

Review Article

A Comprehensive Review on Role of Nanotechnology in Drug Delivery System

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Nanotechnology has become a revolutionary technology in contemporary medicine that can provide new solutions to the inefficiency of the traditional drug delivery systems. Nanoscale properties enable precise drug targeting, controlled release, enhanced bioavailability, and reduced systemic toxicity. The review gives a general description of drug delivery systems that are based on nanotechnology, with liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, and metallic nanoparticles being the main examples of nanocarriers. Critical discussions are made of their design strategies, drug loading capacities, release mechanisms and therapeutic advantages. In addition, more recent technological developments in the areas of targeted delivery, such as ligand-mediated delivery and stimuli-responsive systems, are discussed in the treatment of various diseases in cancer, infections, and neurological conditions. Despite significant advancements, there are still issues of toxicity, stability, large-scale production, and regulatory issues, which are impediments to clinical translation. In general, the field of nanotechnology offers a potential platform in improving therapeutic efficacy and development of biomaterial-based medical applications.

Introduction

Nanotechnology is an interdisciplinary research area that is concerned with the study, design, production, and implementation of materials and devices on a nanoscale, typically between 1 and 100 nanometers [1]. Nanotechnology was coined by the professor Norio Taniguchi in 1974 and over time, nanotechnology has grown to be one of the most transformative scientific fields of the 21st century [2]. Nanotechnology has impacted remarkably on various fields including electronics, agriculture, energy, environmental science, and medical fields in particular by offering a way to manipulate matter at an atomic and molecular scale. Nanotechnology in the healthcare system has enabled the development of novel diagnostic instruments, imaging procedures, and novel treatment plans all collectively referred to as nanomedicine [3].

Drug delivery systems (DDS) are a center of contemporary therapeutics since they dictate the effectiveness of a given drug to reach the target drug location [4]. Traditional methods of drug delivery - such as oral, intravenous, nasal, transdermal and inhalation drug delivery meth-

ods - have numerous limitations that include poor solubility, low bioavailability, degradation, systemic toxicity and lack of site specificity. These disadvantages could result in poor therapeutic results and augmented side effects. A large number of these issues are overcome through nanotechnology-based drug delivery systems (NDDS), which enhance drug solubility, improve pharmacokinetics, provide controlled and sustained release, and targets diseased tissue delivery and reduce harm to normal cells [5].

Nanomedicine has experienced a prosperous industry in the last 20 years. Recent reports show that over 50 nanomedicine products have been approved regulatory globally, where hundreds of nanoformulations are in preclinical and clinical development. A significant percentage of approved nanotherapeutics are liposomal formulations, polymeric nanoparticles, nanocrystals, antibody drug conjugates, and lipid nanoparticles. In recent years the global market of nanomedicine has increased to a range of more than USD 200 billion, and this figure is expected to rise with the current rise on prevalence of cancer, neurological disorders, cardiovascular diseases, and infectious diseases [6].

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The implementation of lipid nanoparticle platforms in mRNA vaccines during the COVID-19 pandemic, itself a successful implementation of nanotechnology-based therapeutics, also demonstrated the clinical and commercial viability of nanotechnology-enabled therapeutics.

Liposomes and dendrimers are examples of nanocarriers that have altered physicochemical characteristics, i.e. high surface area-to-volume ratio, tunable surface chemistry, improved permeability and the capacity to entrap hydrophilic and hydrophobic drugs [3]. These properties permit the enhanced cellular uptake, prevention of enzyme degradation of the drug, a longer time of circulation, and increased pathological tissue accumulation, including the Enhanced Permeability and Retention (EPR) effect. In addition, other sophisticated techniques like ligand-mediated targeting, stimuli-responsive release (pH, temperature, enzymes, redox conditions) and receptor-specific delivery have also improved the therapeutic specificity [5].

The translation of nanotechnology-based systems to the laboratory research to the extensive clinical application has a number of obstacles despite the impressive progress made. The problems associated with mass production, reproducibility of batch-to-batch, long-term toxicity, immunogenicity, standardization of regulations, and cost-effectiveness still demand a high level of research attention [7]. To achieve efficacy and safety, it is important to understand the nano-bio interactions, formation of protein corona, biodistribution, metabolism and clearance mechanisms. Altogether, nanotechnology is a paradigm shift in science of drug delivery. Nanotechnology-based drug delivery systems provide a potential development of precise therapy, decreased systemic toxicity, and the development of personalized medicine through combining material science, chemistry, biology, and medicine. Further multidisciplinary studies and strict regulations will be essential in the complete harnessing of therapeutic capabilities of nanomedicine in the next few decades.

Drug delivery systems based on nanotechnology have evolved beyond the traditional pharmaceutical carriers. These systems are combined with the cutting-edge biomaterials for the localized as well as the controlled therapeutic delivery [8,9]. The biomaterials like electrospun nanofibers, three-dimensional printed scaffolds and biodegradable polymers, hydrogels not only provide the structural support but also serve as the reservoir for therapeutic agents [10–12]. The incorporation of nanocarriers in the biomaterial's aids in the precise control over drug release, also enhances the stability of the drugs, reduces the toxicity as well as promotes the therapeutic responses that are tissue specific [13]. As a result, combining nanotechnology and biomaterials in a synergistic way has become a viable approach to solving difficult biomedical problems in tissue engineering, regenerative medicine, and the creation of artificial organs.

Among the various types of biomaterials based nanocarriers, the biodegradable polymeric nanocarriers such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), chitosan, polycaprolactone (PCL), and alginate has gained significant attention due to their following characteristics: enhanced biocompatibility, tunable degradation behaviour and ability to sustain controlled drug release [14,15]. The drug release profiles, interaction at cellular levels and long-term therapeutic efficacy of these materials is known to influence the degradation kinetics. In addition to this, the advancements in the field of biomaterial engineering have further enabled the development of stimuli-responsive and multifunctional nanocarriers that possess the ability to respond to the various changes such as pH, temperature, enzymes, redox reactions thereby enhancing the therapeutic precision as well as patient outcomes.

Although there has been remarkable progress in the field of nanotechnology-based drug delivery systems yet several challenges are associated with them that hinders their successful clinical translation. The most commonly faced challenges include the complexity of biological barriers, limitations of enhanced permeability and retention effects in human tumours, variability in the responses of the patients, manufacturing difficulties at larger scale and the limitations of regulatory measures [16,17]. Apart from these, the detailed physicochemical characterizations including Zeta Potential analysis, Transmission Electron Microscopy (TEM), Dynamic Light Scattering (DLS), X-ray Diffraction (XRD), etc are necessary to ensure the stability, reproducibility

as well as safety of the nanocarriers systems. Therefore, the development of next-generation nanomedicines requires a critical understanding of material design, characterisation, biological interactions, and clinical translation.

The present review provides an in-depth knowledge of various drug delivery systems based on nanotechnology with main emphasis on the bioengineered nanocarriers, their characterization, material design, degradation behaviour, drug release mechanism, interactions with other biological tissues as well as the applications specifically in the field of tissue engineering and regenerative medicines. Furthermore, recent advances, clinical translation challenges, and future perspectives associated with nanomedicine are critically discussed to provide insights into the development of next-generation biomaterial-assisted therapeutic platforms.

Types of Nanocarriers used in Drug Delivery

Nanocarriers are nanoscale material manufactured to deliver therapeutic agents to targeted locations in the body in a better manner, in terms of precision, stability, and efficacy. They possess unique physicochemical characteristics including high surface-area to volume ratio, tunable surface functionality and controlled drug release behaviour that make them most appropriate in overcoming the limitations of traditional drug delivery systems [18]. The nanocarriers employed in the delivery of drugs are generally categorized as organic or inorganic systems depending on their material structure and the functionality. Polymeric nanoparticles, solid lipid nanoparticles, liposomes and dendrimers are organic nanocarriers. These types tend to be biodegradable, biocompatible, and have a high ability of clinical applications because they have controlled drug delivery as well as a reduced toxicity profile. They improve bioavailability, stability of drugs, and allow delivery of drugs to diseased tissues selectively. Examples of inorganic nanocarriers are metal-based nanoparticles (i.e. gold and iron oxide), carbon-based nanomaterials (i.e. carbon nanotubes and fullerenes) and mesoporous silica nanoparticles. Such systems have their peculiar optical, magnetic, and structural features, which makes them applicable to imaging, theragnostic, and targeted therapy [19]. Yet, their clinical translation is somewhat limited in comparison with organic nanocarriers because of the issue of long-term biocompatibility and accumulation. Various types of nanocarriers used in drug delivery are depicted in figure 1.

