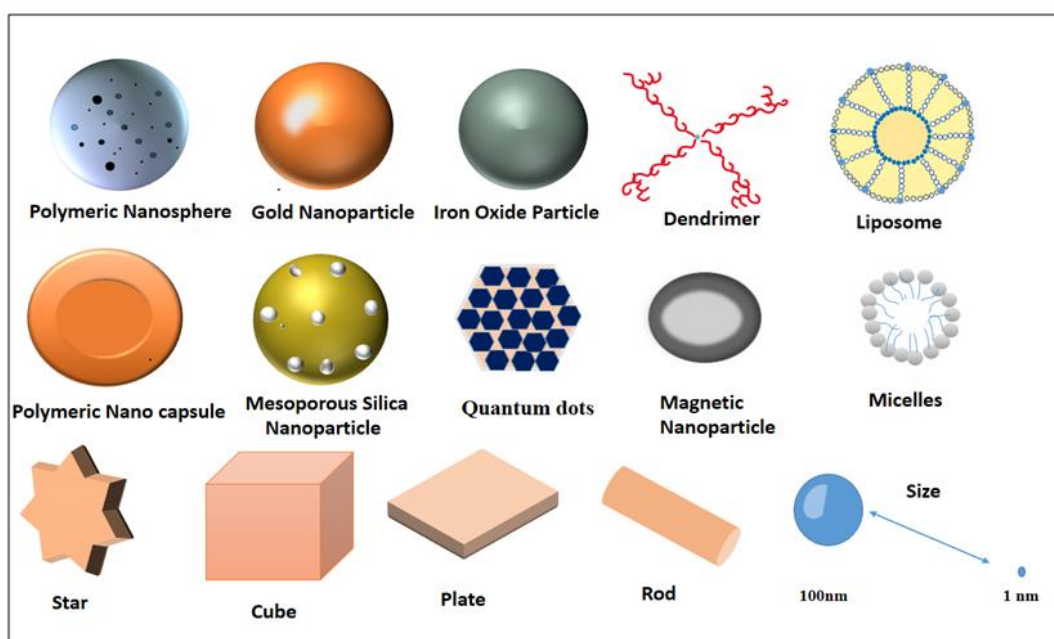


Figure 1: Different Types of Nanoparticles

Table 3: List of Drugs for Nano Drug Delivery System.

Sr. No.	Drug name	Purpose
NANOPARTICLES		
1.	Dexamethasone	To enhance the amount of release of drugs with respect to pure drugs [17]
2.	Praziquantel	To study the effect of formulation variables on size distribution [18]
3.	Salbutamol sulphate	To achieve the shape and sizes of spray-dried Nano-sized particles are suitable for respiratory accumulation in the lungs. [19]
4.	Amphotericin B	To show reduced nephrotoxicity compared to intravenous fungi zone and to improve oral bioavailability.[20]
5.	Naringenin	To enhance hepatic protective effect in-vivo.[21]
SOLID LIPID NANOPARTICLES		
6.	Vinpocetine	To enhance oral bioavailability of poorly soluble drugs and in the treatment of many types of cerebrovascular circular diseases.(oral)[22]
7.	Oridonin	The antitumor effect, anti-inflammatory anti-bacterial especially esophageal carcinoma & prostate carcinoma.[23]
8.	Itraconazole	To improve the therapeutic efficiency and antifungal activity and also reduction of toxicity.[24]
F	Lovastatin	To improve the bioavailability of lovastatin. (Duodenal)
10.	Ubidecarenone	Triglyceride lattice allows sustained release by the immobilization of drug molecules.[25]
NANOSUSPENSIONS		
11.	Itraconazole	To enhance dissolution and aqueous solubility hence increasing the oral bioavailability. (Aerosols)[26]
12.	Diclofenac	To improve the solubility of the drug (intramuscular)[27]
13.	Hesperetin	To improve the effect of a drug through dermal delivery. [28]
14.	Retinoic acid	To achieve high saturation solubility and controlled release of the drug.[29]
15.	Famotidine	To enhance the drug dissolution rate. (Mucoadhesive)[30]
NANOEMULSION		
16.	Aceclofenac	To increase the anti-inflammatory effect compared with aceclofenac gel.[31]
17.	Glycyrrhetic 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 enhance the surface properties for binding of

		biomolecules which improves pharmacodynamic activity[34]
20.	Lecodopa,6-mercaptopurine	To prevent uptake by the mononuclear phagocyte system and to permit penetration through the smallest pores of the membrane.[35]
NANOSPONGES		
21.	Paclitaxel	To enhance oral bioavailability of paclitaxel.[36]
22.	Itraconazole	to greatly boost the drug's solubility in comparison to simple medicines.[37]

