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A Review on Nanotechnology

Surbhi Gupta[1]*, Radhika Baheti[2], Nishigandha Nigade[3],Vrushali Bejgamwar[3], Dr. Karimunnisa S. Shaikh[4]

(Department of Pharmaceutics)

Progressive Education Society's Modern College of Pharmacy, Sector no. 21, Yamunanagar, Nigdi, Pune 411044,Maharashtra, India

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ABSTRACT

Nanotechnology is the chemical, molecular and supramolecular scale manipulation of matter. In various branches of research, it has a broad range of applications, including molecular biology, health and medicine, materials, electronics, transport, distribution of drugs and drugs, chemical sensing, space exploration, electricity, climate, sensors, diagnostics, microfabrication, organic chemistry and biomaterials. Nanotechnology includes drug delivery technologies, fabric design, material reactivity and power, and molecular manufacturing. Nanotechnology applications are distributed across almost all surgical specialties and have revolutionised the treatment of different medical and surgical conditions.. In this review article, we illustrate properties of nanoparticles &a list of most commonly used Nanoparticles with their characteristic features

KEYWORDS

Nano Drug Delivery Systems (DDS),Nanoscale, Nanoscience, Nanoparticle, Nanofiber, Nanocomposite

INTRODUCTION

Manipulation of matter on atomic, molecular and supramolecular scale is known to be nanotechnology. It has number of applications in different streams of science such as molecular biology, Health and medicine, materials, sensors, electronics,microfabrication, transportation, drugs and drug delivery, chemical sensing, environment, space exploration, energy, diagnostics, organic chemistry and biomaterials[1].

Introducing these small size materials in to a biological system, due to their very small size and unique nanoscale properties make it possible for them to be used as delivery probes for biological diagnostics purposes, imaging and therapeutics. The surface area to volume ratio of material increases with decrease in size leading to availability of a vast suitable surface for chemical interactions with biomolecules[2].

Nano Drug Delivery Systems (DDS) normally consist of three vector generation; First generation vectors that comprise of nano spheres and nano capsules. Second generation vectors consist of nanoparticles coated with hydrophilic polymers for example Polyethylene Glycol (PE). Third generation vectors combines biodegradable core and a Polymer Envelope (PEG) with a functionalization agent. These systems develop inherent merits of protecting drug from degradation in the body before it is delivered to its target, enhances the absorption of drug, very well control on drug distribution to tissue and avoiding side effects by preventing the interaction with the normal cells [2].

HISTORY OF EVOLUTION OF NANOTECHNOLOGY

In 1959 lecture of Richard Feynman's that is "There's plenty of room at the bottom" led to the development of a new concept called as nanotechnology. He isthe "Father of Nanotechnology". Norio Taniguchi was the one who gave the term nanotechnology in the year1974.According to him the materials can be precisely manipulated at nanometer level. In the SI length unit meter Nano is known to be as one-billionth, (1.0×10^{-9}) [1], [3].

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Table No.1: History of evolution of nanotechnology

2000 Years ago	Sulfidenanocrystals were used by Greeks and to prepare hair dye by Romans
1000 Years ago	Stained glasses for windows were made from different sizes of gold NPs that emit different colors
1857	Colloidal ruby gold nanoparticles synthesis
1974	Norio Taniguchi gave the term "Nanotechnology"
1981	Scanning Tunneling Microscope (STM) was developed by IBM. Discovery of nanocrystalline Quantum dots in a glass matrix
1983	Colloidal quantum dots discovery
1985	In 1985 "Buckyball"(Fullerenes) was discovered. HarryKroto of Sussex university, Richard Smalley and Robert Curl of Rice University won Nobel Prize in Chemistry in 1996.
1986	K. Eric Drexler was the first one to use the term "nanotechnology" in his book named: "Engines of Creation: The Coming Era of Nanotechnology". Atomic-force microscopy (AFM) was invented.
1991	MITI, Japan announced the concept of bottom-up "atom factory" and multi-wall Carbon nanotubes were discovered by SumioLijima
1992	Mesoporous silica MCM-41 were discovered
1993	Single wall carbon nanotubes were discovered
1997	James R.Von Her ll founded first molecular nanotechnology company (Zyvex). Introduction of first design of Nanorobotic system.
1999	R.Freitas published "Nano Medicine" the first book on nanomedicine. Introduction of Nanotechnology safety guidelines.
2000	National Nanotechnological initiative (NNI) was launched.
2001	Feynman was rewarded for developing "Theory of nanometer–scale electronic devices", carbon nanotubes and synthesis of nanowires.
2002	Feynman was rewarded for making DNA enable the self-assembly which wasutilized for new structures and for model molecular machine system.
2004	Establishment of policy conference on 'Advanced Nanotech' and Centre for nano- mechanical system, Discovery of grapheme and fluorescent carbon dots
2005-2009	Introduction of robotics, 3-D networking and active nano products (3-D nano systems) that change their state during use. Discovery of an improved walking DNA nanorobot.
2011	Starting of the era of molecular nanotechnology. Nano processors that work better with a programmable nanowire circuit were identified. Identification of DNA molecular robots.
2012	The two nanotechnology initiative Nano sensors and Nanotechnology Knowledge Infrastructure (NKI) were launched by NNI.