Liposomes

The pioneer discovery of liposomes happened in 1960s when British haematologist, Alec D. Bangham, discovered the liposomes at the Babraham Institute. These spherical vesicles are made of one to several phospholipid bi-layers with an aqueous core whose size is usually be-

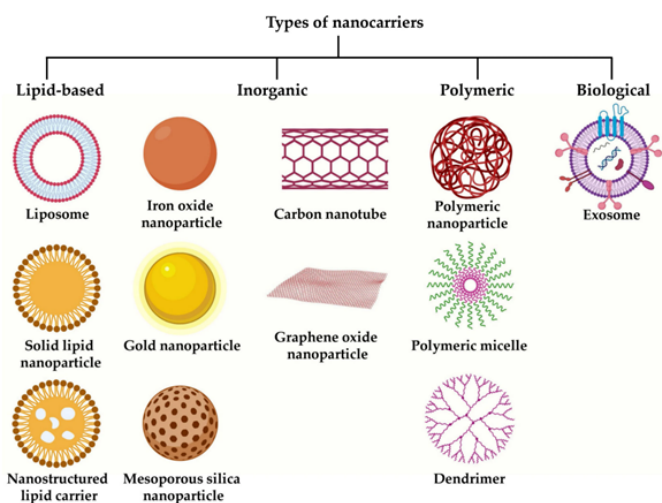


Figure 1: Various types of nanocarriers used in drug delivery system [47]

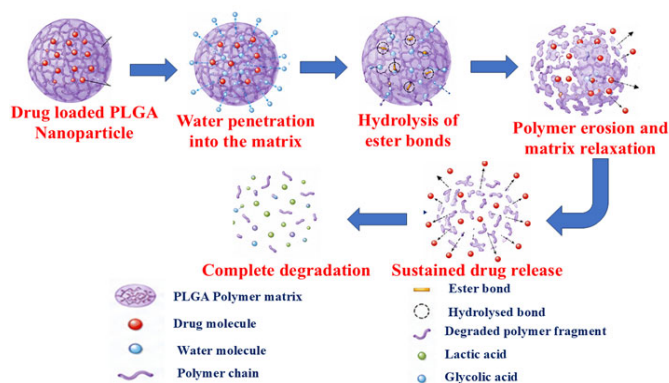


Figure 2: Schematic illustration of the degradation mechanism of drug-loaded PLGA nanoparticles, showing water penetration, ester bond hydrolysis, polymer erosion, sustained drug release, and complete degradation into lactic acid and glycolic acid

tween 30 nm to a few micrometres. Liposomes are highly biocompatible, biodegradable, and immunogenic because they have a structural similarity with biological membranes. Liposomes can entrap hydrophilic (because they are located in the aqueous core) and hydrophobic (because they are located in the lipid bilayer) drugs and can thus be very versatile vectors [20]. Recent developments have been PEGylated liposomes with extended circulation, ligand-functionalized liposomes that target actively and stimuli-responsive liposomes that deactivate at specific pH or temperature [21]. Doxil (liposomal doxorubicin), Abraxane (albumin-bound paclitaxel) and several other liposomal drugs have been clinically approved and have been demonstrated to reduce systemic toxicity and improve therapeutic index in the treatment of cancer [22].

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are solids measuring between 10-1000 nm in diameter and are made of biodegradable and biocompatible polymers that include PLGA, chitosan, PEG and polylactic acid. Depending on the mode of incorporation of the drug, they may be in the form of nanospheres (matrix systems) or nano capsules (core-shell systems). PNPs are also very versatile since their size, surface charge, degradation rate and profile of drug release can be accurately manipulated during their synthesis [23]. These properties lead to increased drug stability,

increased bioavailability and controlled or sustained drug release [24]. Surface modification by site-directed ligands like antibodies or peptides further improves site specific delivery particularly in cancer and brain diseases. Although they are beneficial, issues like mass production, immunity, and chronic toxicity are also being studied.

Polymer degradation kinetics and drug release behavior

The degradation behaviour of polymeric nanoparticles that governs the release of encapsulated therapeutic agents has a strong influence on the success of these particles as drug delivery systems [25]. The biodegradable polymers are gaining significant attention in the field of nanomedicines as they can undergo controlled degradation within the physiological environment thereby removing the need for surgical removal after the release of the drugs [26]. The degradation process not only influence the duration of drug release but it is also known to affect the bioavailability, biocompatibility as well as the therapeutic efficacy of the drug delivery systems. Therefore, for the rational design of nanoparticle-based drug delivery systems a clearer understanding of kinetics of polymer degradation is necessary [27]. The various polymeric nanoparticles that are commonly employed in the drug delivery systems include PLGA, PLA, PCL, chitosan and alginate modified polymers [28]. Out of all these, the most extensively investigated biodegradable polymer is PLGA. It is due to its biocompatibility, biodegradability and the regulatory approval for use in biomedical applications [29]. In PLGA, the hydrolytic degradation occurs via the cleavage of ester bonds that produces lactic and glycolic acid as the degradation products that are finally metabolized via biochemical pathways [30]. By adjusting the ratio of lactic acid (PLA) to glycolic acid (PGA) units within the polymer chain, the pace of PLGA degradation can be accurately regulated. The schematic representation of the hydrolytic degradation and drug release mechanism of PLGA nanoparticles is depicted in figure 2.

It is evident from various studies, that the composition of copolymer influences the degradation behaviour of PLGA nanoparticles. The polymers that have high content of glycolic acid are known to exhibit increased hydrophilicity thereby resulting in greater absorption of water and enhanced hydrolysis. The faster degradation rate is observed for PLGA with a ratio of 50:50 (lactic acid to glycolic acid) whereas the formulations having higher content of lactic acid degrade slowly due to their hydrophobic character and crystallinity [31]. The creation of drug delivery systems that may release therapeutic compounds over times ranging from days to many months is made possible by this controllable degrading property. Several other factors are also known to influence the degradation behaviour and the kinetics of drug release such as particle size, porosity, molecular weight, surface area, pH, temperature, crystallinity and the presence of enzymes. Low molecular weight nanoparticles degrade faster due to the decreased number of polymeric chains that

Table 1: Effect of biodegradable polymers on degradation behaviour and drug release characteristics

Polymer	Degradation Mechanism	Relative Degradation Rate	Drug Release Characteristics	Biomedical Applications
PLGA (50:50)	Hydrolysis of ester bonds	Fast	Rapid sustained release	Cancer therapy, vaccines
PLGA (75:25)	Hydrolysis of ester bonds	Moderate	Extended release	Long-term drug delivery
PLA	Hydrolysis	Slow	Controlled prolonged release	Implants, tissue engineering
PCL	Surface erosion/Hydrolysis	Very slow	Long-term release (months-years)	Bone tissue engineering
Chitosan	Enzymatic degradation	Moderate	pH-responsive release	Mucoadhesive delivery
Alginate	Ionic exchange and hydrolysis	Moderate	Sustained release	Wound healing, regenerative medicine

requires hydrolysis. Likewise, smaller nanoparticles facilitate the water penetration as well as accelerate the process of degradation owing to their large surface to volume ratio [15]. Furthermore, the hydrolytic cleavage of polymeric chains resulting in enhanced drug release rate is increased by the acidic pH and the increased temperature.

