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Pharmaceutical Nanotechnology and Nanomedicine

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ABSTRACT
Pharmaceutical nanotechnology refers to the design, characterization and production of pharmaceutical materials, structures and products which have dimensions approximately between 1nm and 100nm; however 1000nm is often considered as an upper limit. The process of using materials to produce devices and products that equals the dimension of one-billionth of a meter Ione nanometer equals one-billionth of a meter) is referred as nanotechnology. Pharmaceutical nanotechnology is based on nano-sized biomaterials, which promote innovative therapeutic drug delivery systems, advanced diagnostic biosensors and also early diagnosis of the diseases.**Polymer-drug conjugates, dendrimers, nanoparticles and liposomes** are considered as nanomedicines. Due to their small size and high surface area to volume ratio, formulation of drugs into nanomedicines can increase drug potency and efficacy which enhances the solubility and dissolution rate, drug distribution and drug targeting. To improve solubility and dissolution of the drug, they can be conjugated to water-soluble conjugates which are formulated as nanosized drug particles or incorporated into nanocarriers such as dendrimers, micelles, liposomes or any nanoparticles. Nanoparticles impart several advantages concerning efficacy and reduce adverse effects. Nanoparticles can enhance the bioavailability in such a way that they prevent drug renal clearance and protection against the clearance caused by the mononuclear phagocytic system. Nanoparticles have an advantage of passively targeting the tumor sites and inflammation sites through the 'enhanced permeability and retention effect' or through 'receptor-ligand interactions'.

KEYWORDS: Nanotechnology, nanoparticles, nanomedicines, nanocarriers, polymer-drug co0njugates, dendrimers, liposomes.

I. INTRODUCTION

Nanotechnology uses materials to create systems with dimensions of one billionth of a meter. Richard Feynman published the first report on nanotechnology, but Professor Nario Taniguchi coined the word. Nanotechnology applications include physical science and engineering, life and health sciences, and electronics.[1]

The term nanotechnology is the science and technology where the structural units of matter used in the complex macromolecular systems formation on nanoscale. Everything that is smaller than a nanometer is included in the very wide and broad phrase of "nanotechnology."Nanotechnology refers to anything with dimensions of a nanometer or smaller. Nanotechnology can be separated into specific sectors such as nanoelectronics, nanomaterials, medical diagnostic instruments and sensors, flexible display technologies and e-papers, nanotube composites, and printable electronic circuits.The applications are numerous and have a significant impact on various levels, including the economy, social sectors, and living standards.[2] Size reduction is a fundamental unit operation with significant applications in pharmacy. It enhances medication solubility and bioavailability, reduces toxicity, improves release, and opens up new formulation options. Size reduction is often limited to the micron range in pharmaceutical dose forms such as powder, emulsion, and suspension. Nanoscale drugs improve performance across multiple dose forms. Nanosizing offers numerous benefits, including increased surface area, solubility, rate of dissolution, oral bioavailability, faster onset of therapeutic action, lower dose requirements, reduced fed/fasted variability, and decreased patient-to-patient variability. Nanotechnology is an interdisciplinary field that combines basic sciences and practical fields, including biophysics, molecular biology, and bioengineering. It has had a significant impact on several sectors of medicine, including cardiology, ophthalmology, endocrinology, cancer, pulmology, and immunology, as well as specific areas such as gene delivery, brain targeting, tumor targeting, and

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oral vaccine formulations. Nanotechnology is a potentially developing technology that has the potential to significantly impact various industries, including cancer research. Nanotechnology-based treatments are increasing popularity and will hold a larger market share in the pharmaceutical business.

Nanotechnology applications include the formulation and development of nanomedicines to improve drug potency and efficacy, as well as the use of nanomaterials in tissue engineering and implant fabrication to create structures that enable tissue regeneration within the body.Nanotechnology encompasses the development of nanoscale devices, such as implantable sensory systems (nanodiagnostics), to enhance diagnostic accuracy. This article discusses the potential benefits of using nanotechnology in drug formulation, including:

a. Enhanced solubility and dissolution: Nanoparticles improve drug solubility and dissolution due to their high surface area to volume ratio.
b. Enhanced drug delivery: Small particle size enhances drug delivery by extending its circulation, modifying distribution, and allowing for targeted transit across biological barriers.
c. Pharmaceutical technology combines many technologies to prepare and create pharmaceutical products. This discipline of pharmaceutical sciences focuses on developing and applying novel technologies.