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2016	For DNA sequencinggrapheme nano devices were used
2017	A new type of 3D computer chip that combines two cutting-edge nanotechnologies with increased memory and logic circuits. A new drug delivery was developed by an all-women team of researchers from Indian Institute of Technology (IIT) Delhi by using nanoparticles.
2018	New class of nanomaterials was developed known to be as metal-organic frameworks or "MOFs," that takes carbon dioxide from atmosphere and combines it with hydrogen atoms to convert it into chemicals and fuels.
Future 2020	By 2020 an estimated 6 Million workers will be needed worldwide.Development of the first "molecular Assembler".

The primary goals for nano-bio-technologies research in drug delivery include:[5]

- More specific drug delivery and targeting,
- To maintain therapeutic effects with reduction in toxicity,
- Highly safe and biocompatible, and
- New safe medicines faster development.

There are several advantages of using nanoparticles (NPs) for drug administration as compare to conventional DDSs, which are listed below:[6]

- NPs are very small as compare to the basic material unit of conventionally formulated drugs. Nanodrugs will be formed by just attaching small molecule of therapeutic agents to these small nanocarriers.
- Nanoformulation of drugs is one of thestrategies to deliver precisely and accurately pharmaceutical agents to the targeted tissue and reduce the toxic side effects and overall dose of a drug.
- The enhanced permeability and retention (EPR) effect can allow passive targeting and accumulation of nanosized drugs at malignant tumors and other pathological sites.
- In comparison with conventional microsized formulations nanosized formulations lead to an increased bioavailability and active concentration.
- Demonstration of better safety and efficacy by NPs.
- Nanodrugs are found to be cheaper than conventional therapies.
- The release of drug over desired timescale can occur at a constant rate.

The properties of nanoparticles that contributes to their toxicity and the challenges:[4]

- **Dose and exposure time effect:**Molar concentration of NPs in the adjacent medium multiplied by the exposure time gives the number of NMs
- **Reactivity or charge:**Functionalization or spontaneous degradative reactions can charge NPs. For specific functionality and bioavailability of NMs chemical species and their charge-related critical functional groups will prove to be a significant factor.
- **Aggregation and concentration effect.** There are various contradictory reports on the toxicity at different concentrations of NPs. Aggregation is promoted by increasing theconcentration of NP. Most NP aggregates are having size in micrometer, so that large quantity of aggregated NPs may not penetrate cell and lose their toxicity.Weakly bound (agglomeration) and fused particles act as risk criteria as they cause poor corrosion resistance, high solubility and phase change of NMs.
- **Contaminant dissociation:**In NP the contamination of residual impurities is considered to be the major risk factor. For example, Iron oxide NPs may contain sulphur impurities depending on the precursor used for production (FeCl3 or Fe2(SO4).In the same way nickel, yttrium, or rubidium metal impurities may be present in the carbon nanotubes (CNTs) which are adsorbed on the surface of CNT.Inherently, due to NPs high reactivity they interact with impurities. Due to which encapsulation becomes a prime necessity for synthesis of solution-based NP. In the process of encapsulation, the reactive nano-entities are encapsulated within nonreactive species for the stability of the NPs.
- **Particle size effect:** Size-dependent toxicity is shown by NPs.Higher capacity to penetrate and disturb cellular systems of many organisms is seen with Ag NPS with ≈10 nm

