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Review on Nanotechnology in therapeutics: A focus on Nanoparticles as a drug delivery system

Miss Rutuja S. Chavan[1] , Asst. Prof. MsRajeshreeKhandre[2]

[1]Department of Pharmaceutics ,Pratibhatai Pawar College Of Pharmacy, Shrirampur, India.
[2]Department of Pharmaceutics ,Pratibhatai Pawar College Of Pharmacy, Shrirampur,India

ABSTRACT:

The revolution in innovative drug delivery technologies is being driven by advances in pharmacological and therapeutic qualities of medicines. Nanoparticles are the most basic type of structure with a size inthe nanometer range. In theory, a nanoparticle is any collection of atoms bound together with astructural radius of less than 100 nm. Because of their high solubility, small size, and greaterpenetrability, nanoparticles are now frequently used in a variety of dosage forms. Emulsion-Solvent Evaporation Method, Double Emulsion and Evaporation Method, salting out Method, Emulsion Diffusion Method, Polymerization Method, and Concertationor Ionic Gelation Method are some of the methods used to make nanoparticles. Cell-specific nanoparticles are used in micro wiring for internalization vaccine delivery and gene transfer. In the field, nanoparticles are used. Nanoparticles are employed in medicine for a variety of purposes, including cancer treatment and orthopedic implants. Nanoparticles have a high solubility and penetration rate, which is why they are now used in practically every formulation. As a result, this article will discuss recent advances in the use of nanoparticles as a medication delivery mechanism to treat a wide range of disorders.

Keywords**:**Gold particles, drug delivery, nanomaterial, Nano medicine, nanoparticles, nanotechnology.

INTRODUCTION:

Nanotechnology includes the implementation of molecular-scale functional structures. Such systems have unique physical, optical, and digital characteristics that appeal to a wide range of fields, from chemistry to biomedicine. Nano medicine, which applies nanotechnology to extremely distinct scientific interventions for the prevention, prognosis, and treatment of disease, is one of the most active research topics in nanotechnology. The increase in Nano medicine research over the preceding few years is now translating into full-scale commercialization initiatives all around the world, with many products on the market and more on the way. Drug delivery methods currently dominate Nano medicine, accounting for more than 75% of total revenue. Nanomaterials have a measuring range that is equivalent to proteins and other macromolecular materials. As a result, nanoparticles are bound to take use of existing cell machinery to aid medication transport. Encapsulated, dispersed, absorbed, or conjugated pills in nanoparticles (NPs) have unique properties that can contribute to better performance in a variety of dosage forms. When drug particles are properly designed, they are resistant to settling and can have higher saturation solubility, faster dissolution, and better adherence to biological surfaces, resulting in a faster beginning of therapeutic motion and increased bioavailability. Furthermore, the bulk of molecules in a nanostructure reside on the particle floor. allowing cargos such as medicinal medicines, proteins, and other molecules to be loaded and transported more efficient.

- **Historical Background:**

The term "nanotechnology" was coined when physicist Richard Feynman gave a discussion titled "There's Plenty of Room at the Bottom" at a Caltech American Physical Society meeting on December 29, 1959, in which he proposed that the complete Encyclopedia Britannica might be inscribed in the head of a leg. Professor Norio Taniguchi of Tokyo Science University defined the term "nanotechnology" as follows in a 1974 paper: "Nano-technology' largely consists of the processing of, separation, connection, and deformation of materials by one atom or one molecule." Despite the fact that scientists have been working with nanoparticles for decades, their capacity to see the structure of nanoparticles has limited their efficacy. However, after the invention of the scanning electron microscope in the 1980s, nanotechnology began to take off. Millions of dollars and many man hours have been spent learning about and enriching the capability to employ nanotechnology since 1985, when a druggist discovered a football-shaped molecule called buckminsterfullerene made up of 60 carbon atoms (also called fullerene or Bucky ball). A fullerene is a carbon-based molecule that takes the shape of a concave spherical, ellipsoid, or tube. Bulky ball is the name for a spherical fullerene, while carbon is the name for a cylindrical fullerene called nanoparticles.

- **Advantages:**

1) Nanoparticle size and surface properties can be easily modified after parenteral delivery to accomplish both passive and active medication targeting.

2) To achieve high drug therapeutic efficacy and minimal adverse effects, they control and sustain drug release during transit and at the site of localization, modifying drug distribution and subsequent clearance.

3) Site-specific targeting can be done by adding targeting ligands to the surface or using magnetic guiding.

4) The system can be employed for a variety of administration routes, including oral, intraocular, parenteral, and nasal.

5) Drug distribution to small locations within the body is improved by nanoparticles.

6) Engineering allows researchers to exercise previously unattainable precision and control over biomaterials and physical characteristics on a large scale. (B Kumara, 2018).

- **Disadvantages:**

1)Lack of proper knowledge about the effect of nanoparticles on biochemical pathways and processes in human body.

2)Unpredictable genotoxicity due to insufficient ttoxicological assessment studies.

3)Carcinogenesis

4)Elimination and metabolism vary with different types of materials used in nanoparticles synthesis.

Nano carriers and theirapplications

Nano medicine has enormous potential for improving the detection and treatment of diseases. Illnesses that affect humans an environmentally friendly option. The technique for biogenesis of nanoparticles is as follows. The use of microorganisms. Torevolutionize a wide range of industriesNanotechnology is a set of tools used in biotechnology. Potential to make them more affordable, personalization, safety, portability, and ease of useadministrate.