Pharmaceutical nanotechnology enables more precise diagnosis and treatment of diseases at the molecular level. Pharmaceutical nanotechnology is a cutting-edge field that has the potential to transform the pharmaceutical industry in the near future. Pharmaceutical nanotechnology offers innovative prospects for fighting a variety of ailments.

It detects antigens linked to diseases like cancer, diabetes, and neurological diseases, as well as bacteria and viruses that cause infections.Nanotechnology-based delivery methods can also keep medications from degrading. These qualities may promote sustained medication release, reducing the need for several dosages and lowering treatment costs. Nano-based devices enable the delivery of insoluble pharmaceuticals, making difficult-to-administer medications more accessible.Nanoparticle-based drug delivery methods, including liposomes, micelles, nanoemulsions, nanocapsules, solid lipid nanoparticles, magnetic nanoparticles, nanogels, and albumin nanoparticles, have the potential to effectively treat human and animal diseases. Nanoparticle-based drug delivery systems can effectively target cells and chemicals in inflammation and cancer. Drug resistance in target cells can be overcome, and medications can penetrate the blood-brain barrier more easily. The challenge is accurately identifying molecular targets and directing nanoparticles to specific organs without harming healthy tissues. Nanosystems improve drug delivery efficiency, necessitating dose adjustments. Lastly, it is imperative to address risk issues concurrently with the introduction of additional nanotechnology-based products into the clinic, including any dangers arising from the nanoscale features of the materials utilized.[3]

Producing nanoparticles with consistent size, shape, and composition is crucial for effective medication delivery. Lipid nanoparticles' unique size-dependent characteristics make them a promising candidate for novel treatments. Nanocarriers provide a novel medication delivery technique suitable for secondary and tertiary level targeting. Solid lipid nanoparticles have considerable potential for regulated and targeted medication delivery.[4]

1. POLYMER-DRUG CONJUGATES

Polymer-drug conjugate treatments are macromolecular constructions that combine therapeutic substances, such as small molecules, peptides, proteins, and aptamers, with a polymeric carrier. Conjugating bioactives to polymers offers benefits such as better medication solubility, controlled distribution, efficacy, and pharmacokinetics.

Polymer therapeutics have advanced dramatically during the last few decades. Several polymeric medicines have been on the market since the 1990s. There are four major convergent techniques for moving this platform technology forward. First, novel molecular targets in cancer therapy will be exploited, followed by the development of polymer-drug conjugates as therapies for various disorders. The second step is the creation of combination therapies. Third, efforts to improve polymer chemistry, such as the development of novel well-defined designs and the improvement of advanced characterisation

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techniques required to convert a potential conjugation into a candidate for clinical evaluation. Finally, a better understanding of the polymer conjugate properties that regulate clinical risk-benefit is resulting in a greater respect for clinical biomarkers, which will open up new avenues for tailored therapy.[5]

Polymer-drug conjugates are designed in such that they can enhance medication solubility and delivery. Many synthetic polymers that can provide the right quality and stability features can be manufactured, and they can be specially made to have unique characteristics, such as specific molecular weight, size, charge, etc., to build polymer–drug conjugates. These synthesized polymers are often less immunogenic than naturally produced macromolecules. Water-soluble polymers are utilized to create parenterally administered polymer-drug conjugates.[6]

Von Horst Jatzkewitz reported the **first synthesis of a polymer-drug conjugate** back in 1955.Jatzkewitz proposed that conjugating the psychedelic alkaloid mescaline to a copolymer of N-vinylpyrrolidone and acrylic acid would result in a controlled release of the bioactive. [7]

