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Review

Enhancing Drug Bioavailability Through Nanocarrier Systems: Current Progress and Future Perspectives

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Abstract

Poor drug bioavailability remains a major challenge in pharmaceutical development, primarily due to low aqueous solubility, limited membrane permeability and rapid metabolic degradation, which significantly reduces therapeutic efficacy. In this context, nanocarrier-based drug delivery systems have emerged as an effective strategy to overcome these limitations. This review summarizes the main types of nanocarriers, including lipid-based, polymeric, inorganic and hybrid systems, and discusses their design and functional properties. Nanocarriers enhance drug performance by improving solubility, protecting active compounds from degradation, enabling controlled and sustained release, and facilitating targeted delivery to specific tissues. The influence of physicochemical parameters, such as particle size, surface charge and functionalization, on pharmacokinetics and pharmacodynamics is also addressed. Representative case studies illustrate the successful application of nanocarrier formulations in improving bioavailability and therapeutic outcomes. Despite these advances, challenges related to toxicity, large-scale production and regulatory approval remain. Overall, nanocarrier-based systems represent a versatile and promising platform for enhancing drug bioavailability and advancing modern pharmaceutical therapies.

Keywords: nanocarriers; drug bioavailability; drug delivery systems

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1. Introduction

A key challenge in modern pharmaceuticals is the poor bioavailability of many drug candidates, which significantly contributes to the high failure rate in drug development. Despite advances in drug discovery, over 90% of compounds fail during clinical development, with many of these failures being attributed to unfavorable biopharmaceutical properties rather than a lack of pharmacological activity [1]. Key limitations include poor aqueous solubility, inadequate membrane permeability, rapid metabolism and active efflux by transporters. These factors restrict drug absorption and reduce the amount of drug that reaches the systemic circulation [1]. These issues are particularly critical for orally administered drugs, for which dissolution in gastrointestinal fluids and transport across the intestinal epithelium are essential for therapeutic efficacy. Furthermore, conventional drug delivery systems frequently exhibit low solubility, poor absorption and instability in vivo, which further contributes to reduced bioavailability and suboptimal therapeutic outcomes [1,2]. Bioavailability is defined as the extent to which a drug administered in its original form reaches the systemic circulation and is therefore available to exert its therapeutic effect. This process is governed by the collective pharmacokinetic processes

of absorption, distribution, metabolism and excretion (ADME). Low bioavailability can result from several factors, including insufficient solubility, limited permeability across biological membranes and extensive first-pass metabolism, all of which reduce the fraction of the administered dose that becomes systemically available. These limitations have been overcome through the extensive development of nanocarrier-based drug delivery systems. Nanocarriers can enhance drug absorption and stability, as well as enable targeted delivery, thereby increasing bioavailability and therapeutic efficacy. Furthermore, nanocarriers can be engineered to control drug release and enhance biodistribution, minimizing side effects and improving overall treatment outcomes [3]. Although previous studies have extensively described individual nanocarrier types and their applications in drug delivery, this review provides an integrated perspective on the relationship between nanocarrier design and drug bioavailability. Specifically, it examines how the physicochemical properties and composition of nanocarriers, drug-loading strategies, routes of administration, and interactions with biological barriers influence drug absorption and, consequently, pharmacokinetic and pharmacodynamic outcomes. Beyond summarizing current progress in lipid-based, polymeric, inorganic, and hybrid nanocarrier systems, this review critically considers the factors responsible for variability in their effects on bioavailability and therapeutic performance. Attention is also given to the challenges that limit clinical translation, including safety, biological interactions, formulation stability, reproducibility, and scale-up. By integrating these aspects, this review aims to provide a framework for understanding the relationship between nanocarrier characteristics and in vivo drug performance and to identify priorities for the development of safer, more effective, and clinically translatable drug delivery systems.

In this review, drug delivery system (DDS) refers broadly to systems designed to transport therapeutic agents, whereas nanocarrier refers specifically to nanoscale structures used for drug delivery. The term nanoparticle is used when referring to the physical or physicochemical properties of particulate nanostructures. These terms are used consistently throughout the manuscript.

2. Types of Nanocarriers

Nanocarriers are nanoscale drug delivery systems typically ranging from 1 to 1000 nm in size. They are engineered to transport and deliver therapeutic agents within the body in a controlled and targeted manner. Composed of materials such as lipids, polymers, or inorganic substances, they can encapsulate, absorb, or chemically bind drugs. Modifying their size, surface properties, and composition can enhance drug solubility, protect active compounds from degradation, improve absorption across biological barriers, and enable site-specific delivery. These features contribute to increased bioavailability, reduced toxicity, and improved therapeutic efficacy compared to conventional drug delivery systems. The main types of nanocarriers discussed in this review are illustrated in Figure 1.