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diameter as compare to Ag^+ ions and Ag NPs of larger diameters (20–100 nm)

- **Particle shape effect:**Shape-dependent toxicity which is, different toxicity levels at different aspect ratios is exhibited by NPs. For example, lung cancer can be caused by asbestos fibers of 10 µm length, mesothelioma due to shorter asbestos fibers (5–10 µm) and asbestosis due to 2 µm length fibers.
- **Surface area effect**: By decreasing particle size and increasing surface area the toxicological effect can be increased of NPs. It is to be noted that even if nano and microparticles are of same mass dose they react with the human cells differently.
- **Crystal structure effect**: NPs may show different cellular uptake, oxidative mechanisms and subcellular localization based on the crystal structure. For example, rutile and anatase the two crystalline polymorphs of TiO_2show different toxicity. In the dark condition,DNA damage via oxidation is induced by rutile NPs (200nm), while anatase NPs (200 nm) doesn't induce DNA damage.
- **Surface functionalization effect.** Drastic effects related to translocation and subsequent oxidation processes has been shown due to surface properties of NPs
- **Pre-exposure effect:** Due to shorter exposure time or the pre-exposure of lower NP concentrations the cellular phagocytic activity can be stimulated. This pre-exposure to certain degree results in the adaptability of the human body against NPs.

Table No.2: A list of most commonly used Nanoparticles with their characteristic features. [7]

Name (s)	Features
Fullerenes-Buckeyball	• Soccer ball-like structures having hollow cores which are to be filled with drugs. • Inert, water-insoluble NPs made up of 20, 60, or 100 carbon atoms and which interact easily with cells and viruses. • For diagnostic imaging (as contrast agents), treatment (photothermal method), and treatment monitoring aw-up (contrast agents) delivers nanodrugs inside the cells.
Nanotubes-buckytubes	• Cylindrical tubes which are formed from atleast 60 pure carbon atoms. • Capable of being inserted selectively in the bacterial cell membrane. • Eliminates especially drug-resistant microbes.
Nano-bubbles	• Bubble like structure at room temperature • Can selectively deliver drugs/DNA to target cells. • Used for cancer treatment and gene therapy
Liposomes	• Vesicle shaped of a double lipid (or phospholipid) layer with a hollow aqueous core. • Used as a vehicle for hydrophobic and hydrophilic delivery of nanodrugs. • Can be applied topically, IV, or IM but not orally (due to degradation in the GIT) and can be conjugated to antibodies/antigens for the use in vaccination and gene therapy.
Polymeric micelles	• Spherical amphiphilic polymers with hydrophilic shell and hydrophobic core. • Can convert the water-insoluble preparations to water soluble ones. • Used for delivery of poorly water-soluble material.

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Name (s)	Features
Polymeric Nanospheres	• Spherical shaped NPs which are made up of biodegradable polymers. • Deliver topical drugs and even used in diagnosis of cancer.
Dendrimers	• Large complex and a highly branched spherical structure. • Used in Imaging, antimicrobial properties (against MRSA, Pseudomonas), vaccination, treatment of cancer.
Polymer coated CuS-nanocrystals	• Spherical structures having diameter of about 18 nm. • It prevents clumps and stabilizesnanosuspensions. • It is used for imaging, treatment of cancer and treatment of HIV
Nanoshells	• Spherical glass coated with a gold layer. • Have non-conducting (dielectric) core which is coated by a thin metallic shell (usually gold). • It combines infrared optical activity with the gold biocompatibility. • Used for imaging and treatment of cancer
Superparamagnetic iron oxide nanoparticles (SPIO NPs)	• Spherical shape. • To maximize light absorption NPs with magnetic core can be coated with silica. • It is used for MRI contrast imaging (cancer diagnosis), as drug delivery, treatment of cancer (magnetic hyperthermia and photothermal therapy).
Quantum dots (QD)	• These are the Semi-conducting dots. • Having unique optical and electrical properties. • It is found to be ideal imaging agents (through production of fluorescence light), as biosensors to detect pathogens in a very sensitive and specific manner.
Nano-emulsion	• It is an emulsion of nanoscaled oil drops (coated with a surface film of surfactant) which is dispersed in water (O/W) or water in oil (W/O).