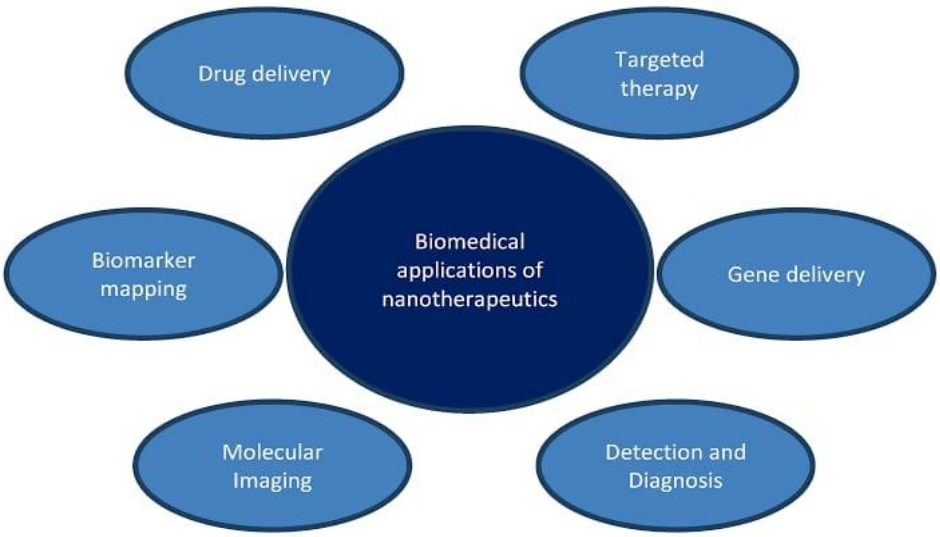


Figure 1: Application of nanoparticles

1)Time release of the drug

The medicine must not cause nonspecific toxicity to avoid nonspecific toxicity. While the particle is still in the air, diffuse out of itand must be kept encased in the circulatory systemuntil the particle has bound itself to the target. Nanoparticles can be used to treat disease at the source. Because of its effectiveness, it is often employed in targeted drug delivery. This has a lot of key influences, like as

1.The use of nanoparticles can improve drug bioavailability.

2. Drugs that are targeted to a specific site

3. To boost the uptake of poorly soluble substancesdrugs

4. Chemotherapeutic drugs like5-dexamethasone, dexamethasone, doxorubicinFluorouracil and paclitaxel have been used to treat cancer. Developed effectively withnanomaterials.

2)Cell specificity

Conjugating cells improves cell specificity.Antibodies to carbon nanotubes (fluorescent or non-fluorescent)radiolabeling.

3)Internalization

Internalization of mammalian cells can be difficult. Carbon with a surface-functionalized surface is used to achieve thisnanotube.

4)Vaccine delivery

Peptide conjugation could be utilized as a vaccinationstructures of delivery.

5)Gene Silencing

For cancer, very selective therapy is essentialtherapy in which tumor cells are specifically removedmodulated. In this scenario, small interfering RNA (siRNA) is used. Silencing of genes has been accomplished. By focusing onsingle-walled carbon nanotubes that have been functionalized to silence targeted gene expression.

Compounds attached to nanotubes have been shown to improve the efficiency of diagnostic procedures. This functionalization characteristic and which has a high length-to-diameter aspect ratio) allows for a high surface-to-volume ratio), and aids in creating high-performance biosensors Because ofConsider physical properties that are extremely interestingadditional carbon-neutral medication delivery and diagnostic systemsNanotubes have a number of advantages. The high thermal physicochemical characteristics conductivity, a well-organized structure with a high aspect ratioexcellent electrical resistance, ultra-light weight, metallicHigh mechanical strength, conductivity, or semi-conductivitymetallic behavior. (B Kumari,2018).

Types of Nanoparticles

Silver: These have been shown to be the most efficient antimicrobials against bacteria, viruses, and other eukaryotic microbes. They are the most frequently utilized nanomaterials as antibacterial agents, sunscreen lotions, water treatment, and textile industries, among other applications. The plants Capsicum Annul Azadirachta indicia and Carioca papaya11 were used. It has been reported that silver nanoparticles can be biosynthesized successfully.

Gold nanoparticles :are utilized to identify protein interactions in immunochemical research. They are employed as a lab tracer in DNA fingerprinting to detect the presence of DNA in a sample. These nanoparticles may also detect aminoglycoside drugs including streptomycin, gentamycin, and neomycin. Gold nano rods were used to detect cancer stem cells, diagnose cancer, and identify different kinds of bacteria.

Alloy: The structural properties of alloy nanoparticles differ from bulk samples.14 Silver flakes are the most commonly used metal filler because they have the highest electrical conductivity among other metal fillers, and their oxides also have relatively high electrical conductivity among other metal fillers. By both metals and over ordinary metallic NPs bimetallic alloy nanoparticles properties are influenced, which show more advantages.

Magnetic nanoparticles: such as magnetite and magnetite, are known to be biocompatible. They have been intensively considered for magnetic resonance imaging (MRI), guided drug administration, targeted cancer treatment (magnetic hyperthermia), gene therapy, stem cell sorting and manipulation, and DNA analysis.

Properties of nanomaterial

1)structural characteristics

Nanomaterials' crystal structure may or may not be the same as that of bulk materials, depending on the lattice parameters. In bulk form, gold (Au) and aluminium (Al) have facecentered cubic (FCC) crystal structures, whereas the crystal structure in nanoform is icosahedral. Indium is facecentered tetrah edral, and if the size is less than 6.5 nm, it will be FCC. Because of the presence of electrostatic forces in the long range and core repulsio in the short ra nge, nanomaterials have less interatomic separation than heir bulk counterparts. In the instance of Al, the binding energy reduces from 3.39 to 2.77 V as the interatomic distance decreases from 2.86 to 2.81. Materials with nanostructures offer special properties.

2)Thermal characteristics

As the size of the particle shrinks toward nanoscale, the thermal characteristics will change. The melting property of nanomaterials decreases as the surface energy increases and the interatomic distance changes. It indicates that when the size of gold nanoparticles decreases, the melting point decreases.