1.1 Classes of polymer-drug conjugates

1.1.1 Polymer-protein conjugates:

Polymer-protein conjugation has been extensively studied for applications including enzyme immobilization and bioaffinity purification. Proteins can be conjugated onto premade polymer nanoparticles including micelles, dendrimers, and latex particles using two alternative strategies: covalent and non-covalent. Covalent conjugation methods include carboxylic acid-amine group reactions using carbodiimide chemistry or amine-aldehyde addition-elimination reactions, which result in non-site-specific conjugations, as well as orthogonal thiol-ene, alkyne-azide, and click reactions, which result in site-selective conjugations. Non-covalent conjugations use layer-by-layer techniques such as electrostatic interactions, hydrophobic attractions, or highly selective bioaffinity binding.Adagen, the first marketed PEG-protein therapy, was clinically approved in 1990. Adagen, a PEG-adenosine deaminase conjugate, is used to treat severe combined immunodeficiency due to a hereditary lack of the enzyme. [8]

Abuchowski et al. pioneered the use of PEG conjugation in 1977 to reduce protein immunogenicity, improve solubility, and increase plasma half-life. PEG is a highly water-soluble, flexible, uncharged, and biocompatible polymer commonly employed as an excipient in the pharmaceutical industry. PEG, when attached to a protein therapy, reduces immunogenicity by shielding antigenic epitopes through steric repulsion. Steric repulsionhinders proteolytic enzyme breakdown, opsonization, and clearance by the mononuclear phagocyte system (MPS). Polymer conjugation increases the molecular mass and hydrodynamic radius, leading to decreased plasma clearance by renal filtration. Improvements in protein stability, plasma half-life, and immunogenicity lead to reduced dosage frequency and improved therapeutic agent safety.

1.1.2 Polymer-small-molecule drug conjugates:

Jatzkewitz produced the first polymer–small-molecule drug conjugate in 1955. He showed that conjugating the psychedelic alkaloid mescaline to a copolymer of N-vinylpyrrolidone and acrylic acid prolongs the bioactive's residence time in mice.In the 1970s, Ringsdorf postulated a pharmacologically active polymeric carrier capable of drug solubilization and targeting1. In the late 1970s, Kopecek and colleagues developed the first synthetic polymer-small molecule drug combination that advanced to clinical trials, followed by several more. Ligating small-molecule bioactives to polymeric carriers provides benefits such as improved aqueous solubility, stability, extended plasma half-life, active intracellular delivery, altered biodistribution, and targeted delivery with targeting moieties. The linker chemistry used determines the molecule's release and activity. These benefits are especially relevant for cytotoxic chemotherapeutics, which frequently have low solubility, quick clearance, and limited tumor exposure. Anticancer drugs' efficacy is hampered by off-target toxicity, highlighting the need for techniques that modulate biodistribution and activity.Polymer-small molecule drug conjugates are being developed for non-cancer

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applications. Naloxegol (Movantik), the only marketed polymer-small-molecule drug hybrid, was clinically approved in 2014 to treat opioid-induced constipation in chronic pain patients94. Movantik, an orally administered drug, demonstrates the possible use of polymeric carriers in non-parenteral therapy. Movantik, a PEG oligomer compound of opioid antagonist naloxone, has lower permeability and penetration into the central nervous system compared to the small-molecule medication. Movantik improves opioid-related constipation and reduces naloxone's efficacy to treat opioid-induced analgesia.[5]

2. DENDRIMERS

Dendrimer is derived from a Greek word in which dendra means reminiscent of a tree. Dendrimers are nanosized polymeric star-shaped macromolecules with a high degree of branching. Dendrimers are formed through regulated chemical synthesis and consist of three major constituents – a central core, an internal dendritic structure and the external surface of the dendrimer.Dendrimers can be constructed in various shapes and sizes, allowing for drug delivery within the construct or conjugation to the surface. Dendrimer surfaces can be changed with targeting groups or hydrophilic coatings to improve solubility.