The various mechanisms via which the drug release takes place from the polymeric nanoparticles include a diffusion polymeric degradation as well as erosion. In the initial stage, the drug molecule present on the surface of particle may undergo rapid release. This is known as burst release mechanism. After this, the process of drug release is governed by the diffusion through the polymeric matrix followed by the degradation of polymeric network [32]. Based on the characteristics of the polymer, the degradation may occur via bulk or surface erosion mechanism. In the bulk erosion, the entire polymer matrix is penetrated by water very rapidly thereby causing the degradation over the entire particle volume. This phenomenon is commonly observed in PLGA systems. On the other hand, surface erosion takes place usually at the exterior side of the particle, resulting in more predictable and sustained drug release profiles [33]. The degradation behaviour exhibited by natural polymers such as chitosan and alginate is different from that exhibited by synthetic ones. In case of chitosan, the enzymatic degradation mediated by lysozyme and other biological enzymes takes place whereas in case of alginate the degradation is affected by the ionic exchange and the hydrolytic process. The natural polymers exhibit pH-responsive behaviour thereby making them the suitable candidate for site-specific drug delivery applications. Moreover, the enhancement in the circulation time, reduction in protein absorption as well as overall improvement in the therapeutic applications can be brought about by the surface modification of polymeric nanoparticles [34]. Table 1 summarizes the effect of biodegradable polymers on degradation behaviour and drug release characteristics, highlighting how polymer properties influence degradation rate and controlled drug release.

One of the most important advantages of polymeric nanocarriers is their ability to tailor the degradation kinetics as well as the release profiles. Researchers can design nanocarriers systems that are capable of delivering drugs in controlled and sustained manner by carefully selecting the polymer composition, preparation parameters as well as molecular weight. This enables the reduction in dosing frequency, minimizes the systemic side effects and brings improvement in the patient compliance. As a result, biodegradable polymeric nanoparticles are still essential to the creation of sophisticated drug delivery systems, tissue engineering structures, and applications in regenerative medicine.

Dendrimers

Dendrimers are monodispersing tree-like synthetic macromolecules that are highly branched. Dendrimer is a name derived in Greek language as dendron, which denotes a tree. In the 1980s, researchers including Donald Tomalia made progress in early dendrimer synthesis. These nanostructures are made up of three major components which include a central core, repeated branching units (generations) and several terminal functional groups. Their polyvalent surface allows them to bind more than one drug, targeting ligand, imaging or gene at the same time. The most common and widely studied are poly(amidoamine) dendrimers, which are water-soluble and cross the epithelial barriers [35]. Dendrimers have shown specific potential in the brain-targeted delivery of drugs, gene therapy and against cancer. Recently, there are biodegradable dendrimers as a way of minimizing long-term toxicity and pH-sensitive dendrimer-drug conjugates as a way of tumor-specific delivery [36].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are lipid-based nanoparticles that are lipids that are solid at room and body temperature, with a diameter of about 50-1000 nm. They have the benefits of liposomes and polymeric nanoparticles and are associated with enhanced physical stability and reproducible drug delivery. The lipid matrix formed is solid but keeps drugs encapsulated so that they are not affected by chemical degradation and release can be sustained over a long time. SLNs have found their place especially in topical, oral, ocular, and in injecting drugs. They

increase the solubility of drugs, mitigate systemic toxicity and improve pharmacokinetic characteristics. Recent studies have been done to enhance scalability, storage stability, and targeting efficiency of anticancer and antifungal therapy [37].

Nanostructured lipid carriers

The second generation of lipid based nanocarriers that are developed to overcome the challenges and limitations of SLNs is the nanostructured lipid carriers (NLCs) [38]. SLNs are composed of solid lipids whereas the NLCs are made up of both solid and liquid lipids [38]. The incorporation of liquid lipids in the SLNs causes the disruption of ordered arrangement that is found in SLNs thereby making imperfections in the lipid matrix that provides additional space for drug accommodation [39]. Due to this only, the NLCs have higher drug loading ability, enhanced stability as well as reduced leakage of drugs during the storage [40]. Various techniques employed for the preparation of NLCs include ultrasonication, microemulsion technique and high-pressure homogenization [41]. All these processes produce nanoparticles ranging in size from 50 to 500 nm. The controlled and sustained drug release is enabled by the presence of imperfect liquid matrix that minimizes the burst release effect. In addition to this, NLCs lipid-based composition offers various advantages to the NLCs such as enhanced biocompatibility, biodegradability thereby making them the suitable candidate for the delivery of hydrophobic drugs, proteins, nucleic acids and peptides [42]. NLCs have found applications in various fields such as in oral, ocular, topical, pulmonary and targeted cancer delivery systems.

NLCs when compared to SLNs, provide better formulation flexibility as well as enhanced therapeutic performance. NLCs have various advantages such as greater drug loading capacity, tunable release profile as well as the better storage stability. All these features make them the most promising lipid nanocarrier that can be used for advanced drug delivery systems. Because of these characteristics, these NLCs have been explored for various biomedical applications including tissue engineering and regenerative medicines where the sustained and localized drug release is necessary. A comparative of SLNs and NLCs is presented in table 2.

Metal-based nanoparticles

Nanoparticles of metal (especially gold, silver, iron oxide and other metallic nanostructures) are extensively investigated in drug delivery because of their special optical, electronic and catalytic characteristics. Gold nanoparticles in particular are highly precious due to their surface plasmon resonance, functionalization capability, and biocompatibility and can find application in targeted drug delivery, imaging, and photothermal cancer therapy [43]. Silver nanoparticles have high antimicrobial activity, and they are usually used in the process of preventing infections during wound healing. Nanoparticles of iron oxide find application in magnetic targeting and imaging guided drug delivery. The surface-area-volume ratio of metal nanoparticles is high, which facilitates conjugation of drugs and ligands to be attached to receptors to enable the targeting of them. The most recent developments are multifunctional nanoparticles equipped with therapy and diagnostic properties under the concept of theragnostic. Nonetheless, issues on long-term accumu-

Table 2: Comparative table of SLNs and NLCs

Feature	SLNs	NLCs
Lipid composition	Solid lipids	Blend of solid and liquid lipids
Internal structure	Highly ordered crystalline matrix	Imperfect/disordered matrix
Drug-loading capacity	Moderate	High
Drug expulsion during storage	Possible	Significantly reduced
Release profile	Controlled release	More sustained and tunable
Major limitation	Drug leakage during crystallization	Formulation complexity

lation, oxidative stress and toxicity induced by the metal are to be considered carefully in terms of their safety [44].

Carbon-based nanomaterials

Carbon nanomaterials can be classified as fullerenes, carbon nanotubes (CNTs), graphene, and graphene oxide; they are all characterized by outstanding mechanical strength, electrical conductivity, and chemical versatility. Fullerenes (e.g., C₆₀) have a cage structure able to incorporate drugs and act as antioxidants. Carbon nanotubes are considered drug carriers due to their high surface area and high cellular penetration ability, which is attributed to the fact that nanotubes are cylindrical sheets of graphene that exist either as single-walled (SWCNTs) or as multi-walled (MWCNTs) [45]. Graphene-based materials offer extensive surface sites in the loading and finite release of drugs. They are especially used in cancer therapy, gene delivery, biosensing and photothermal applications in these nanomaterials [46]. Carbon nanomaterials have a high degree of functionalization to enhance their solubility and biocompatibility that is otherwise a significant drawback. Though they provide impressive therapeutic promise, issues of biodegradability, respiratory toxicity and bio persistent effects remain focus of active investigation.