3)Physical characteristics

Nanoclusters have a higher ionization energy than bulk materials. Because of their bigger surface area to volume ratio, nanomaterials have a higher efficiency of chemical reactions, rate of chemical reactions, very high radical change in chemical reactivity, and selectivity. As a result, the catalysis is limited to nanoparticles. Nanoscale materials have a larger ionization potential than bulk materials.

4)Mechanical characteristics

During the production of nanomaterials, a considerable number of flaws are introduced, affecting the mechanical properties. Because of their atomic structural arrangement, some nanostructures have extremely diverse qualities from their bulk structure and may have different mechanical properties, such as carbon nanotubes (single or multi-walled), which have a higher mechanical strength, elastic limit, and flexibility. At high temperatures, nanospheres ceramics exhibit ductility, whereas coarse-grained ceramics exhibit brittleness. When the ratio between the atom size and the particle size is less than 0.01 to 0.1, Qi and Wang18 discovered that the cohesive energy reduces, and this fall in cohesive energy effects the melting point lowering. Nanda and coworkers14 examined the surface energy of several materials in 2003.Nanda and her colleagues 14studied the surface energy of various materials at different scales. He claimed that the surface energy of nanoparticles is larger than that of embedded nanoparticles and that it is also higher

than that of bulk nanoparticles.

5) Magnetic characteristics

Nanomaterials with a large surface to volume ratio have a distinct magnetic interaction with nearby atoms, resulting in a different magnetic property than bulk materials. In the case of a ferromagnetic substance, as illustrated in there are several magnetic domains, however in the case of nanoscale materials, there is only one domain that shows superparamagnetic events. Nanoparticles have a magnetic that is much smaller than their bulk size.

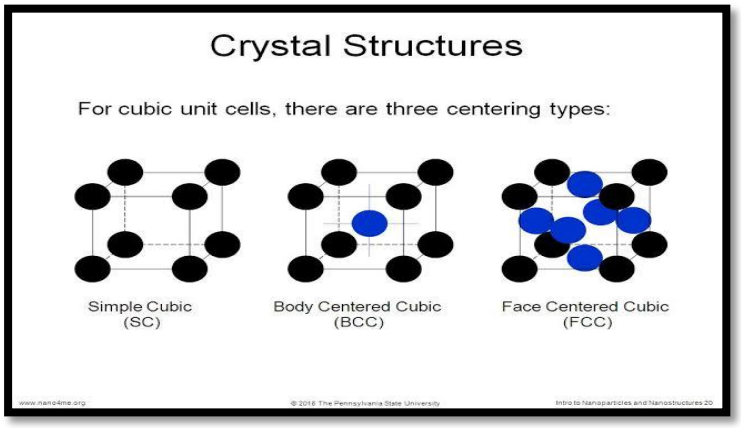


Figure 2: Crystal Structures

- **Nanomaterials with respect to their dimensions**

Nanomaterials are materials or structures with at least one dimension in the nanoscale range. Thus, nanomaterials do not have to be so small that they are invisible to the naked eye; they can be a huge surface or a long wire with a nanometer-scale thickness (as seen in the illustration). As a result, nanomaterials can be classified as follows:

1.Nanomaterials with zero dimensions,

2.Nanomaterials with one dimensions

3.Nanomaterials with two dimensions

4.Nanomaterials with three dimensions

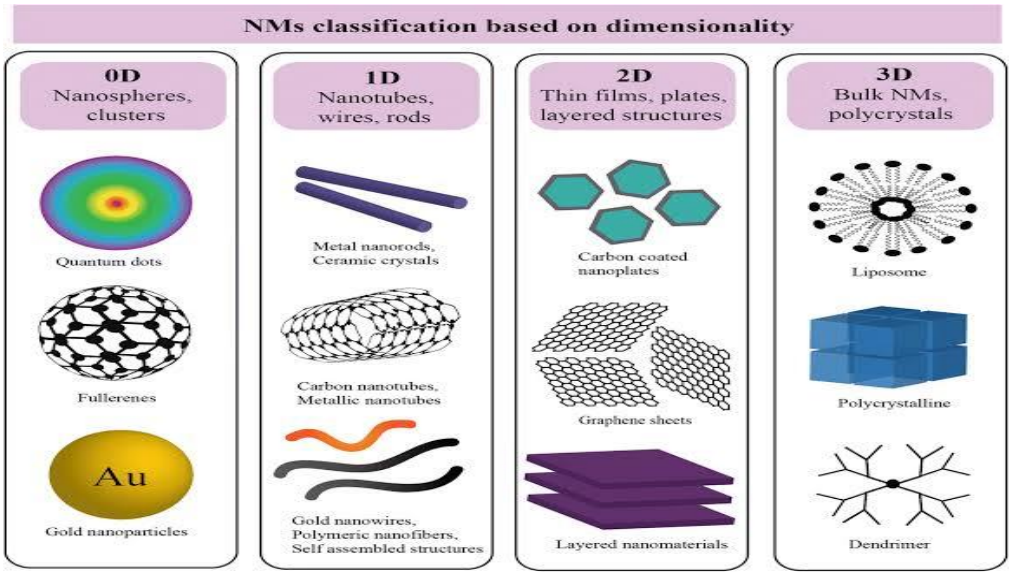
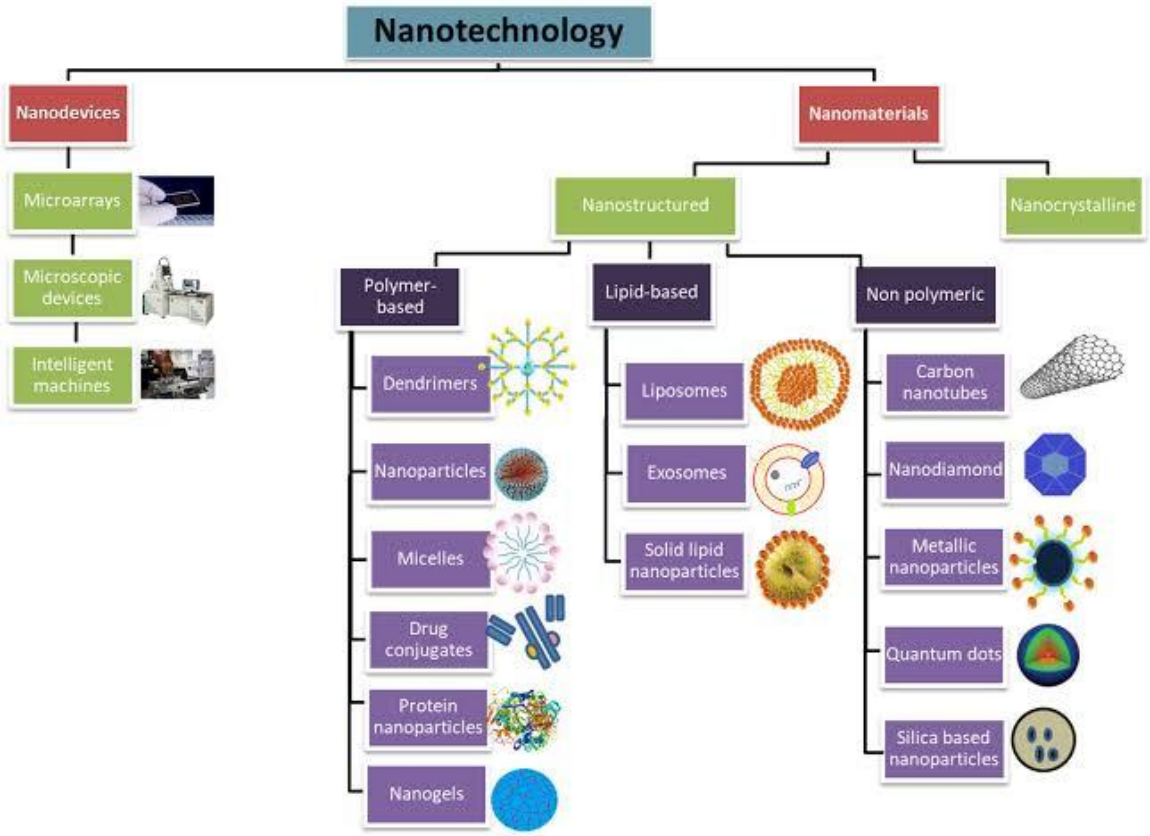


Figure 3: NMS classification based on dimensionality

All of the axes of zero-dimensional nanomaterials are in the nanoscale range. The most popular representation of zero-dimensional nanomaterials is nanoparticles. There are two dimensions at the nanoscale and one dimension at the macroscale in one-dimensional nanomaterials. This appears to be a needle. Nanotubes, Nano rods, thin films, platelets, and surface coatings are examples of one-dimensional materials. There is one dimension at the nanoscale and two dimensions at the macroscale in two-dimensional nanomaterials. Plate-like shapes can be found in two-dimensional nanomaterials. Nanowires, nanofibers, and nanotubes, as well as Nano films, monolayers, and Nano coatings, are two-dimensional nanomaterials. There are no nanoscale dimensions in three-dimensional nanomaterials, and all of the dimensions are macroscale. Bulk nanomaterials have no nanoscale dimensions,

but were measured arbitrarily over 100 nm. Bulk nanomaterials are made up of a variety of different types of nanoparticles. Threedimensional nanomaterials are dispersion of nanoparticles, precipitates, colloids and quantum dots, bundles of nanowires and nanotubes or multinanolayers.

Classification of Nanotechnology



Flow chart 1: Classification of Nanotechnology

Nanocrystal

The ability to convert current medications with poor water solubility and dissolution rate into readily water-soluble dispersions by converting them into nanosized drugs is one of the most evident and crucial nanotechnology tools for product development. To put it another way, the medicine itself may be created at the nanoscale to act as its own 'carrier.' Many strategies have been investigated, but the most practicable one involves shrinking drug particles to the nanometer range and stabilizing the drug NP surface with a layer of nonionic surfactants or polymeric macromolecules. The drug's surface area is enhanced significantly by lowering the particle size of the active pharmaceutical ingredient, boosting its solubility and dissolution and, as a result, raising both the maximum plasma concentration and the area under the curve. The medicine can then be manufactured into a variety of dosage forms, including oral, nasal, and injectable. Thesenanocrystal pharmaceuticals may have an advantage over association colloids (micelle solutions) in that the quantity of surfactant used per unit of medication can be significantly reduced, with only the amount required to stabilize the solid–fluid interface being used.

Organic Nano platforms

Liposomes

Liposomes are artificial vesicles that self-assemble from amphiphilic phospholipids. The size of these vesicles, which are made up of a spherical bilayer structure around an aqueous core domain, can range from 50 nanometers to several micrometers. Liposomes have a number of biological advantages, including general biocompatibility, biodegradability, drug isolation from the environment, and the ability to entrap both hydrophilic and hydrophobic medicines. Liposome characteristics, such as size, surface charge, and functionality, can be easily modified by adding agents to the lipid membrane or changing the surface chemistry. Liposomes are the most well-established Nano systems for drug delivery in clinical trials. Their effectiveness has been