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Name (s)	Features
Solid Lipid NPs (SLN)	• It is a fatty suspension in aqueous solution. • Lipids which can change in to solid at room temperature • They have high drug trap capacity and can be administrated orally, topically, or IV. • It delivers basically hydrophobic drugs and offers controlled slow-release of drugs over weeks and can deliver drugs across BBB.
Metallic NPs	• These are Spherical in shape. • Made of silver, copper, or gold. • Used in treatment of cancer.
Ceramic NPs	• These are extremely inert and spherical in shape. • They are easy to prepare and design and are made up of silica or titanium to protect the delivered drug from extreme pH, temperature or denaturation.
Respirocytes	• These are Nano-robotic which delivers 236 times more O_2 than RBCs. • They provide gas exchange at tissue level that is they provide the tissues with O_2 and remove CO_2
Microbivores	• Nano-robotic that can trap circulating pathogens. • Clear the blood during septicaemia.

Types of Therapeutic Nanoparticles

Nanomaterials are classified in to two main categories: Nano-structured and nanocrystalline. Nano-structured materials are further classified into polymer-based, non-polymeric, and lipid-based nanoparticles. Polymer-based nanoparticles include dendrimers, nanoparticles, micelles, nanogels, protein nanoparticles, and drug conjugates while non-polymeric nanoparticles consist of carbon nanotubes, nanodiamonds, metallic nanoparticles, quantum dots, and silica-based nanoparticles. Lipid-based nanoparticles can be subdivided into liposomes and solid lipid nanoparticles.Till now the clinically approved nanoparticles for therapeutic use are basically polymer-based or lipid-based components. Besides this nanocrystalline particles that are prepared by the combination of crystalline therapeutic agents are also used in some clinical applications [8].

Dendrimers

Due to hyperbranched, compartmentalized structure, and high monodispersity of dendrimers they are widely used polymers in clinical applications.They can be fabricated by polymerization in spherical shape, which leads to the formation of cavities within the dendrimer molecule. Thus, high generation dendrimers causes high entrapment efficiency e.g. dendrimers containing more than 64 surface groups are used for the delivery of therapeutic agents. Dendrimers have free end groups additionally that can be easily modified so as to enhance low cytotoxicity and high bio-permeability of the molecule. Such surface modifications can also be applied to improve the target-specific delivery of therapeutic agents. It can be synthesized from both synthetic and natural monomers e.g. aminoacids, monosaccharides and nucleotides. Assembling dendrimers by either encapsulation or complexation makes them attractive vehicles for the concomitant delivery of biologically active molecules such as vaccines, drugs, and genes to the target locations. Currently, mono- or copolymers, such as polyethyleneimine, polyamidoamine, poly(propyleneimine), chitin, etc., are used for therapeutic applications in the form of

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dendrimers.Dendrimers are classified based on their functionalization moieties: PAMAM mostly studied for oral drug delivery as it is water soluble and can pass through epithelial tissue icreasing transfer via paracellular pathway, core–shell, chiral, PPI, liquid crystalline,peptide, glycodendrimers and PAMAMOS. Due to presence of amine groups dendrimers are limited in clinical uses. As the groups are positively charged or cationic which makes them toxic thedendrimers are usually modified to reduce the toxicity issue or to eliminate it. Following are the mechanism by which drug is loaded in dendrimer: Simple encapsulation, electrostatic interaction and covalent conjugation [8],[9],[11],[12],[13],[14].

Nanoparticles

Polymer-based nanoparticles, synthetic or natural, provide an alternative way for therapeutic applications due to certain characteristics, such as biocompatibility, non-immunogenicity, non-toxicity, and biodegradability. In order to decrease the immunogenicity and toxicity of synthetic polymers, like polycaprolactone (PCL), polylactic acid (PLA), and their monomers, the polyester forms are used. On the other hand, natural polymer-based nanoparticles such as chitosan, gelatin, albumin, and alginate seem to overcome toxicity issues and provide significant improvement in the efficiency of therapeutic agents compared to conventional methods.