Characterization of Nanocarrier-Based Biomaterials

The characterization is an integral part of the design of biomaterials in the form of nanocarriers as it helps to determine their physicochemical properties, stability, drug loading and bioactivity level. Characterization

of nanocarrier systems for drug delivery applications is significant when it comes to safety, efficacy and reproducibility [48]. These characteristics directly influence drug release kinetics, cellular uptake, therapeutic efficacy, and long-term biocompatibility. Therefore, systematic characterization is essential for optimizing nanocarrier performance and ensuring reproducibility, quality control, and successful clinical translation. Multiple analytical methods are needed for a thorough characterization of these properties, each giving specific information about the physicochemical and biological properties of the nanocarriers. The main characterization parameters, common analytical techniques and information used to evaluate the quality and performance of nanocarrier-based biomaterials are summarized in table 4. These characterization techniques are equally applicable to nanoparticle-loaded hydrogels, electrospun nanofibers, implant coatings, and three-dimensional (3D) scaffold systems used in tissue engineering and regenerative medicine.

For polymeric nanocarriers and nanocomposites, characterization techniques such as FTIR, XRD, DSC, and TGA are particularly important for confirming polymer blending, intermolecular interactions, crystallinity, and thermal stability, all of which influence degradation kinetics and controlled drug release.

Particle size and size distribution

The size of the particles is a parameter that plays a significant role in the loading of a drug, its cellular uptake, its biodistribution, circulation time and therapeutic effects. The size of nanocarriers is typically 1 – 1000 nm; most of the drug delivery systems are in the range of 10 – 200 nm [49]. Most commonly Dynamic Light Scattering (DLS), Nanoparticle Tracking Analysis (NTA), and Electron Microscopy are used to measure

Table 3: Comparative characteristics of major nanocarriers used in drug delivery systems, highlighting their composition, size range, drug-loading mechanisms, release behavior, biomaterial advantages, and limitations

Nanocarrier Type	Primary Material Composition	Typical Size Range	Drug Loading Mechanism	Drug Release Characteristics	Major Biomaterial Advantage	Limitations/Toxicity Concerns
Liposomes	Phospholipid bilayers with aqueous core	30 nm–several μ m	Hydrophilic drugs in aqueous core; hydrophobic drugs in lipid bilayer	Diffusion and membrane destabilization	Highly biocompatible, biodegradable, and biomimetic	Structural instability and premature leakage
Polymeric Nanoparticles (PNPs)	PLGA, PLA, PCL, Chitosan, PEG	10–1000 nm	Matrix entrapment or core–shell encapsulation	Diffusion, polymer degradation, bulk or surface erosion	Tunable degradation kinetics and controlled drug release	Burst release, swelling challenges, residual solvent toxicity
Dendrimers	Highly branched polymers (e.g., PAMAM)	Typically <100 nm	Surface conjugation and internal cavity encapsulation	Bond cleavage and diffusion-controlled release	Monodispersity and high functionalization capacity	Cationic toxicity, membrane disruption
Solid Lipid Nanoparticles (SLNs)	Solid lipids such as triglycerides, waxes, and fatty acids	50–1000 nm	Drug incorporation within solid lipid matrix	Diffusion-controlled release	High biocompatibility and protection of labile drugs	Drug expulsion on storage and limited loading capacity
Nanostructured Lipid Carriers (NLCs)	Blend of solid and liquid lipids	50–500 nm	Drug entrapment within imperfect lipid matrix	Sustained and tunable release	Higher drug loading and improved storage stability compared with SLNs	Formulation complexity and lipid oxidation
Metal-Based Nanoparticles	Gold, silver, iron oxide, and other metallic nanomaterials	1–100 nm	Surface adsorption, covalent attachment, and ligand conjugation	Stimuli-responsive release (light, pH, magnetic field)	Optical, magnetic, and theranostic properties	Long-term bioaccumulation, oxidative stress, toxicity concerns
Carbon-Based Nanomaterials	Carbon nanotubes, graphene, graphene oxide, and fullerenes	1–100 nm	Surface adsorption, π – π interactions, and covalent functionalization	Stimuli-responsive and diffusion-controlled release	High surface area, mechanical strength, and cellular penetration	Poor biodegradability, respiratory toxicity, and bio-persistence

Table 4: Characterization techniques used for evaluating nanocarrier-based biomaterials in drug delivery systems

Characterization Parameter	Technique's Used	Information Obtained
Particle size and distribution	DLS, NTA	Size, PDI, dispersion quality
Morphology and structure	SEM, TEM, AFM	Shape, surface characteristics
Surface charge	Zeta potential analysis	Colloidal stability and cellular interaction
Drug loading and encapsulation	HPLC, UV-Vis spectroscopy	Drug content and entrapment efficiency
Chemical composition	FTIR, Raman, NMR	Functional groups and drug-carrier interactions
Crystallinity	XRD	Crystal structure and phase identification
Thermal properties	DSC, TGA	Thermal stability and degradation behavior
Drug release profile	Dialysis and diffusion studies	Release kinetics and controlled release
Biocompatibility	MTT, XTT assays	Cytotoxicity and biological safety

the particle size and polydispersity index (PDI). The low PDI value indicates the formulation of particles uniformity and stability [50].

Surface morphology and structure

The interaction between nanocarriers and biological system and the drug release behavior is influenced by their morphology and structural properties. The shape, surface texturing and integrity of the particles are provided by detailed information from Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM). For effective drug delivery, spherical and uniform distribution of nanoparticles are usually preferred [51].

Surface charge (zeta potential)

Surface charge is a key factor that influences the stability and circulation behaviour of nanoparticles, as well as the interactions between them and cells. The zeta potential can be used to predict the colloidal stability of nanocarriers. The higher the positive or negative value of zeta potential, the more stable the product is because the particles have less tendency to aggregate during storage and use [52].

Drug loading capacity and encapsulation efficiency

The drug loading amount of the nanocarriers is called the drug loading capacity and the fraction of the initial amount of the drug which is successfully entrapped is called the encapsulation efficiency. The amount of drug present is normally determined by High Performance Liquid Chromatography (HPLC), UV-VIS Spectroscopy and Fluorescence Spectroscopy. These parameters have an important role in the therapeutic dosage and treatment efficacy [53].

Chemical composition and functional groups

Nanocarriers have chemical composition that plays a role in their biocompatibility, biodegradability and drug binding properties. Fourier Transform InfraRed (FTIR) spectroscopy, Raman spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy are used to identify the functional groups, to confirm the incorporation of the drug and to evaluate the interaction between the carrier and the loaded drug [54].

Crystallinity and thermal properties

The effect of crystallinity on the drug release and stability may occur in nanomaterials. X-Ray Diffraction (XRD) is used for the determination of crystallinity, Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) is used for the evaluation of thermal behaviour, phase transition and degradation characteristics of nanocarrier systems [55].

In vitro drug release studies

Drug release studies are done to study the release of nanocarriers and their controlled delivery under simulated physiological conditions. Dialysis membrane techniques are used for release studies and diffusion studies can be used to predict the in vivo performance. If the drug

remains in the body for long periods, then a certain concentration of the drug is desired in the body for an extended period of time. This is known as controlled and sustained drug release [56].

Biocompatibility and cytotoxicity assessment

The safety of nanocarrier-based biomaterials is essential and should be performed by biocompatibility assessment. Common assays for cytotoxicity are MTT, XTT and Live/Dead cell assays. Hemocompatibility, cellular uptake and inflammatory response studies are further investigations that are needed before clinical use for evaluating the interaction of nanocarriers with biological systems [57].

Collectively, these characterization techniques provide complementary information regarding the physicochemical, structural, and biological properties of nanocarrier-based biomaterials. Comprehensive characterization not only ensures formulation quality and reproducibility but also establishes critical structure–property relationships that govern degradation behavior, drug-loading efficiency, release kinetics, and interactions with biological tissues. Consequently, thorough characterization forms the foundation for the rational design and successful clinical translation of advanced nanocarrier systems for drug delivery, tissue engineering, and regenerative medicine [58].

Mechanism of Nano Particle in Drug Delivery System

The drug delivery systems based on nanoparticles act in a highly coordinated and multi-step process that improves the therapeutic effects and reduces the systemic toxicity of the system. Contrary to traditional methods of drug administration, nanoparticles are designed to regulate drug protection, targeting, internalization, release, and elimination. The entire process is referred to as drug loading, systemic transport, targeting, cellular uptake, intracellular trafficking, linker cleavage, carrier degradation control and final clearance [59].