established in lowering systemic effects toxicity and slowing medication clearance. At the nanoscale, modified liposomes have been proven to exhibit excellent properties. examples of commercialized liposomal medications that have superior efficacy and lower toxicity than their no liposomal analogues. Doxorubicin is an anticancer medication that is commonly used to treat a variety of tumor forms. It's a very toxic substance that affects not only tumor tissue but also the heart and kidneys, which restricts its therapeutic potential. The creation of doxorubicin in liposomes, on the other hand, resulted in an FDA-approved nonmedical drug delivery system. Due to the EPR effect, this unique liposomal formulation inhibited doxorubicin transport to the heart and renal system while increasing doxorubicin accumulation in tumor tissue. In addition, a number of liposomal medicines are now being studied, including anticancer medications like camptothecin and paclitaxel (PTX), as well as antibiotics. Liposomes also have several drawbacks, such as limited encapsulation efficiency, rapid burst drug release, poor storage stability, and the lack of customizable drug release triggers. Additionally, because liposomes are unable to pass through cells, medications are discharged into the extracellular fluid. As a result, various efforts have been made to improve their stability and increase circulation half-life in order to achieve effective targeting and long-term therapeutic action. After oral or parenteral delivery, surface modification is one means of giving stability and structural integrity against a hostile bioenvironmental. Surface modification can be accomplished by affixing polyethylene glycol (PEG) units, which form a protective layer over the liposome surface (known as stealth liposomes) to slow liposome recognition, or by affixing other polymers, such as poly(meth acrylic acid co-cholesteryl methacrylate) and poly(meth acrylic acid co-cholesteryl methacrylate) and poly(meth acrylic acid co-cholesteryl methacrylate (acrylic acid), to increase the time that liposomes circulate in the blood Medicines like doxorubicin can be encapsulated in the liposomal aqueous phase by an ammonium sulphate gradient to avoid the quick burst release of chemotherapeutic drugs from liposomes. Even after prolonged residency in the blood stream, this technique allows for sustained drug trapping with minimal drug loss throughout circulation. Liposomes whose release is driven by the environment have been designed to improve control over the rate of release and drug bioavailability. As a result, a change in pH, temperature, radiofrequency, or magnetic field triggers drug release from liposome sensitive polymers, or hydrogel. For target-specific drug delivery, liposomes have also been coupled with active-targeting ligands such as antibodies or folate.

Polymeric NPs

Polymeric NPs are colloidal particles that range in size from 10 to 1000 nanometers and can have spherical, branching, or core shell morphologies. Biodegradable synthetic polymers, such as polylactide polyglycolide copolymers, polyacrylates, and polycaprolactone, as well as natural polymers, such as albumin, gelatin, alginate, collagen, and chitosan, have been used to make them. The NPs were made using a variety of techniques, including solvent evaporation, spontaneous emulsification, solvent diffusion, salting out/emulsification diffusion, supercritical CO2, and polymerization. Smart polymer (stimuli-sensitive polymer) has been developed as a result of advances in polymer science and engineering. It can change its physicochemical properties in response to environmental signals. Temperature, ultrasound, light, electricity, and mechanical stress have all been utilized as triggers, as have chemical (pH and ionic strength) and biological (enzymes and biomolecules). have been used as triggering stimuli. Various monomers having sensitivity to specific stimuli can be tailored to a photopolymer in response to a certain signal or copolymers answering multiple stimuli. The versatility of polymer sources and their easy combination make it possible to tune up polymer sensitivity in response to a given stimulus within a narrow range, leading to more accurate and programmable drug delivery.

Polymer drug conjugate (Prodrug)

Many polymer–drug conjugates have been developed since the first combination reported in the 1970s. Conjugation of macromolecular polymers to drugs can significantly enhance the blood circulation time of the drugs. Especially, protein or peptide drugs, which can be readily digested inside the human body, can maintain their activity by conjugation of the water-soluble polymer PEG (PEGylating). For example, it was reported that PEGylated l-asparagine increased its plasma half-life by up to 357 h. Without PEG, the half-life of natural l-aspire-kinase is only 20 h. In addition to PEGylating of proteins, small molecular anticancer drugs can also be PEGylated to improve their Pharmacol-kinetics for cancer therapy. For instance, PEG-camptothecin (PROTHECAN®) has entered clinical trials for cancer therapy.

Polymeric micelles

When amphiphilic surfactants or polymeric molecules spontaneously combine in an aqueous media to form core–shell structures, polymeric micelles are generated. A micelle's hydrophobic inner core is surrounded by a shell of hydrophilic polymers; such as PEG . Their hydrophobic core acts as a reservoir for medications that are weakly water soluble or amphiphilic, while their hydrophilic shell stabilizes the core, prolongs blood circulation time, and enhances tumor tissue accumulation. Physical encapsulation or Cova-lent attachment have been used to insert a wide range of therapeutic compounds into polymeric micelles thus far.

Hydrogel NPs

Because of their unique features, hydrogel NPs have attracted a lot of interest in recent years as one of the most promising nanoparticulate drug delivery technologies. Hydrogels are cross-linked networks of hydrophilic polymers that can absorb and retain more than 20% of their weight in water while maintaining the polymer network's characteristic three-dimensional structure. External stimuli or physiological characteristics can alter the swelling properties, network topology, permeability, or mechanical stability of hydro-gels. Hydrogels have been intensively researched for controlled therapeutic release, stimuli-responsive release, and biological implant applications. However, most hydrogel systems' hydration responses to changes in stimuli are