Dendrimers, like polymer-drug conjugates, can be either biodegradable or nonbiodegradable based on design.Higher generation dendrimers have several internal and external functional groups, which allow them to operate as hosts for various ions and molecules due to their three-dimensional structure. Depending on the type of guest, the size of the cavity, and the chemical makeup of the dendrimer's interior and exterior, dendrimers selectively retain guest molecules. Covalent bond formation, electrostatic interactions, complexation reactions, steric confinement, different kinds of weaker forces (van der Waals, hydrogen bonding, etc.), and combinations of these can all be the driving forces behind guest encapsulation within dendrimers.[9]

Since the initial synthesis of poly(propyleneimine) (PPI) dendrimers by Vo¨gtle et al. in 1978, numerous novel dendrimer classes have been identified.Dendrimers have gained popularity due to their well-defined structures and chemical flexibility.

Dendrimers' structure and chemical characteristics can be modified by modifying their core, repeated branch units, and terminal functional groups. Higher-generation dendrimers have a densely packed spherical perimeter around their interior cavities due to surface functional group crowding.[10]

Vögtle et al. published the first example of an iterative synthetic technique to achieve well-defined branched structures, known as "cascade synthesis". Tomalia et al. presented a report on den-32 K. Esumidrimers at the first international polymer conference in Kyoto in 1984, which was later published in Polymer Journal. Tomalia'spoly(amidoamine)dendrimer(PAMAM) and Newkome'sarborol were synthesized using the divergent method, while Hawker and Fréchet pioneered the convergent methodology for precision dendrimer synthesis.Dendrimers have unique functional capabilities due to their chemical structure, molecular weight, distribution, size, and shape. Dendrimers can be designed using core, branched chain, and surface functional groups, as well as utilizing their pore space. Dendrimers offer unique dimensional functionality compared to linear polymers. While branched chains can be added to linear polymers, dendrimers excel at creating three-dimensional structures. Dendrimers have various applications, including nanocapsules, gene vectors, catalysis, magnetic resonance imaging, electron conduction, and photon transduction. Dendrimer science has evolved through collaboration with disciplines such as physical and materials chemistry, biotechnology, and applied physics. PAMAM and poly(propyleneimine)dendrimers are commercially available and manufactured using the divergent approach.

There are two ways proposed for creating high-generation dendrimers: divergent and convergent.

The divergent approach involves growing dendrimers step-by-step from a central core, resulting in many reactions on a single molecule. This approach produces a high yield. PAMAM dendrimers and poly(propyleneimine)dendrimers have been commercially produced using this approach.The divergent technique requires complete branched reaction substitution to avoid a limited number of statistical flaws. Defects are more noticeable when dendrimer production increases. Dendrimers are functional molecules and materials, therefore minor flaws have minimal impact on basic research and industrial

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applications.

The diverging approach, which involves size exclusion chromatography, can produce highly purified dendrimers.

The convergent technique involves synthesizing dendrimers from the peripheral to the core. This approach requires a constant and small number of reaction sites in each reaction step throughout the synthesis. As a result, each reaction produces few side products. After the reaction, a purification process is required to eliminate any unreacted or defective dendrons. As a result, this process appears to be difficult for large-scale dendrimer production. However, dendrimers generated convergently can produce defect-free ones.

Dendrimers with symmetrical branched architectures can form spherical molecules as their generation increases. Numerical calculations using the kinetic growth model predict that the branches' ends are substantially backfolded, rather than at the surface. These findings indicate that the surface end groups and interior molecules of dendrimers can move freely and fluidly. Dendrimers' regular branching nature allows for systematic control over their form and size. Dendrimers are nanometer-sized and get larger with each generation. The branched chain stretching results in a greater diameter, yet it is better regulated compared to ordinary linear polymers. Dendrimers are larger than fullerenes (0.7 nm) and smaller than tiny particles (0.1-10 μm). Dendrimers enable molecular synthesis at the nanoscale. In nature, many biopolymers, such as proteins, have nanoscale diameters and consistent molecular structures.Dendrimers can greatly improve the precision of molecular building by controlling both form and size.

Transmission electron microscopy was used to assess dendrimer size and shape [14]. Better photos of dendrimers could provide answers to fundamental problems such as their uniform size, spherical shape, and dense core. Visualizing dendrimer assemblies can confirm their structure and morphology, making it useful for various applications. Metal nanoparticles have been extensively studied for their usage in electrooptical, electrical, imaging, and catalytic applications.Fabrication of nanoparticles has become an important topic in nanotechnology. To accomplish this, reliable nanoscale devices that can control particle size, shape, and size distribution of metal nanoparticles are required.