Drug loading and encapsulation mechanism

Mechanism of nanoparticle delivery of drugs starts with drug loading, or encapsulation in the nanocarrier. The therapeutic agent can be physically encased within a polymeric matrix, or lipid core; it can be adsorbed onto the surface or it can be chemically conjugated to the carrier by a cleavable linker. Encapsulation shields the drug against enzyme-induced, hydrolysis-induced, or oxidation-induced premature drug degradation in the biological environment. It further increases the solubility of poorly water-soluble drugs and increases their bioavailability. In chemically conjugated systems, the carrier carries the drug, which is inactive until it reaches the target site; when doing so, the drug will not cause unintended pharmacological action. Therefore, drug loading is used to provide stability, protection and better therapeutic effect [60].

Controlled carrier degradation and sustained drug release

Besides cleavage of the linkers, the nanocarrier per se might be subject

to controlled degradation. Biodegradable polymers are either hydrolyzed or broken down by enzymes to non-toxic by-products, whereas lipid-based nanoparticles wear away over time. Such a degradation process aids in the controlled and long-standing drug delivery, which keeps therapeutic drug concentrations at the required range over time [61]. The controlled release will decrease the number of doses, increase patient adherence, and limit changes in drug concentration. Finally, the components of the nanoparticles are excreted out of the body via renal or hepatic routes after the release of the drugs and the degradation of the carrier, thus bringing about safe clearance without the accumulating effects. Overall, nanoparticles have a mechanistic process in drug delivery through a cascade of drug preservation, drug prolonged circulation, targeted concentration, efficient absorption at the cellular level, stimuli-responsive linker cleavage, controlled degradation of the carrier, sustained release, and safe removal. This highly controlled and integrated process is what makes nanoparticle-based systems stand out of the more traditional drug delivery systems and makes them very useful in precision medicine and other advanced therapeutic uses.

Stimuli-responsive drug delivery

Targeted drug release is the regulated and localized release of a therapeutic molecule of a nanocarrier in the diseased tissue and reduced release in the healthy tissues. Its ultimate aim is to ensure that therapeutic efficacy and systemic toxicity are maximized. This process starts with the encapsulation or conjugation of the drug in the nanoparticle which is stable so that the drug is not destroyed throughout the systemic circulation. The nanocarrier inhibits premature degradation, metabolism or non-specific distribution of the drug in the bloodstream [62]. Drug release occurs at the target location through certain internal or external stimuli when the nanoparticle is delivered to the target site. Pathological differences are used by internal stimuli-responsive systems to utilize differences between healthy and diseased tissues. It is possible, as an example, to consider the pH of tumor tissues (acidic microenvironment, pH ~6.5), the pH of endosomes and lysosomes within the cell (even lower, pH 5 -6) [63]. Nanocarriers having pH-sensitive bonds or acid-labile linkers become structurally destabilized in such acidic environments resulting in the release of the drug in tumor cell confinement. On the same note, redox-responsive systems make use of the high glutathione level present in the cancer cell to break the disulfide linkage and liberate the drug. Enzyme-activable nanocarriers have been designed to react to excessively expressed tumor-associated enzymes like proteases that specifically cleave peptide linkers leading to localized drug release [64].

Some triggers in external stimuli-responsive systems include light, heat, ultrasound, or magnetic field to trigger drug release. As an example, in photothermal nanoparticles it is possible to produce localized heat when irradiated with near-infrared light to break the carrier structure and release the drug at the tumor target. The spatial and temporal control provides the accuracy of dosing and reduction of exposure to normal tissues. Targeted release is also associated with controlled carrier degradation. The biodegradable polymers are broken down in the physiological environment and make long-term release of drugs to be possible. Combining these mechanisms, targeted drug release systems keep drugs stable throughout circulation and only activate at the target site of action, enhancing the therapeutic index and patient safety.

Targeted drug delivery of cancer cells

Targeting of cancer cells with nanoparticles entails selective delivery of therapeutic agents to the malignant tissues but not the normal cells. This targeting is achieved in two major processes which include passive targeting and active targeting. The mechanism of active and passive targeting of cancer cells is depicted in Figure 3. Passive targeting is based on the Enhanced Permeability and Retention (EPR) effect, which is a solid tumor phenomenon. Tumor tissues have irregular and permeable blood vessels as a result of fast angiogenesis. These vessels have big endothelial loopholes through which nanoparticles, which are usually between 10 and 200nm in size, can extravasate and be deposited in the tumor interstitial space. Secondly, the tumours have limited lymphatic drain and this fact does not allow an effective extraction of the

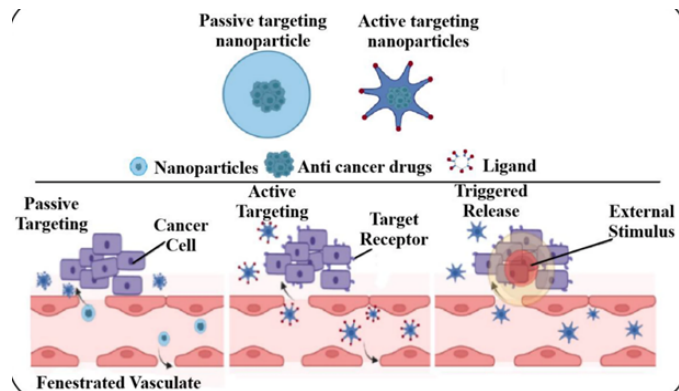


Figure 3: Mechanism of active and passive targeting of cancer cells [72]

nanoparticles and hence long retention within the tumor. This inherent concentration increases at local levels without the requirement of targeting ligands [65].

Although the EPR effect has been recognized as the key mechanism involved in passive tumor targeting yet it is associated with various limitations in terms of its clinical applicability as demonstrated by recent studies [66]. The EPR effect is supported by the evidences that originate from the preclinical studies that are conducted in rodent tumor cells [67]. In these the tumors exhibit highly permeable vasculature and show relatively homogeneous growth. On the other hand, the human tumors are heterogeneous in terms of vasculature permeability, extracellular matrix, stromal composition as well as interstitial fluid pressure [68]. All these characteristics found in human tumors restricts the penetration by nanoparticle as well as their retention within the tumor tissues thereby resulting in highly variable therapeutic outcomes among the patients [69]. As a result, the EPR effect should not be treated as the universal mechanism for the tumor targeting in case of clinical settings. One of the main causes of the poor association often seen between promising preclinical findings and clinical outcomes of nanoparticle-based anti-cancer therapy is thought to be the limited and variable manifestation of the EPR effect in human malignancies. In order to increase tumor selectivity and improve clinical translation, current research efforts are increasingly concentrating on integrating passive targeting with active targeting strategies and biomimetic nanocarrier systems.

Active targeting also increases specificity by surface functionalization of nanoparticles with ligand monoclonal antibodies, peptides, folic acid, aptamers, or transferrin. These ligands are specific to those receptors, which are over expressed on the membrane of cancer cells, which include folate receptors, HER2 receptors or epidermal growth factor receptors [70]. When the ligand and receptor bind, the nanoparticle is endocytosed through receptor-mediated endocytosis resulting in effective intracellular delivery of the drugs. The method enhances cellular uptake, decreases the efficacy of therapy and minimizes off-target toxicity to significant levels [71]. Moreover, future approaches involve dual-targeting systems, in which nanoparticles are used in dual mode of passive accumulation and receptor-mediated recognition, and biomimetic coatings, which can be used to increase immunity evasion and tumor homing. Combined, these processes enable nanoparticles to be accumulated in cancer tissues, enter cancer cells, and release therapeutic agents in a localized way, which is the basis of modern precision oncology.