too sluggish for therapeutic uses. Further development of hydrogel structures at the micro- and nanoscales is needed to overcome this constraint. Recent studies have revealed some progress in the development of Poly-N-isopropylacrylamide micro and angels with rapid responses and appealing rheological features. In mice, this hydrogel technology showed greater efficiency in inhibiting tumor growth and extending lifespan. The hydrogel implant results in high concentration and retention of the medication, according to the in vivo bio distribution experiment. By integrating the magnetic properties of NPs with the conventional characteristics of the hydrogel, a multifunctional hybrid hydrogel was created. By applying an external magnetic field to these hybrid hydrogels, they might be utilized to load a large number of medicines and transport them to the target region .Core–shell angels, which use tamers as the recognition element and near-infrared light as the delivery system, were created to improve the specificity of hydrogel drug delivery systems.tamers are used as the recognition element, and near-infrared light is used as a triggering stimulus for drug delivery, in ore–shell angels. In this method, gold (Au)–silver Nano rods were coated with DNA cross-linked polymers, which have intense absorption bands in the near-infrared range, allowing pharmaceuticals to be released swiftly and controllably upon near-infrared irradiation. Biodegradable hydrogel NPs with diameters of approximately 200 nm were synthesized via inverse miniemulsion reversible addition fragmentation chain-transfer polymerization of 2-(dimethylamine)ethyl methacrylate, as the fate of hydrogel NPs after in vivo administration may be a concern for clinical applications. The NPs were cross-linked with a disulfide cross-linker such that when exposed to a reductive environment, the polymer network may be destroyed to its constituent primary chains.

Dendrimers

Dendrimers are branched macromolecules with a tree-like structure that are synthesized. Dendrimers, unlike most linear polymers, can have their chemical composition and molecular weight carefully controlled, making their biocompatibility and pharmacokinetics relatively easy to anticipate. Dendrimers are highly uniform and have very low polydispersities, and they are frequently made with dimensions that are incrementally grown in nanometer steps ranging from 1 to 10 nm. Drugs can be enclosed within the macromolecule interior, and internal cavities are used to offer regulated release from the inner core, thanks to their globular shapes and the presence of internal cavities. Although the modest size of dendrimers (up to 10 nm) prevents significant drug integration, their dendritic architecture and branching allow drug loading onto the structure's outer surface via covalent bonds. Divergent or convergent techniques can be used to make dendrimers. Dendrimers are synthesized from the core and then built up into layers called generations in the divergent approach. However, because the reactions must be carried out on a single molecule processing a high number of comparable reaction sites, this technique yields a low yield.Furthermore, the last phases of synthesis necessitate a considerable quantity of reagents, complicating purification. Synthesis begins at the periphery of the dendrimer molecules and ends at the core in the convergent process. Each manufactured generation can then be purified using this method.

Nanomaterials made of carbon

Because they can be surface functionalized for the grafting of nucleic acids, peptides, and proteins, carbon-based nanomaterials have piqued interest. CNTs, fullerene, and Nano diamonds [129] have all been researched extensively for drug delivery applications. Single-wall nanotubes (SWNTs), multiwall nanotubes (MWNTs), and C60 fullerenes are attractive drug carriers due to their size, shape, and surface properties. The main disadvantage of carbon-based nanomaterials, however, appears to be their toxicity. CNTs have been shown in experiments to suppress cell proliferation and induce apoptosis. Although CNTs are less poisonous than carbon fibers and NPs, when carbonyl, carboxyl, and/or hydroxyl functional groups are present on their surface, their toxicity increases dramatically. CNT research for medication administration are still being done due to the reported toxicity of the material. Researchers have functionalized the surface of CNTs to make them more suitable for drug delivery. Unfortunately, fears that functionalized CNTs will revert to a hazardous condition if the functional group detaches have hampered the use of these modified CNTs in biological applications.

Integrated composite particles

A wide range of Nano platforms have been developed for a wide range of applications, each with its own set of benefits and drawbacks. New hybrid nanocomposite materials can be created by integrating the distinct functions of each constituent. Liposomes and polymeric NPs, for example, are two of the most widely investigated drug delivery platforms, with attempts to combine the benefits of both systems. Nano cells containing nuclear poly(lactic-co-glycolic acid) NPs within an extra nuclear PEGylated phospholipid sheath were used in a recent study to temporally target tumour cells and neovasculature. In addition, liposomes are frequently coated with a hydrophilic polymer, such as PEG or poly (ethylene oxide), to enhance in vivo circulation time, which is an example of a liposome–polymer composite. Similarly,when compared to pure liposomes, liposomal locked-in dendrimers, which combine liposomes and dendrimers in one formulation, have resulted in higher drug loading and slower drug release from the composite. Another Lipoma formulation, consisting of an oleic acid-coated magnetic nanocrystal core and a cationic lipid shell, was used to magnetically deliver and silence genes in cells and tumors in mice. (S Bamrungsap,*et al.*,2012).

- **Targeting strategies**

Two basic requirements should be realized in the design of Nano carriers to achieve effective drug delivery (Figure 3). First, drugs should be able to reach the desired tumor sites after administration with minimal loss to their volume and activity in blood circulation. Second, drugs should only kill tumor cells without harmful effects to healthy tissue. These requirements may be enabled using two strategies: passive and active targeting of drugs .

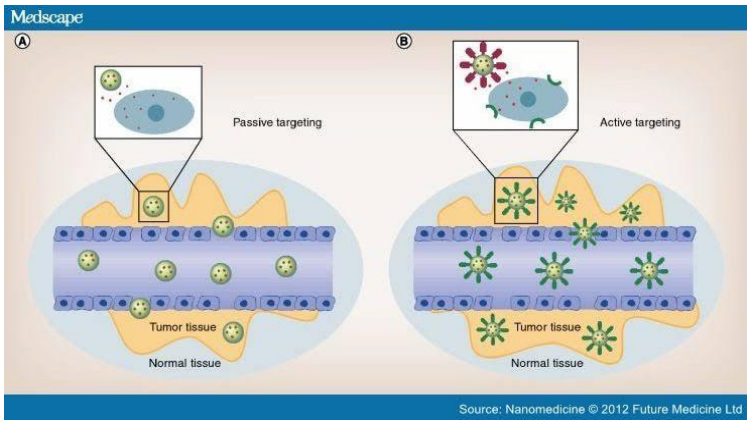


Figure 3: Targeting Strategies

1.Passive targeting:

Nano drugs can accumulate in tumor tissues thanks to passive targeting, which takes advantage of the pathophysiological properties of tumor vasculature. Tumor arteries are typically disordered and dilated with a significant number of holes, resulting in increased gap junctions between endothelial cells and a lack of lymphatic outflow. The EPR effect permits macromolecules up to 400 nm in diameter to migrate into the surrounding tumor zone, which is referred to as "leaky" vascularization. The use of liposomes was one of the first nanoscale technologies for medication passive targeting. A synthetic polymer is placed on more advanced liposomes to protect the agents from immunological attack. Furthermore, the EPR effect, or the microenvironment around tumor tissue, differs from that of healthy cells, a physiological phenomenon that supports the theory. Fast-growing tumor cells demand more oxygen and nutrients since their metabolic rate is so high. As a result, glycolysis is boosted in order to obtain more energy, creating an acidic environment. pH-sensitive liposomes have been developed to be stable at physiological pH 7.4, but disintegrate at acidic pH to release medicinal molecules. Despite the fact that passive targeting techniques are the cornerstone of clinical therapy, they have a number of drawbacks. Because some medications do not distribute well, and the random nature of the technique makes it difficult to manage, targeting cells within a tumor in this manner is not always possible. The passive method is further hampered by the fact that some tumors do not have an EPR effect, and vascular permeability may vary.

2.Active targeting:

A number of conjugation chemistries can be used to attach affinity ligands (antibodies, peptides, tamers, or tiny molecules that only bind to certain receptors on the cell surface) to the surface of Nano carriers, overcoming the constraints of passive targeting. The expression of receptors or epitopes on the cell surface will allow Nano carriers to recognize and bind to target cells via ligand–receptor interactions. Those receptors should be highly expressed on tumor cells but not on normal cells in order to attain high specificity. Furthermore, the receptors should all express in the same way and not be shed into the bloodstream. After binding to target cells, targeting conjugates can be internalized by receptor-mediated endocytosis, allowing for drug release inside the cells. On the basis of receptor-mediated endocytosis Targeting conjugates bind to their receptors first, followed by plasma membrane enclosure around the ligand–receptor complex to create an endosome, according to the receptor-mediated endocytosis mechanism. Drugs could be released by acidic pH or enzymes once the newly created endosome is delivered to certain organelles. Although the active targeting technique appears intriguing, most Nano drugs currently licensed for clinical use are basic and lack active targeting or triggered drug release components. Furthermore, Nano drugs that are currently in clinical trials lack particular targeting. To fully investigate the application of targeted drug delivery, we must first determine whether the specific diseases are the correct application for targeting, whether the therapeutic drugs' properties, as well as their site and mode of action, are suited for targeting, and whether the therapeutic drugs' properties, as well as their site and mode of action, are suited for targeting. (S Bamrungsap, *et al.*,2012).

Factors that have an impact on the drug delivery system

To accomplish successful drug delivery, Nano carriers must have sufficient circulation time to prevent pharmaceuticals from being eliminated before reaching their intended destination. Size, shape, and surface features are significant elements that influence the efficacy of drug delivery systems, according to earlier research.

1.Size and shape

Particle size is important for particle functions such degradation, vascular dynamics, targeting, clearance, and uptake. Depending on their size, particles have varied velocities, diffusion characteristics, and adhesion properties, resulting in different uptake efficiencies.Nano drugs should be large enough to prevent rapid leakage in blood capillaries while also being tiny enough to avoid macrophage capture in the reticuloendothelial system, which includes

organs like the liver and spleen. The size limits for NP internalization through endocytosis are obviously cell dependent; particles less than 200 nm in size will primarily follow endocytic routes; particles larger than this size can be either engulfed or absorbed. Surprisingly, the highest uptake was observed with Au NPs 50 nm in diameter in the case of spherical Au NPs. In a separate investigation, it was discovered that a diameter of 50 nm is the ideal size for MNS endocytosis. Apart from size, current research has revealed that particle shape can have an intriguing effect on particle functions, particularly in biological processes like as internalization, blood vessel movement, and sick site targeting. There have also been reports of varying toxicities of materials with the same chemical makeup (silica) but different shapes (nanowire versus NP). Recent developments, with a focus on the relevance of particle form and the problems that remain to be resolved.

2.Properties of the surface

Surface properties of NPs, in addition to size and shape, can influence their longevity during blood circulation. The discovery that particles coated with hydrophilic polymer molecules, such as PEG, may resist serum protein adsorption, extending the particle's systemic circulation, was one of the main advances in this field. Since then, a variety of PEG and other hydrophilic polymers have been tested for improved circulation. The particle's surface charge also influences other functions, such as macrophage internalization. Positively charged particles have been demonstrated to have a higher rate of internalization by macrophages and dendritic cells than neutral or negatively charged particles, albeit the effect of surface charge may vary depending on the cell type. Particle size and surface chemistry effects.

Challenges of nanotechnology for drug delivery

Although there has been significant and effective progress in the application of nanotechnology to medication delivery, as indicated by some Nano drugs already on the market, there are still numerous major obstacles in this field.

1.Biological comprehension

A greater knowledge of the mechanisms underpinning intracellular absorption, trafficking, and the fate of nanomaterials in complex biological networks is required for bio nanotechnologies to proceed toward human applications. Current delivery techniques have a number of significant drawbacks (e.g., quick immune system clearance, low targeting efficiency, and difficulty overcoming biological barriers). Given these challenges, a complete understanding of the fundamental science of NP transport will lead to the ability to control and manipulate medication delivery.

2.Safety concern

Nano toxicology is a field that has arisen in tandem with the development of Nano medicine. The study of the potential harmful effects of interactions between nanoparticles and biological systems is known as Nano toxicology. Some preliminary nontoxicity studies have suggested that nanoparticles may play a role in the production of free radicals.