Nanoparticles are submicron-sized polymeric colloidal particles with therapeutic agents of interest encapsulated or dispersed within their polymeric matrix or adsorbed or conjugated onto the surface. Commonly used synthetic polymers to prepare nanoparticles for drug delivery are generally biodegradable. Nanoparticles may also be composed of or transport a variety of substances such as silica, gold or other heavy metals, medicaments, quantum dots, nanocrystals, quantum rods and various contrast agents. Inorganic nanoparticles include silver, gold, iron oxide and silica nanoparticles are included. Metal nanoparticles, silver and gold, have particular properties like SPR (surface plasmon resonance), that liposomes, dendrimers, micelles do not possess. They showed several advantages such as good biocompatibility and versatility when it comes to surface functionalization. Drugs can be conjugated to gold nanoparticles (AuNPs) surfaces via ionic or covalent bonding and physical absorption and they can deliver them and control their release through biological stimuli or light activation.Silver-nanoparticles exhibited antimicrobial activity and detect toxic ions such as Cd, Hg and Pb in water while silica coating silver colloids were used for the stability of the colloids. [8],[9],[10],[11],[12],[13].

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) also known asliposphere or solid lipid nanospheres, or the particles that are generally solid at human physiological temperature (37^0C) having a diameter of less than 1000 nm. SLNs forms strongly lipophilic matrix and have been examined for various cancer treatments such as breast cancer, colon cancer. Polymer-based nanoparticles have been examined as drug nanocarriers. The Synthetic polymers which are widely researched are polylactide (PLA), poly (D,L-lactide-co-glycolide) (PLGA) and poly ethylene glycol (PEG) which are hydrolized in vivo and are biodegradable in nature. There are even other polymers which are examined based on biological polysaccharides such as chitosan, Cyclodextrin and dextrans.[8],[10],[14].

Table No.3: SLN composition and their applications

SLN composition	Drug	Application
Stearic acid	Rifampicin, isoniazid, pyrazinamide	Mycobacterium tuberculosis
Glyceryl tripalmitate and tyloxapol	Clotrimazole	Fungi
Glyceryl behenate, propylene glycol, tween 80, and Glyceryl monostearate	Miconazole nitrate	Fungi
Cetylpalmitate	Insulin	Type 1 diabetes

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SLN composition	Drug	Application
Lecithin, SODIUM taurocholate	Nimesulide	Inflammation
Poly(lactide) (PLA), poly(lactideco-glycolide) (PLGA), poly-ε-caprolactone (PCL) and poly(ortho esters)	Bacterial and viral antigens	Immunity
Stearic acid, soya phosphatidylcholine, and sodium taurocholate	Tobramycin	Pseudomonas aeruginosa
Soyabean-oil	Doxorubicin	Breast cancer
Hyaluronic acid–coupled chitosan	Oxaliplatin	Colorectal cancer

Quantum Dots

Quantum dots (QDs) are nanocrystals of a semiconducting material with diameter of 2-10 nm. They consist of a semiconductor inorganic core such as CdSe and an aqueous organic coated shell such as ZnS.Thecore structure of QDs detects the emitted color, while the outer aqueous shell is used for conjugation of biomolecules that is peptides, protein, or DNA.QDs has been studied as sensors, bioimaging and as targeted drug delivery in the medicinal field.Bio-conjugated QD consist of different sizes of nanoparticles which are embedded in tiny beads made of polymer material.The new class of quantum dot conjugate consist of an amphiphilic triblock copolymer layer as an in vivo protection and multiple PEG molecules for biocompatibility improvement and circulation, which inturn makes it stable and produce bright signals.[8],[9],[11],[13],[14].