Nanocarriers in Biomaterial Scaffolds

Biomaterial scaffolds are 3D structures that play a role in cell growth, tissue regeneration and local drug delivery. The use of nanocarriers in these scaffolds increases the stability of the drug, increases the efficiency of its action and allows for targeted and controlled delivery of bioactive molecules [73]. These hybrid systems offer the best of both nanotechnology and biomaterials and are therefore ideal for applications in regenerative medicine, tissue engineering, and implantable medical

Table 5: Analysis of the nano-material-based biomaterial scaffold systems, advantages of such systems and biomedical applications

System	Nanocarriers Used	Key Advantages	Major Applications
Hydrogel-based systems	Liposomes, polymeric nanoparticles, SLNs	Sustained release, high biocompatibility, localized delivery	Wound healing, cancer therapy, tissue regeneration
Electrospun nanofibers	Polymeric nanoparticles, liposomes	ECM mimicry, high drug loading, enhanced cell growth	Wound dressings, skin and bone regeneration
3D printed scaffolds	Drug-loaded nanoparticles, nanocomposites	Customized design, controlled release, patient-specific treatment	Bone and cartilage repair
Artificial organs and implantable biomaterials	Metallic and polymeric nanoparticles	Infection prevention, improved biocompatibility, prolonged implant life	Cardiovascular stents, orthopedic implants, artificial organs

devices [74]. The structural properties, drug delivery systems and biomedical applications of various scaffold platforms ranging from hydrogels and electrospun nanofibers, 3D-printed scaffolds, to implantable biomaterials are different and are depicted in figure 4. Table 5 shows a comparison of these nanocarrier-based biomaterial scaffold systems with the most important features and the representative therapeutic applications.

Hydrogel based drug delivery systems

Hydrogels are three-dimensional polymeric network which can absorb and retain large quantities of water, resembling the structural similarity to natural biological tissues. The combination of hydrogels and nanocarriers (liposomes, polymeric nanoparticles, solid lipid nanoparticles) allows to create a drug delivery platform, which combines the best features of both biomaterials and nanotechnology [75]. The hydrogel matrix is used to create a moist environment and biocompatible environ-

ment, whereas the nanocarriers are used to protect the drug encapsulated in the nanocarriers, as well as control the drug released from the nanocarriers. Hydrogel based systems, therefore, can deliver drugs locally and sustainably, enhance their stability and bioavailability, decrease the number of doses and the occurrence of systemic side effects. The utilization of these systems has been widespread in the fields of wound healing, tissue engineering, cancer therapy and regenerative medicine [76].

Electrospun nanofiber systems

Nanofibers are fibers produced by electrospinning technology, that is, forming continuous fibers from a polymer solution under an electric field, whose dimension is within the nanotechnology range. They have similar fibril architecture as natural ECM, which can be ideal for cell attachment, proliferation and differentiation [77]. Nanocarriers can be embedded in the fibers or anchored to their surface to enhance con-

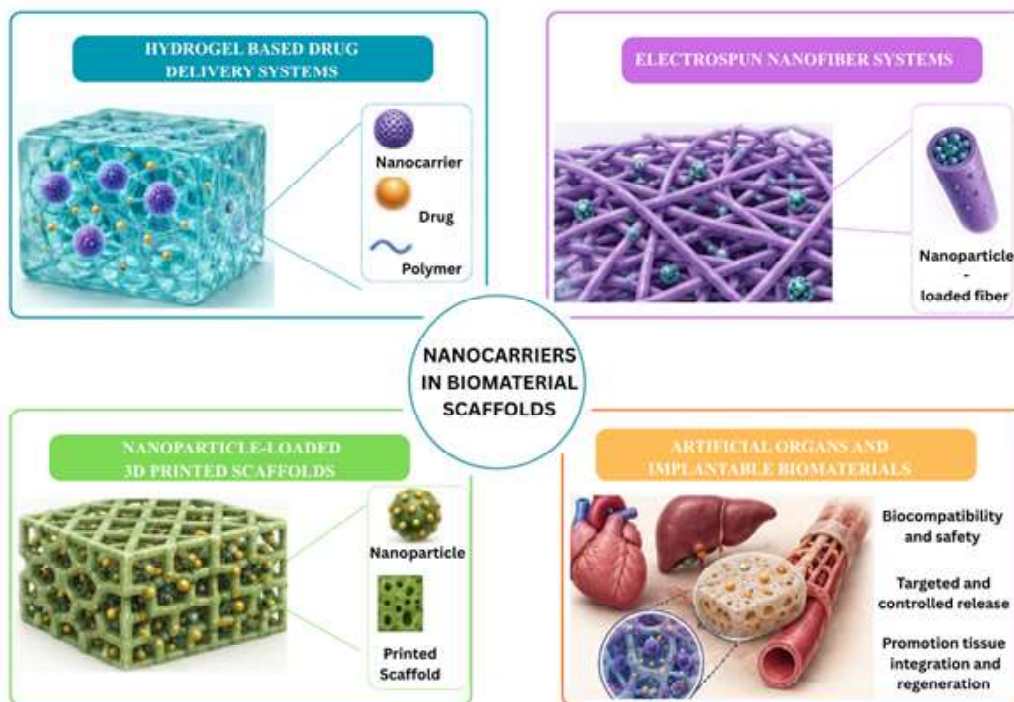


Figure 4: Various types of nanocarrier integrated biomaterial scaffold systems that are widely used for controlled drug delivery and in tissue engineering applications

trolled drug release. High surface area to volume ratio of nanofibers helps to load the drug and it interacts with the nearby tissues quickly. So, electrospun nanofiber systems have been shown to have therapeutic effect, improve tissue regeneration and provide a prolonged drug delivery. They are useful in wound dressings, antimicrobial coatings, skin regeneration and bone tissue engineering among other applications, due to the aforementioned properties [78].

Nanoparticle-loaded 3D printed scaffolds

Three-dimensional (3D) printing technology can generate scaffolds that have optimum geometries, interconnected porosity, and mechanical properties which can be tailored to specific biomedical applications. The drug loaded nanoparticles and the scaffolds make the resulting biomaterials multifunctional providing both structural support and therapeutic action [79]. Controlled and localized delivery of drugs, growth factors or genes at the target site, using the embedded nanoparticles. The integration of this process leads to more efficient treatment, repair of the tissue, less exposure to systemically acting drugs and even patient-specific treatment with drugs. Therefore, 3D printed scaffolds filled with nanoparticles are emerging as an exciting tool to bone regeneration, cartilage repairing and personalized regenerative medicine [80].

Artificial organs and implantable biomaterials

Artificial organs or implantable biomaterials are artificial substitutes for damaged tissues or organs or to aid their function. When nanocarriers are integrated in these systems, their therapeutic activity is improved, as the drugs, growth factors or bioactive molecules could be delivered more locally [81]. The controlled delivery of therapeutic agents from nanocarrier functionalized implants can reduce inflammation, prevent infections and enhance the integration of the tissue around the implant surface. Nanotechnology further contributes to the biocompatibility and functionality of artificial organs, minimizing immune reaction and enhancing their longevity. They have been applied to cardiovascular stents, orthopedic implants and artificial devices for the skin and have even been utilized in a variety of advanced medical devices [82].

Applications of Nanotechnology in Drug Delivery

Cancer therapy and tumor targeting

Nanotechnology has also made a great impact on the cancer treatment with the ability to deliver chemotherapy agents in a targeted and controlled way. The Enhanced Permeability and Retention (EPR) effect utilizing nanoparticles increases drug solubility, increases the duration of circulation and drug accumulation in tumors [84]. Nanoparticles can accumulate passively in the tumor site by taking advantage of this leaky vasculature and inadequate lymphatic drainage of the tumor tissues and the resultant high concentration of drugs in the tumor and low systemic toxicity. Besides passive targeting, active targeting techniques have been used, which entails surface coating of nanoparticles with ligands like antibodies, peptides, or folic acid which attach to receptors overexpressed on cancer cells. This improves cellular internalization by endocytosis via receptors. Also, nanotechnology allows to combine chemotherapy with photothermal therapy and with chemo-photodynamic therapy to improve therapeutic effects. Altogether, the systems of nanoparticles improve the therapeutic efficacy, mitigate adverse effects, and offer a platform of precision oncology [85].