- **Manufacturing issue**

The large-scale production of nanomaterials in terms of scaling up laboratory or pilot technologies for consistent and repeatable production and commercialization is another issue for nondrug delivery. Due to the nature of the preparation process and the high cost of materials used, a number of nondrug delivery systems may not be suitable for large-scale production. Low nanomaterial concentrations, agglomeration, and the chemical process are all hurdles in scaling up. At the laboratory scale, it is considerably easier to adjust or maintain the size or composition of nanomaterials for greater performance than it is at a large scale. When working with nanomaterials, the biomedical community should reconsider the level of control required. Rather than requiring full control of nanoparticles' physical dimensions, a statistical method could be used. Because it is unrealistic to establish the toxicological of every size or aspect ratio of a nanomaterial, this would fit nicely with the creation of a toxicology database.

- **Economical and financial barriers**

Nano medicine implementation can potentially be hampered by financial and economic hurdles. The lack of payment by public and private health insurers for relatively expensive novel diagnostic procedures has emerged as a key hindrance to the deployment of customized medicine in general, and Nano products are expected to face even bigger obstacles due to their costs and complexity. Despite the fact that nondrug delivery systems have received numerous patents, commercialization is still in its early stages. Because Nano drugs and medical devices have such high development costs, startups have little chance of bringing goods to market without the help of 'Big Pharma,' which can provide the financial resources and expertise needed to meet regulatory requirements.

- **Marketing products of nanotechnology**

Table no 1: Marketing products of nanotechnology

Product	Company name	Therapeutic agent	Nanotechnology	Therapeutic role	Route of Administration.
Pacliall	Panacea	Paclitaxel	Nanoparticles	Lung cancer	(i.v)
Myocet	ZeneusPharma, Sopherion	Doxorubicin	Liposome	breast cancer	(i.v)
LEP-ETU	Neopharm	Paclitaxel	Neolipid	Advanced Cancer	(i.v)
Clinical trial	-	SN38	PAMAM dendrimers	Hepatic colorectal cancer	Oral
Allovectin -7	VICAL	Plasmid DNA	Liposomal DNA/Lipidic complex	Melanoma	(i.v)
DepoCyt®	SkyePharma Enzon	Cytarabine	Liposome	Lymphomatousmeningitis	(i.v)
Avinza®	King Pharma, Elan	Morphine sulfate	NanoCrystal	psycho-stimulant	Oral
Tricor	Abbott Lab(USA)	Fenofibrate	Nanocrystal particles	Primary lipidemia	Oral
Clinical trial	AlphaRx	Streptomycin	Nanocapsule	tuberculosis	(i.m)
MiKasome	NeXstarPharmceutical	Amikacin	Liposome	tuberculosis	(i.v)
Clinical trial	-	Rifampicin + isoniazide	SLN Nebulization	tuberculosis	Inhalation
Emend	Merck, Elan	Aprepitan	DepoFoam,	antiemetic	Oral

Future perspective

The union of nanotechnology and medicine has produced a child that is poised to make significant advancements in the fight against a variety of ailments. Nano medicine is actually an older child, with two therapeutic Nano carrier families – liposomes and albumin NPs – now in clinical use around the world and several in the preclinical stages of development. It's critical to understand how nanoparticle bio distribution, which is primarily governed by their ability to negotiate biological barriers, affects the body's complex biological network, as well as mass transport across compartmental boundaries in the body, in order to move nanotechnologies from basic research to clinical products. Furthermore, the establishment of a toxicological database to promote safety is critical to the field's continued expansion. Toxicity as a function of material, size, shape, cell type, or animal, duration of exposure, and assay methods should all be included in the database. In addition, the ability to scale up drug particle production is essential. Nano drug delivery's manufacturing complexity could be a challenge for generic drug businesses. Finally, protocols for storage and handling must be determined. The translation of biomedical nanotechnology from the lab to the general public will be substantially hastened with such a database. To achieve this goal, scientists from diverse fields, including as medicine, materials science, engineering, physics, and biotechnology, must collaborate. Better cross training would result in stronger proposals with a higher chance of success. To translate breakthrough laboratory innovation into commercially viable medical goods, experts from several disciplines must collaborate. Furthermore, there must be ongoing collaboration between federal agencies and the pharmaceutical business. Nano drug delivery systems' ultimate goal is to create clinically relevant formulations for treating illnesses. Traditional regulatory classifications and criteria may be progressively challenged, and maybe invalidated, as nonmedical applications for personalized medicine become more advanced and multifunctional. As a result, regulatory regimes must provide oversight and well-defined review paths for Nano medicine products while staying flexible enough to react to quickly evolving nonmedical technologies and products.

CONCLUSION:

Nanotechnology is a new science that has the potential to change the way drugs are delivered. Some Nano medicines on the market now have desired pharmacokinetic features, lower toxicity, and increase patient compliance, as well as clinical outcomes, advancements in this area. The employment of nanoparticulate drug delivery methods in reformulation work not only speeds up the discovery of new therapeutic moieties, but it also reduces the attrition of new molecular entities due to unfavorable biopharmaceutical and pharmacokinetic features. Standardized metrics for classifying nanomaterials, as well as techniques for handling them, will be required to optimised their integration into medication delivery systems. As a result, we'll have a greater grasp of how nanomaterials interact with biological systems, allowing us to better customize their properties for specific applications. The creation of such drug carriers will necessitate a better understanding of both nanomaterial surface chemistry and their interaction chemistry with biological systems. This can only be accomplished by combining the efforts of scientists from many areas. Those working in this new field should be aware of current toxicity issues, prospective health and safety dangers, and the regulatory environment that will affect patient use. Understanding both the benefits and hazards of these new nanotechnology applications will be critical for drug developers, regulators, and, ultimately, customers and patients who will benefit from novel drug delivery systems to make informed decisions.

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