Dendrimers' regular internal and external functional groups serve as templates for the growth of inorganic crystals, resulting in organic-inorganic hybrid nanostructures.[11]

The earliest synthetic dendrimers were polyamidoamine (PAMAM). These compounds and their changes are now being studied extensively. PAMAM dendrimers primarily contain ammonia or ethylenediamine (EDA) particles as their core molecule.

Synthesis of PAMAM dendrimer using EDA core involves two steps: In the first stage, Michael addition of a primary amine (EDA) to methyl acrylate. The resulting tetraester is then amidated with EDA. This procedure yields a generation zero (G0) dendrimer with four free amino groups that can react with methyl acrylate monomers and ethylenediamine molecules. The second reaction yields G1 dendrimers.

Aside from PAMAM dendrimers and their derivatives, additional compounds are extensively studied.Since the discovery of dendrimers in the 1980s, over 100 families and 1000 surface alterations have been documented.

Enzymatic catalysis is used to manufacture dendrimers, such as polyethylene glycol (PEG).Previous research has focused on modifying dendrimers, including butyl-glycidylether-modified PPI dendrimers (created by reacting butyl glycidyl ether with PPI).Other types of dendrimers include carbazole, ferrocenyl, phosphorous, carbosilane, siloxane-based, perylenebisimide-cored, and N-glyoxylamidedendrimers.

Peptide dendrimers are molecules with a peptidic surface grafted onto a dendrimer framework, or dendrimers with amino acids as the central or branching unit. The first known peptide dendrimers were L-lysine dendrimers.

Glycodendrimers are compounds that include carbohydrates into the dendrimer structures. Glycodendrimers often feature saccharide moieties on their outer surface, but can also have a sugar unit as the focal point or carbohydrates as the primary building components.

Chiral dendrimers have chiral components in their structure, creating chiral surfaces that can operate as exo-receptors or endo-receptors.

The next category of dendrimers is those with catalytic activity. Catalytic sites may be located on the dendrimer's surface or within the particle's inner sphere.

The features of a catalytically active site are determined by its location. The former allows

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for the study of potential allosteric or cooperative effects across catalytic centers, while the latter allows for adjustments to catalyst reactivity and selectivity.

Liquid crystalline dendrimers are made up of mesogenic monomers, such as carbosilanedendrimers. Carbosilanedendrimers with 36 mesogenic units and a C-5 spacer create a wide smeticA phase at temperatures ranging from 17 to 130◦C.

The dendrimer family includes electrochemically active dendrimers with redox-active organic and organometallic components, as well as photoresponsivedendrimers with chromophores. "Janus" dendrimers have fluorescent entities on one side and water-solubilizing functions on the other. These dendrimers may be useful for marking materials or biological organisms.

Tecto-dendrimers are made up of a core dendrimer that may or may not include a therapeutic substance, surrounding by dendrimers. Dendrimers play a crucial role in the functioning of smart therapeutic nanodevices.

Hybrid dendrimers combine linear and dendritic polymers in hybrid blocks or graft copolymer blocks. The combination of reactive chain ends and dendrimer segments can be used as surface active agents or adhesives, such as hybrid dendritic linear polymers.

When compared to linear, branching, and cross-linked polymers, dendrimers have the following special properties: three-dimensional architecture; a uniform molecular weight without a specific molecular weight distribution; a systematically increasing size and diameter with an increase in generation number; a smaller hydrodynamic volume and lower molecular volume when compared to linear polymers of similar molecular weight; peripheral groups determine the solubility of dendrimers:; densely packed surface and empty interior space of higher generation dendrimers offer the ideal conditions for a wide range of applications, such as drug encapsulation; higher generation dendrimers lack the chain entanglement typical of linear polymers, even with a high number of peripheral groups.[12]