Drug delivery for neurological disorders

The brain is encircled by the blood-brain barrier (BBB), and this makes the treatment of the neurological disorders very difficult because most therapeutic agents cannot enter the brain. Nanotechnology provides a new way out, through the development of nanoparticles that are able to cross or bypass the BBB. Nanoparticles that have undergone surface modification can use receptor-mediated uptake, e.g. transferrin or insulin receptors, to enable brain uptake. These nanocarriers ensure that drugs are not degraded by enzymes and can be released gradually in the brain tissues. Nanoparticles have promise in the delivery of drugs to such conditions like Alzheimer disease, Parkinson disease, brain tumors, and epilepsy. Moreover, nanoformulations can decrease system toxicity and increase the concentration of drugs at the target site, which can increase the therapeutic efficacy of central nervous system disorders [86].

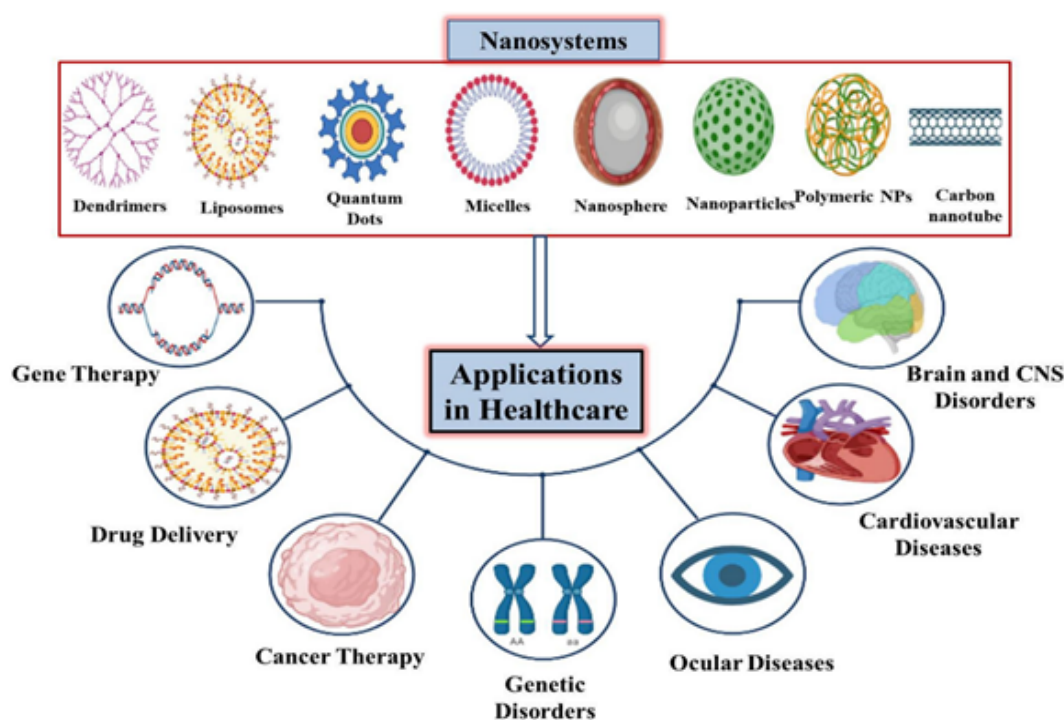


Figure 5: Various types of nanocarriers and their applications [83]

Cardiovascular disease treatment

Nanotechnology is becoming actively involved in diagnosing and curing cardiovascular diseases (CVDs) such as atherosclerosis, hypertension and myocardial infarction. The nanoparticles have the potential of transporting anti-inflammatory medications, thrombolytic medications or cholesterol medications to pathologic vascular tissues. Specific nanocarriers are designed to identify certain biomarkers that are present in the atherosclerotic plaques thus allowing the delivery of local therapy while reducing the overall side effects of the system. Nanoparticles have also found use in imaging where they are also utilized to detect presence of vascular abnormalities early on. Tissue engineering techniques also rely on nanotechnology and in this case, nanomaterials have been used to regenerate heart tissue after heart damage. The developments help enhance therapeutic accuracy and positive patient outcomes [87].

Infectious disease management

Nanotechnology is very important in the fight against infectious diseases by facilitating the delivery of antimicrobial drugs and also improving the diagnostic process. Antibiotics or antiviral agents can be encapsulated in nanoparticles and avoid degradation and release at the site of infection. Wound dressing and infection control use Metallic nanoparticles like silver and gold nanoparticles which have inherent antimicrobial characteristics. Nanocarriers assist in overcoming antimicrobial resistance as well because intracellular delivery of drugs improves and circumvents efflux pathways in pathogens. Besides this, the nanotechnology aids in the fast diagnostic instruments and biosensors which help in the early detection of the infectious agents. Such versatile properties of nanotechnology make it an extremely effective instrument in the contemporary management of infectious diseases [88].

Gene therapy and vaccine delivery

Nanotechnology offers more progressive platforms on gene therapy and vaccine delivery, even to targeted areas due to the ability to safely and effectively transport genetic content. Nanoparticles have the capability of transferring DNA, RNA or small interfering RNA (siRNA) to the target cells without being broken down by enzymes. Surface modifications enable specificity in transfection of tissues or cell types and enhance transfection efficiency and therapeutic accuracy [89]. Lipid-based and polymeric nanoparticles are useful in the development of vaccines to stabilize antigens, increase the uptake by immune cells, and as adjuvants to boost greater immune response. The use of nanoparticle systems to deliver vaccines has proved to become highly successful in new vaccine technology, where the nanoparticles are able to enhance immunogenicity and stability. In general, nanotechnology presents a flexible and bright future of genetic therapies and the development of the next generation vaccines.

Tissue engineering and regenerative medicine

The drug delivery systems based on nanotechnology has emerged as a significant tool in tissue engineering and regenerative medicines because of their capacity to ensure controlled as well as localized delivery of biologically active molecules [90]. Tissue regeneration is a very complex process that usually involves cell proliferation, differentiation, angiogenesis, and extracellular matrix (ECM) remodelling [91]. Conventional methods of administration of growth factors, cytokines, and therapeutic agents often suffer from several limitations such as rapid degradation, poor bioavailability, and lack of site-specific delivery [92]. To curtail these limitations, the nanocarriers provide an effective solution thereby protecting the therapeutic agents from degradation as well as enabling them for the sustained release at the specific target site. For enhancement in tissue regeneration, various types of nanocarriers such as polymeric nanoparticles, liposomes, dendrimers, lipid nanoparticles, and inorganic nanomaterials have been incorporated into the biomaterial matrices like hydrogels, electrospun nanofibers, and three-dimensional (3D) scaffolds [93]. These systems serve as a structural support for the cell attachments and growth and at the same time they act as a reservoir for the controlled and sustained release of growth factors, genes, and therapeutic agents. The combination of nanotechnology with

biomaterials has enabled the development of multifunctional platforms capable of simultaneously promoting tissue repair and preventing infection or inflammation.

Nanoparticle based drug delivery has been investigated for the sustained and controlled release of osteogenic growth factors like bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF) in the field of bone tissue engineering [94]. Incorporation of hydroxyapatite nanoparticles, bioactive glass nanoparticles, and polymeric nanocarriers into scaffold materials has demonstrated to increase osteoblast proliferation, mineralization, and bone regeneration. Likewise in the field of cartilage engineering, nanocarriers help in the localized delivery of chondrogenic factors that promotes the formation of cartilage and its repair while minimizing systemic side effects [95].