Table No.4:Composition of quantum dots and their applications

Quantum dot's composition	Applications
Quantum dots	It is used to measure protein conformational changes, to monitor protein interactions, for assay of enzyme activity, in Fluorescence resonance energy transfer (FRET) technologies and used as a barrier invivo.
QD-conjugated oligonucleotide sequences (attached via surface carboxylic acid groups)	Used in gene technology
Conjugation of quantum dot with Tat protein, and by encapsulation in cholesterol-bearing pullulan (CHP) modified with amine groups coating with a silica shell	Fluorescent labeling of cellular proteins and different intracellular structures
QDs encapsulated in phospholipid micelles	Color imaging of live cells and cell tracking
Transferrin-bound QDs, wheat	Detection of pathogen and toxin

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Quantum dot's composition	Applications
germ agglutinin and transferrin-bound QDs,p53 conjugated with QDs	
PEG-encapsulated QDs	Mapping of lymph node and in vivo animal imaging
Combination of QD imaging with second-harmonic generation (SHG), CdTe bound QDs	Investigation of tumor biology, Cell motility and metastatic potential and measurement of different cancer antigens

Fullerenes

A fullerene is a molecule composed of carbon entirely in the form of tube, ellipsoid or hollow sphere. Buckyballs are the spherical fullerenes whilecylindrical ones are called carbon nanotubes or buckytubes. Fullerenes have same structure as that of graphite, with stacked grapheme sheets of linked hexagonal rings; they may also contain pentagonal (or heptagonal) rings additionally to give potentially porous molecules. Buckyball clusters or buckyballs contain less than 300 carbon atoms commonly called as endohedral fullerenes which include buckminsterfullerene, C_{60} the most common fullerene. Megatubes have larger diameter as compare to nanotubes and are prepared with walls of different thickness which is potentially used for the transport of different size molecule.Nano "onions" are spherical shaped based on multiple carbon layers surrounding a buckyball core. In health and personal care these properties of fullerenes hold a great promise.[11],[13],[14].

Liposomes

Liposomes are the vesicles synthesized by hydration of dry phospholipids. They can be prepared in different structure, composition, size, and flexibility with various types of lipid molecules. The ability of liposome to fuse with cell membrane and release the contents in cytoplasm is one of the most important advantage which makes them suitable carrier system for targeted delivery.The simplest liposome with diameter of 50-1000nm composed of a lipid bilayer surrounding a hollow core. The uptake by macrophage is reduced by coating liposomes with PEG which favours its prolonged presence in the bloodstream. Stealth liposomes are successfully used in the delivery of doxorubicin for the treatment of solid tumors and are marketed as 'Doxil' or 'Caelyx'. There are obstacles with the use of liposomes for drug delivery purposes in the form of the RES (reticuloendothelial system), opsonization and immunogenicity [8],[9],[10],[11],[12],[13],[14].

Nanocrystals

Nanocrystals are pure solid drug within range of 1000 nm. These are 100% drug without any carriers molecule and are generally stabilized by using a surfactant or polymeric steric stabilizers.Nanocrystals show specific characteristics that help them to overcome difficulties such as increased dissolution velocity, increase saturation solubility and increased glueyness to surface/cell membranes. There are two methods by which nanocrystals are synthesized known as top-down and bottom-up. Sono-crystallization, precipitation, high gravity controlled precipitation technology, multi-inlet vortex mixing techniques and limited impinging liquid jet precipitation technique are included in top-down method. While use of an organic solvent and at end its removal makes the process somewhat expensive. The bottom-up method includegrinding procedures along with homogenization at higher pressure[9].

Nanopores

Nanopores are about 20 nm in diameter having high density of pores that helps in the entry of oxygen, glucose and other chemicals such as insulin to pass through. Nanopores can be used to protect the transplanted tissues from the host immune system, at the same time, utilizing the transplantation benefit.β-Cells of pancreas can be implanted in the recipients body by just enclosing it within the nanopores.It can even be employed in DNA sequencing. Nanopores are developed in such a way that they have ability to differentiate purines from pyrimidines [13].

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Micelles

For systemic delivery of water-insoluble therapeutic agents polymeric micelles are mostly used. Their size ranges in less than 100 nm size and forms aggregates in solution. The molecules of polymeric micelles are arranged in spheroidal structure, in which a hydrophilic mantle surrounds hydrophobic cores. The existence of hydrophilic surface provides protection from nonspecific uptake by the reticuloendothelial system that ensures high stability within the physiological systems. On the other hand, the hydrophobic core has the ability to physically trap the water-insoluble, hydrophobic therapeutic agents. The dynamic structure of polymeric micelles prove to be a prominent delivery system for therapeutic agents, that allows versatile loading capacity, conjugation of targeted ligands, and lower rate of dissolution. Formation of micelles takes place by self-assembly,this process starts only when minimum concentration is achieved, known to be as criticalmicellar concentration. [8],[9],[11],[12].