3. SOLID NANOPARTICLES

Particles that fall between 1 and 100 nm in size, at least in one of the three dimensions, are referred to as nanoparticles. They have a large surface area per unit volume, a high percentage of atoms in the surface and near-surface layers, and the capacity to display quantum phenomena due to their incredibly small size scale. One cannot simply extrapolate the characteristics of bulk materials to predict the unique properties of nanoparticles that result. There is a wide range of chemical forms that nanoparticles can take, including those of metals, metal oxides, polymers, carbon compounds, semiconductors, organics, and biological materials. Along with their amazing morphological diversity, they have shapes including hollow spheres and tubes, platelets, cylinders, disks, and spheres. Several synthetic techniques based on gas, liquid, or solid phase approaches can be used to create nanoparticles. Because of their nanoscale, which makes them chemically and/or physically aggregative, the produced nanoparticles typically require surface modification in order to passivate and stable. Additionally, the nanoparticles are surface functionalized to suit the requirements of particular uses. The basic building blocks of many applications in nanotechnology are nanoparticles.

Nanoparticles can be manufactured by gas, liquid, or solid phase techniques. Gas phase processes such as flame pyrolysis, high temperature evaporation, and plasma synthesis, microwave irradiation, physical and chemical vapor deposition synthesis, colloidal or liquid phase methods involving chemical reactions in solvents, molecular self-assembly, and mechanical size reduction processes like grinding, milling, and alloying are examples.[13]

Solid nanoparticles can be created through various manufacturing methods, including particle size reduction (e.g., milling) or molecular agglomeration (e.g., precipitation). The former method is utilized to create nanosized drug particles without any carrier material, while the latter method is usually employed to create drug-loaded nanoparticle carriers. [14]

3.1 Nanosized Drug Particles and Drug Nanocrystals

Reducing medication particle size to nanoscale enhances the system's overall surface area, leading to increased solubility. This feature can enhance the solubility and bioavailability of oral medicines. Using nanosized drug particles in oral medication administration helps prevent differences in bioavailability due to a patient's fed/fasted state. Nanosized drug particles have a

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high surface area and interfacial energy, leading to instability and particle aggregation. Surface-active agents, such as Elan Corporation's NanoCrystal technology, can help address this issue. NanoCrystals are made from pure medication and stabilized using nonionic and anionic surfactants during size reduction for increased stability. Drugs in nanoparticles might be crystalline or amorphous. Small particle size leads to increased dissolving and saturation solubility. Nanocrystals are often administered orally through tablets or capsules. High nanocrystal loading in tablets may cause crystal fusion during compression, making medication loading a crucial factor to consider. Several drug nanoparticle products on the market use NanoCrystal technology.[14]

3.2 Solid Lipid Nanoparticles:

Solid lipid nanoparticles, developed in 1991, offer a superior alternative to typical colloidal carriers such emulsions, liposomes, and polymeric micro and nanoparticles. Solid lipid nanoparticles are colloidal carriers made up of a solid core of high melting point lipid and an aqueous surfactant layer. Lipid pellets, such as Mucosolvan® retard capsules, have long been used as a drug delivery matrix material. Lipids can refer to triglycerides, partial glycerides, fatty acids, hard fats, and waxes. Solid lipid nanoparticles offer the advantage of being manufactured from physiological lipids, reducing the risk of acute and chronic toxicity. Using solid lipid instead of liquid lipid improves control over encapsulated chemicals' release kinetics and stability, particularly for chemically sensitive lipophilic components.[15]

Solid lipid naoparticles were generated using a modified high shear homogenization and ultrasonic technique. Melting the lipid matrix at 80°C and adding mifepristone resulted in a clear solution. After heating tristilled water with surfactants to a similar temperature, the hot lipid phase was poured into the solution. The new method was used to create the nanoemulsion, which was then refrigerated to form the solid lipid nanosuspension.[16]