Nanotechnology has demonstrated significant potential in the field of wound healing as well as skin regeneration also. Various types of nanoparticles such as zinc oxide, silver and polymeric nanoparticles have demonstrated exceptional antimicrobial and anti-inflammatory characteristics [96–98]. These properties of nanoparticles accelerate the process of wound closure thereby reducing the risk of infection. For achieving the sustained therapeutic effects as well as improved tissue regeneration, these nanoparticles can also be incorporated into hydrogel dressings and electrospun wound-healing scaffolds. Moreover, the nanocarriers based drug delivery systems are further explored for neural, cardiovascular, and soft tissue regeneration. For the nerve repair and regeneration, these nanoparticles have demonstrated significant potential by providing controlled delivery of neurotrophic factors [99]. On the other hand, nanoparticle-loaded vascular grafts and cardiac patches have been investigated to improve angiogenesis and tissue integration. Recent advancements in the field of 3D bioprinting and smart biomaterials have further extended the use of nanotechnology in the field of regenerative medicine by enabling the fabrication of personalized tissue constructs with controlled drug release capabilities [99]. Overall, the incorporation of nanocarriers into the biomaterial scaffolds have significantly advanced the field of tissue engineering and regenerative medicines. The nanocarrier systems have the ability for the development of next-generation regenerative therapies and implantable biomedical devices as these systems demonstrate advantages like sustained and controlled drug release, enhanced cellular interactions and increased therapeutic efficacy.

Advantages of Nanotechnology in Drug Delivery

The advantages of nanotechnology in drug delivery are numerous since it improves the therapeutic efficacy, safety as well as the accuracy of the traditional therapies. These are the enhanced bioavailability and solubility of drugs. There is a majority of therapeutic agents, in particular, anticancer and hydrophobic agents, which are not soluble in water, and this decreases their absorption and clinical outcome. Nanoformulations increase the surface area and could be closed within suitable carriers, which increase the speed of dissolution and systemic availability. Another valuable advantage is targeted drug delivery. Active targeting is achievable through ligand receptor interactions and passive targeting is achievable through the Enhanced Permeability and Retention (EPR) effect of accumulation of nanoparticles in diseased tissues. The selective delivery produces high concentration of the drug in target tissue and low exposure in healthy cells thereby reducing the systemic toxicity and negative effects [100].

The other significant benefit of the systems based on nanotechnology is regulated and constant release of drugs. Nanocarriers can be designed to release drugs at a slow rate and long duration or a response to some physiological conditions such as pH, enzymes, temperature or redox conditions. It is a controlled release profile, which maintains the concentrations of therapeutic drugs in the body, reduces the dosing frequency and also enhances patient compliance. Nanotechnology is also applied in the field of stability of the drug and conservation of sensitive therapeutic agents against premature degradation. The enveloping of nanoparticles safeguards the drugs against enzyme destruction, the chemical destruction and quick metabolism particularly in the biological fluids. The protection enhances circulation time, ensures that the larger percentage of the dose administered reaches the target site of action

[101].

Moreover, nanocarriers can penetrate the biological barriers, such as blood-brain barrier, cell membrane, and the mechanism of tumor resistance to microenvironment. This has increased the chances of treatment of difficult disorders such as neurological disorders and multidrug resistant cancers. Nanotechnology also makes combination therapy, where a number of drugs or therapeutic agents are co-delivered using the same carrier, possible to enhance synergistic therapeutic effects. Altogether, nanotechnology improves the effectiveness of drugs, toxicity, pharmacokinetics, and makes it possible to practice precision medicine, turning it into a revolution in the contemporary drug delivery systems.

Challenges and Limitations in Nanotechnology-Based Drug Delivery

In spite of all this advancement, there are a number of scientific and practical constraints that render nanotechnology-based drug delivery. Nanoparticle toxicity and long-term safety are one of the significant issues. Although most nanocarriers can be biocompatible, the build-up in other organs including the liver, the spleen and lung can lead to unexpected toxicological effects. One of the factors that play a critical role in biodistribution and immune response is surface charge, size, shape, and composition. Also, mass production and reproducibility are also challenging because of the variation of batches and complicated synthesis processes. The other limitation is the stability problems during storage and circulation. Before reaching the target site, nanoparticles can be aggregated and leak prematurely or their structure can be degraded. Moreover, the biosystems include biological barriers like the quick clearance by the mononuclear phagocyte system (MPS) decreasing the circulation time and therapeutic efficacy. The heterogeneity of tumors is also a limiting factor when it comes to the efficiency of targeted therapy because not every tumor has a high EPR effect. All of these limit the complete clinical translation of nanomedicine [102].

The poor correlation between preclinical and clinical outcomes remains a major challenge in nanomedicine development. Although many nanoparticle systems show promising results in *in vitro* and animal studies, these outcomes often fail to translate into human trials due to differences in tumor microenvironment, immune response, metabolism, and disease progression. Additionally, the lack of standardized evaluation protocols and difficulties in dose scaling further hinder clinical translation. Regulatory approval of nanomedicine is also complex due to the absence of unified guidelines and the intrinsic variability of nanoparticle systems. Minor changes in composition or surface properties can significantly affect biological behaviour, complicating characterization and approval processes. Variations in international regulations, high clinical trial costs, and long-term safety concerns further delay progress. Therefore, harmonized regulatory frameworks, improved characterization techniques, and interdisciplinary collaboration are essential for successful translation [103].

Future Perspectives and Emerging Trends

The future of drug delivery using nanotechnology is the creation of very specific, smart, and personalized systems of therapy. New studies being concerned are the development of smart nanocarriers with the ability to react to various physiological signals, including pH, temperature, enzymes, redox gradients, and hypoxic tumor conditions. By providing better spatial and temporal control of drug release, such multi-stimuli-responsive systems provide enhanced therapy precision and reduced off-target toxicity. Another promising direction is personalized nanomedicine [104]. Recent technological progress in genomics, proteomics and biomarker profiling is facilitating the creation of nanoformulations that are specific to the characteristics of the disease in the patient. Precision medicine coupled with nanotechnology could help a lot in improving treatment outcomes especially in cancer therapy where the issue of tumor heterogeneity has been a major challenge. There is also a growing trend of the introduction of artificial intelligence (AI) and machine learning into nanoparticle design. Computational modeling has the ability to predict nanoparticle-biological inter-

actions, optimization of formulation parameters, and enhancement of translational efficiency [105]. The AI-based drug delivery systems have the potential to save time, decrease the expenses, and improve the clinical successes. Theragnostic nanoplatfroms Theragnostic (combination of therapies and diagnostics) nanoplatfroms are becoming potent tools in real-time monitoring of disease and treatment. These multifunctional systems facilitate both imaging and treatment at the same time, which allows clinicians to assess the response to therapy in real time. Moreover, biomimetic nanoparticles that are coated with cell membranes or those designed to take after natural biological systems are also being considered to enhance immune evasion, duration of circulation and targeting capabilities. Large-scale manufacturing technologies, reproducibility, and regulatory harmonization will be the key factors in increasing the pace of clinical translation. The interdisciplinary cooperation of materials scientists, pharmacologists, clinicians, and regulatory authorities will be important in solving the existing barriers. Nanotechnology will help reinvent drug delivery approaches and develop precision therapeutics further with further innovation.

Conclusion

Nanotechnology has transformed drug delivery by providing a new solution to the restrictions of the traditional therapeutic methods. Nanoparticles are known to increase the drug solubility, pharmacokinetics, targeted delivery, and controlled release of a drug and sustained release. Their capacity of transcending the biological obstacles and localizing in diseased areas selectively has greatly enhanced the effects of therapy especially in cancer treatment and other complicated illnesses. Nevertheless, in spite of significant advancements, it is affected by toxicity issues, biological variability, mass production, translational failure, and regulatory success, all of which complicate its extensive clinical use. These limitations have to be resolved by using better preclinical models, standardized characterization methods, and global harmonized regulatory frameworks. In the future, the combination of smart nanocarriers, personalized medicine, artificial intelligence, and theragnostic platforms possess an enormous potential of changing the modern healthcare. As more innovative studies and ideas are shared, nanotechnological based drug delivery devices will become central to future generation precision medicine, providing more efficient, safer and specific therapeutic approaches to patients.

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