Protein Nanoparticles

Viruses are found to be very efficient and natural carriers for transferring their genetic material that are encapsulated by the capsid proteins. Virus-like particles (VLP) is a type of protein nanoparticles defined as nano-carrier systems having a morphologically similar, virus-isolated structure but with an absence of the viral genetic material. Additionally, caged proteins (CP) are the self-assembled protein nanostructures, which are morphologically similar to viruses, but are not derived from viruses. Both VLPs and CPs are attractive nano-carrier systems for developing the vaccines for cancer as they can induce antigen-specific immune responses against the cancer cells. Moreover, there are certain protein nanoparticles made by self-assembly of protein polymers that are isolated from animal or plant origin such as collagen, gelatin, silk, albumin, elastin, and soy. Abraxane® is an FDA-approved protein nanoparticle drug that enables paclitaxel delivery by albumin. On the other hand, an HIV vaccine made from VLPs led to critical developments that have accelerated research on protein nanoparticles for the clinical use. [8],[9].

Nanogels

The gels are the non-fluid colloidal or network of polymer that swells when comes in contact with fluid. A nanogel has same properties but with a diameter of less than 100 nm by the International Union for Pure and Applied Chemistry (IUPAC). Hydrogels are known to be biocompatible, nontoxic, and biodegradable with high absorption capacity ensuring a wide range of biomedical applications in drug delivery, tissue engineering, and wound dressing/healing[12].

Carbon Nanotubes

Carbon nanotubes are carbon-based tubular structures with 1 nm diameter and 1–100 nm length.By just wrapping a single layer of graphite called graphene into a seamless cylinder the structure can be formed. The configuration of carbon nanotubes consist of single-walled nanotubes (SWNTs), multi-walled nanotubes (MWNTs), and C60 fullerenes. Their size and stable geometric shape make them an attractive non-polymeric carrier for therapeutic agents.Carbon nanotubes can be made more soluble by just incorporating carboxylic or ammonium groups to their structures and can be used for the transport of peptides, nucleic acids and other drug molecules. Nanotubes have ability to transport DNA across cell membrane. DNA can be attached to the tip of nanotubes or just be incorporated within the tubes. [8].

Nanodiamonds (NDs)

Nanodiamonds (NDs) belongs to carbon-based nanomaterials with a diameter of less than 100 nm and different shapes with two types of discrete facets, which are generated from various methods, such as the detonation, chemical vapor deposition (CVD), and high-pressure/high-temperature methods. NDs show unique properties, such as surface electrostatic properties, low cytotoxicity by a chemically inert core, and low photo-bleaching by the addition of nitrogen defects and can be functionalized by immobilization of various types of biomolecules, which make them remarkable for biomedical applications such as magnetic resonance imaging (MRI), synthesis of contact lenses, and drug delivery for cancer therapy. The signal generated by coupling NDs with gadolinium [Gd] (III) as a contrast agent for MRI, is several times higher as compare to Gd (III)-based contrast agents.[8].

Scaffold

The application of scaffolds in biomedicine and tissue engineering is very much importantas it promotes cell adhesion, proliferation, and differentiation for tissue growth. A porous

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network is provided by the scaffold for the optimum growth of cells that will eventually leadto the formation of tissue. The use of scaffolds is of great importance as biocompatible biomaterial matrix is needed for optimum cell growth.Importantly, scaffolds offer key morphological and mechanical characteristics for clinical application, such as high porosity, interconnectivity, and mechanical strength, along with high biocompatibility. In comparison to traditional solid surface scaffolds, nanofibrous scaffolds have shown application in tissue regeneration. The scaffold of particular interest can be designed primarily by varying the solvent and polymer concentration, which provides a scaffold construct with specific size, shape, and porosity[12].