3.3 Protein Nanoparticles:

Proteins can also be used to create nanoparticles, in addition to lipids and polymers. Protein nanoparticles for therapeutic protein or peptide administration may benefit from matching material properties, as the carrier and medication have the same amino acid structure. A crowded protein environment can better simulate the natural environment of proteins in the body, promoting native and functional conformations. Protein nanoparticles can be produced through self-assembly or desolvation, which are currently the two main methods. Self-assembled structures are formed by non-covalent interactions under physiological or near-physiological conditions. They are often composed of proteins that naturally form macromolecular assemblies or synthetic copies of these proteins.To create desolvated protein particles, add a desolvent to a protein solution and stir. The particles are then crosslinked for stability. Protein nanoparticles have been used to deliver a wide range of therapies, including small molecule medicines like Abraxane®, nucleic acids, peptides, and proteins.[17]

3.4 Inorganic Nanoparticles:

Nanoparticles can be made from inorganic materials such as metal oxides, metal sulfides, carbon nanotubes, calcium phosphate, and ceramics. Nanoparticles are not biodegradable and so have limited use. Abdoscan®, a metal oxide nanoparticle product, is no longer available in Europe. Abdoscan®, a superparamagnetic iron oxide nanoparticle formulation taken orally, is suitable for bowel MRI diagnosis. The particles have a diameter of at least 300 nm. This negative contrast agent is ideal for peroral bowel MRI diagnosis due to its strong magnetic signal and low cytotoxicity.

To prevent particle aggregation in vivo, they are suspended in viscous substances like starch.Metallic nanoparticles have captivated scientists for over a century and are widely used in biomedical sciences and engineering. Chemically modified materials can be conjugated with antibodies, ligands, and drugs for biotechnology, magnetic separation, targeted drug delivery, gene delivery, and diagnostic imaging.[18]

4. LIPOSOMES

Alec D Bangham discovered liposomes in the 1960s at the Babraham Institute, University of Cambridge, and they are made up of one or more concentric lipid bilayers that encapsulate an aqueous compartment. The early formulations had

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just natural lipids; today, they might contain both natural and synthetic lipids as well as surfactants. They are capable of entrapping lipophilic and hydrophilic substances in the lipid membrane and aqueous core, respectively. These almost spherical lipid vesicles vary in size from a few nanometers to many micrometers. Liposomes used in medicine, on the other hand, have sizes ranging from 50 to 450 nm.Liposomes appear to be an almost ideal drug-carrier system, as their shape is similar to that of biological membranes and they may include a variety of chemicals. As a result, liposomes have been extensively studied over the last 50 years and continue to be the focus of ongoing research. They are prized for their biological and technological benefits as ideal delivery systems for physiologically active compounds, both in vitro and in vivo, and are widely regarded as the most successful drug-carrier system to date.Citation4 During the previous two decades, significant progress has been made, and numerous biomedical uses of liposomes are currently in clinical studies or are about to be released to the market, while others have already been approved for public use.

Liposomes are mostly made up of phospholipids, amphiphilic molecules with a hydrophilic head and two apolar hydrophobic chains. When phospholipids are disseminated in aqueous solutions, their amphipathic nature causes them to form membranes. On the one hand, their polar heads like to interact with the aqueous environment, while their lengthy apolar aliphatic chains encourage contact among themselves. In aqueous solution, these dual characteristics promote the creation of two lipid layers.Each layer's hydrophobic chains face one another and form a lipophilic inner compartment that serves as an inward and outward permeability barrier. These lipid bilayers are formed by hydrophobic contacts, and this architecture is strengthened by van der Waals forces that hold the long hydrocarbon tails together. Finally, this arrangement is stabilized by hydrogen bonds and polar contacts between the polar heads of lipids and the water molecules in the aquatic environment. Lipids' ultimate arrangement is determined by their composition, temperature, geometric shape, and concentration. These membranes can include chemicals or ions that are present during the formulation process.[19]

Liposomes can be prepared using a variety of methods. Several factors influence the selection of an appropriate method: the physicochemical characteristics of the liposome components and those of the drug to be loaded; the toxicity and concentration of the loaded substance; the type of the medium in which the liposomes are dispersed; the additional processes during the application/delivery of the liposomes; the size and half-life desired for the successful application; and the costs, reproducibility, and applicability of large-scale production for clinical.