IV. CHALLENGES

Although several Nano medication products on the market show that nanotechnology in drug delivery has been successful, not all methods have had the same level of success. There are difficulties that must be overcome with the new nanomaterials that are being developed. The physicochemical properties of the nanomaterials have been altered to improve properties like long blood circulation, increased functional surface area, protection of the incorporated drug from degradation, the crossing of biological barriers, and site-specific targeting. However, some of the challenges encountered have been and are still being addressed in this way. Large-scale production is a problem in the research and development (R&D) of nanomaterials for medication delivery. For ultimate commercialization, laboratory or pilot technology must always be scaled up. A number of Nano drug delivery systems might not be scalable because of the production process and high cost of materials used, together with the production method. Low concentrations of nanomaterials, agglomeration, and the chemical process are obstacles to scaling up; it is simpler to alter nanoparticles at a small scale for better performance than at a large one. Another difficulty is maintaining the size and make-up of nanomaterials at a big scale. [9]

V. CONCLUSION

The experimental development of nanotechnology continues to advance quickly, but there are still considerable obstacles to converting these platforms into treatments that can be used in clinics. Therefore, to ensure continued translational success, experts involved in all phases of pharmaceutical development of nanotechnologies—including pharmaceutical design and manufacturing, cellular interactions and toxicology, as well as preclinical and clinical evaluation—will need to communicate with one another and work together. The delivery and targeting of new drugs is the subject of extensive study. However, exploratory research is currently being done in this field. There are several issues that need to be resolved in research, production, and application. Additionally, more focus should be placed on the study of carrier substances in order to create better carriers that can lessen the toxicity of medications, increase their activity, and boost the general effectiveness of the agents. Novel drug delivery systems serve to boost therapeutic value by decreasing toxicity, enhancing bioavailability, and other factors, as well as by minimizing the need for repeated administration to overcome non-compliance. Therefore, the creation of innovative drug delivery methods for various dosage forms has enormous promise. The world is being upended by nanotechnology, which is rewriting "old" technologies and developing brand-new solutions. We'll get the chance to learn about an intriguing worry about how the nanoworld is advancing work on drug delivery systems and being used in medicine. The

world is being upended by nanotechnology, which is rewriting "old" technologies and developing new answers. We'll have the chance to learn about an intriguing topic relating to how the nanoworld is advancing study into Drug Delivery systems and being used in healthcare.

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, BrhamPrakash 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*, vol 4, no. 6, pp 621-633, 2007.
- [15] Rahman, Heshu Sulaiman, Hemn Hassan Othman, Nahidah Ibrahim Hammadi, Swee Keong Yeap, Kawa Mohammad Amin, Nozlina 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, pp 265-269, 2002.
- [18] Mainardes, Rubiana M., and Raul C. Evangelista, "PLGA nanoparticles containing praziquantel: effect of formulation variables on size distribution." *International journal of pharmaceuticals*, 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 CCl₄-induced acute liver failure," *Pharmaceutical research*, vol 26, pp 893-902, 2009.
- [22] Luo, YiFan, DaWei Chen, LiXiangRen, 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, SandyaPapishetty, and SarikaBandlapalli, "Nanotechnology in development of drug delivery system," *International journal of pharmaceutical sciences and research*, vol 3, no. 1, pp 84, 2012.
- [24] Maravajhala, Vidyavathi, SandyaPapishetty, and SarikaBandlapalli, "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, SandyaPapishetty, and SarikaBandlapalli, "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 Hesperetinnanosuspensions for dermal delivery," *International journal of pharmaceuticals*, 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 PharmSci*, vol2, no. 2, pp 122-7, 2010.
- [31] Shakeel, Faiyaz, SanjulaBaboota, AlkaAhuja, Javed Ali, Mohammed Aqil, and Sheikh Shafiq, "Nanoemulsions as vehicles for transdermal delivery of aceclofenac," *AapsPharmscitech*, vol8, 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 Pharmaceuticals, Biopharmaceutics and Pharm. Tech, Geneva*. 2006.
- [33] Chu, Boon-Seang, Sosaku Ichikawa, SumiyoKanafusa, 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, ArchanaChaudhary, 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*, vol17, no. 6, pp 419-425, 2010.
- [38] Miele, Evelina, Gian Paolo Spinelli, ErmannoMiele, Enzo Di Fabrizio, ElisabettaFerretti, SilverioTomao, 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, SlavkoKralj, Marko Jagodic, DarkoHanzel, and DarkoMakovec, "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." *vol15*, pp 6905, 2022.
- [43] Ali, Arbab, Tufail Shah, RehmatUllah, Pingfan Zhou, ManlinGuo, Muhammad Ovais, Zhiqiang Tan, and YuKuiRui. "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, ZhichuanXu, YanglongHou, 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, BenoîtDenizot, 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, DoaaRagab, 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@Fe₃O₄ 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 NanomedNanotechol* 4, vol e130, 2013.
- [58] Shalihah, D.Haibus, N.Nashikudin, M.Munasir, and Y. A. Hariyanto, "Effect of ZnO on the Nanostructure, Magnetic, and Optical Properties of Fe₂O₃/MWCNT/ZnONanocomposites", *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 NanomedNanotechol* 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 MnFe₂O₄ 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. Praver, 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.J.M, 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 BiophysicaActa (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", *AngewandteChemie 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, "Microfabricatedimmunosulatingbiocapsules", *Biotechnology and bioengineering* 57, vol no. 1, pp. 1108-120, 1998.
- [101] Leoni, Lara, and T.A. Desai, "Nanoporousbiocapsules 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.Esquina, 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.