Nanostructured lipid carriers (NLC)

Nanostructured Lipid Carriers are produced from mixture of solid and liquid lipids, but at body temperature particles are in solid state. Lipids are found to be the molecules that can form differently structured solid matrices, such as the nanostructured lipid carriers (NLC) and the lipid drug conjugate nanoparticles (LDC), which have been created to improve drug loading capacity. The production of NLC depends on solidified emulsion (dispersed phase) technologies. There can be an insufficient loading capacity in NLC due to drug expulsion after polymorphic transition during storage. LDC nanoparticles are useful for targeting water-soluble drug. They even have applications in cosmetics, food and agricultural products. They had found to increase bioavailability and drug loading capacity[14].

Table No.5:Different types of nanoparticles combined with drugs or biologics

Polymer nanoparticles-synthetic polymer particles combined with drugs or biologics				
Name	**Material description**	**Nanoparticle advantage**	**Indication(s)**	Year approved
Cimzia®/certolizumabpegol (UCB)	PEGylated antibody fragment (Certolizumab)	Improved circulation time and greater in vivo stability	Crohn's disease; Rheumatoid arthritis; Psoriatic Arthritis; Ankylosing Spondylitis	2008; 2009; 2013; 2013
Mircera®/Methoxy polyethylene glycol-epoetin beta (Hoffman-La Roche)	Chemically synthesized ESA (erythropoiesis-stimulating agent)	Improved stability of aptamer as a result of PEGylation	Anemia associated with chronic kidney disease	2007
Neulasta®/pegfilgrastim (Amgen)	PEGylated GCSF protein	Improved stability of protein through PEGylation	Neutropenia, chemotherapy induced	2002
PegIntron® (Merck)	PEGylated IFN alpha-2a protein	Improved stability of protein through PEGylation	Hepatitis C	2001
Somavert®/pegvisomant (Pfizer)	PEGylated HGH receptor antagonist	Improved stability of protein through PEGylation	Acromegaly	2003
Plegridy® (Biogen)	Polymer–protein conjugate (PEGylated IFN beta-1a)	Improved stability of protein through PEGylation	Multiple Sclerosis	2014
ADYNOVATE (Baxalta)	Polymer–protein conjugate (PEGylated factor	Improved stability of protein through	Hemophilia	2015

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	VIII)	PEGylation		
Liposome formulations combined with drugs or biologics				
DepoCyt© (Sigma-Tau)	Liposomal cytarabine	Increased delivery to tumour site.	Lymphomatous meningitis	1996
Marqibo® (Onco TCS)	Liposomal vincristine	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Acute lymphoblastic leukemia	2012
Onivyde® (Merri mack)	Liposomal irinotecan	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Pancreatic cancer	2015
DepoDur® (Pacira Pharmaceuticals)	Liposomal morphine sulphate	Extended release	Analgesia (post-operative)	2004
Doxil®/Caelyx™ (Janssen)	Liposomal doxorubicin	Improved delivery to site of disease; decrease in systemic toxicity of free drug	Karposi's sarcoma; Ovarian cancer; multiple myeloma	1995; 2005; 2008
Abelcet® (Sigma-tau)	Liposomal amphotericin B lipid complex	Reduced toxicity	Fungal infections	1995
Micellar nanoparticles combined with drugs or biologics				
Estrasorb™ (Novavax)	Micellarestradiol	Controlled delivery of therapeutic	Menopausal therapy	2003
Protein nanoparticles combined with drugs or biologics				
Abraxane®/ABI-007 (Celgene)	Albumin-bound paclitaxel nanoparticles	Improved solubility; improved delivery to tumor	Breast cancer; NSCLC; Pancreatic cancer	2005; 2012; 2013
Tricor® (Lupin Atlantis)	Fenofibrate	Increases bioavailability simplifies administration	Hyperlipidemia	2004
Avinza® (Pfizer)	Morphine sulphate	Increased drug loading and bioavailability; extended release	Psychostimulant	2002 (2015)
Ritalin LA® (Novartis)	Methylphenidate HCl	Increased drug loading and bioavailability	Psychostimulant	2002
Invega® Sustenna ® (Janssen Pharms)	Paliperidonepalmitate	Allows slow release of injectable low solubility drug	Schizophrenia; Schizoaffective disorder	2009; 2014

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Ferrlecit® (Sanofi Avertis)	Sodium ferric gluconate	Allows increased dose	Iron deficiency in chronic kidney disease (CKD)	1999

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