The thin-film hydration, also known as the Bangham method, is one of the most extensively used liposome manufacturing procedures.This process comprises dissolving the lipid in an organic solvent, evaporating the solvent, and dispersing the resulting lipid film in aqueous medium. The drug to be entrapped can be found in aqueous fluids (for hydrophilic drugs) or in lipid film (for lipophilic drugs).

Liposomal medications have also been utilized to treat bacterial infections, photodynamic treatment, and cardiovascular disease. Liposomes have been investigated for use in nanotechnology as signal enhancers in medical diagnosis, solubilizers for diverse substances, and penetration enhancers in cosmetics. Because of their unique properties, liposomes have been designed as carriers for brain delivery of bioactive ingredients and utilized to treat a variety of central nervous system illnesses, including Alzheimer's disease, ischemic disease, and Parkinson's disease. However, in order to achieve clinical translation, liposomal formulations must undergo additional studies to further prove their efficacy, such as evaluating the combinations of bioactive molecules, measuring the dosage of bioactive molecules administered, and performing assessments in patients with various central nervous system disorders.

When compared to free (unentrapped) pharmaceuticals, liposomes offer several advantages, including reduced adverse effects, improved pharmacokinetics, and increased delivery efficiency to target sites. However, liposomes continue to face some obstacles. One major issue is medication leakage from the liposome during circulation, before it reaches the tumor site. Unwanted leakage would not only result in inadequate circulation times, but it would also cause the premature release of cytotoxic chemicals, causing harm to healthy organs and tissues. The primary cause of drug leakage in liposomes is serum proteins such as lipoproteins, which can disrupt the integrity of liposome bilayers. Other parameters that may influence liposome stability include phospholipid type, drug-to-lipid ratio, and

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liposome makeup. Polymer-stabilized liposomes are liposomes that have had their surfaces modified with polymers, most often PEG.

The development road for liposomes has been long and painful over the last several decades, from their initial use in therapeutic applications to their recognition as the mainstream and most successful drug delivery platforms. Liposomes are now widely used in cosmetics, dietetics, and pharmaceuticals, as well as in clinical applications for treating and managing a wide range of diseases and conditions (such as cancers, infectious diseases, and pain) and improving vaccine and gene therapeutic delivery. Notably, several studies credit liposomal medications with reducing side effects and toxicities rather than increasing efficacy when compared to free pharmaceuticals. While encapsulating free drugs into liposomes can minimize their toxicity, the therapeutic effects in patients are unlikely to improve. Liposomes require more improvement; yet, important clinical demands and obstacles remain to be addressed by liposomes in the future.[20]

II. CONCLUSION

Pharmaceutical nanotechnology has the potential to significantly improve disease diagnostics and therapies by providing new tools, opportunities, and scope. Pharmaceutical nanotechnology holds significant potential for delivering bioactives and diagnostics, as well as creating smart materials for tissue engineering. Pharmaceutical nanotechnology specializes in medication delivery, diagnostics, prognostics, and illness treatment using nanoengineered tools. Only a few nanotechnology-based goods and delivery systems are currently available in the market. Pharmaceutical nanotechnology can enhance materials and medical devices, as well as generate new technologies that are beyond the limits of traditional methods.

Nanomedicine is a very recent area of research and technology. It appears to be ill-defined at times, and interpretations of the term may differ, particularly between Europe and the US. Nanotechnology opens up a wide range of research and application opportunities by interacting with biological molecules at the nanoscale. Interactions between artificial molecular assemblies or nanodevices and biomolecules can be studied both in the extracellular environment and within human cells. Operating at the nanoscale enables the exploitation of physical features other than those observable at the microscale, such as the volume/surface ratio.The researched diagnostic applications can be used for both in vitro and in vivo diagnostics. In vitro, synthesized particles and manipulation or detection equipment enable biomolecule recognition, capture, and concentration. In vivo, synthetic molecular assemblies are primarily intended as a contrast agent for imaging. A second area of rapid growth is "nanodrugs," in which nanoparticles are used for tailored drug delivery. The use of such carriers increases drug biodistribution by directing active molecules into sick areas while sparing healthy tissue. A third field of use is regenerative medicine, where nanotechnology enables the development of biocompatible materials that promote the proliferation of cells utilized in cell therapies.

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