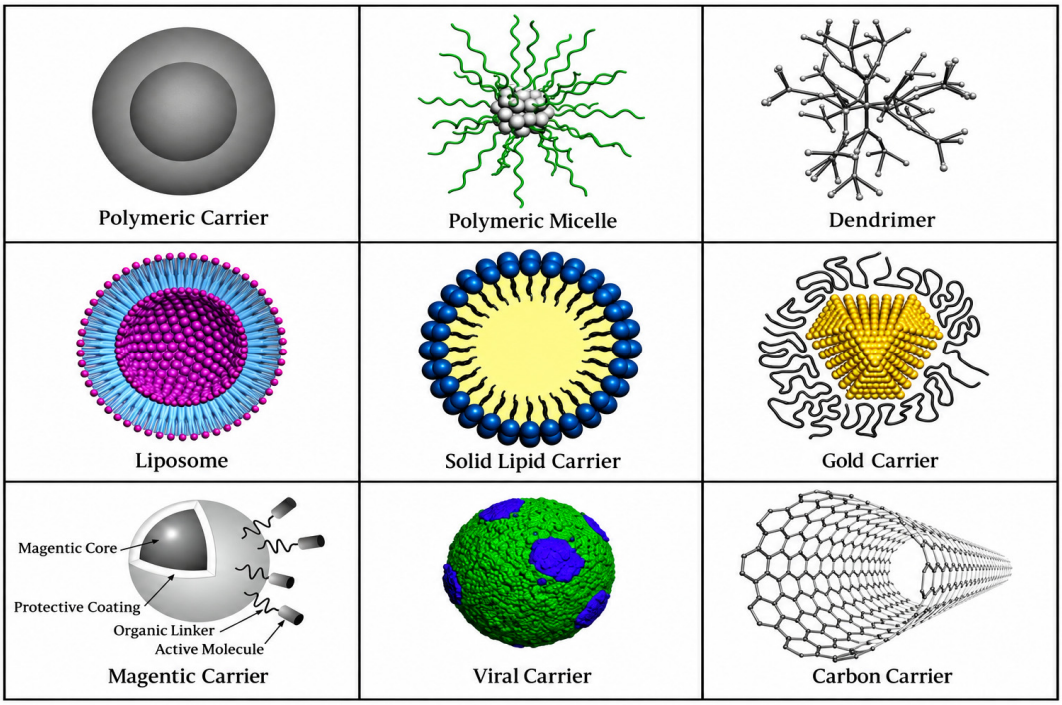


Figure 1. Different types of nanocarriers used in drug delivery systems [4].

2.1. Lipid-Based Nanocarriers

Lipid nanocarriers or lipid nanoparticles (LNPs) are delivery systems that can transport drugs or genetic material (siRNA, mRNA, and DNA [5]) into the body [6]. These vesicles are usually between 10 and 100 nm in size [7]. In treating a variety of diseases, LNPs have shown remarkable therapeutic efficacy in delivering both hydrophobic and hydrophilic drugs [5]. A doxorubicin-loaded liposome was one of the first nanodrugs used for cancer treatment. In addition to their low toxicity, high biocompatibility and biodegradability, liposomes exhibit high encapsulation efficiency and can reduce adverse effects through targeted drug delivery [5,6]. The creation of lipid nanocarriers requires the selection of many parameters and characteristics. The appropriate parameters depend on the raw materials and preparation conditions [6]. Lipids used in carriers can be synthetic and/or natural [8]. Natural lipids are typically sourced from microorganisms (e.g., algae, yeast, bacteria), plants, humans (tissues, cells), and animals (tissues, cells or their products) [6]. Important lipid components in these systems include phospholipids, cholesterol, ionizable and cationic lipids (essential for nucleic acid delivery), and PEG-lipid (e.g., for stabilization). Cholesterol controls membrane fluidity and stability, whereas, phospholipids provide the structural foundation, mainly in liposomes [7]. The choice and source of the lipids used have a major impact on composition, structure, effectiveness, stability, drug-loading capacity, and biocompatibility of nanocarriers [6]. Additionally, modifiers are added to the external part of lipid nanoparticles, such as polymers and peptides, to impart additional functional features [8]. The preparation technique (both high and low energy) significantly affects the structure of the platform. LNPs manufacturing methods include microemulsion, supercritical fluid, solvent evaporation, microfluidics, high-pressure and ultrasonic homogenization [6]. The majority of nanocarriers used in clinical trials are lipid-based [8]. LNPs are widely used in clinical therapies in the form of vaccines and cancer drugs (as chemotherapeutic agents delivered to tumor sites), as well as in gene therapy and genome editing applications [7].

2.1.1. Liposomes

Liposomes are small spherical nanostructures discovered in 1965 [5,6,9]. Their core–shell composition consists of an internal aqueous core and an amphipathic (unilamellar or multilamellar) phospholipid double layer [5–8,10–12]. The phospholipid bilayer is around 4–5 nm (one or more bilayers are possible [12]), while the aqueous compartment can range in size from 30 nm to micrometers [6]. Liposomes may transport small and large lipophilic and hydrophilic molecules, such as nucleic acids, proteins, and imaging agents [8]. Hydrophilic active substances are typically trapped in the aqueous phase of the core, while hydrophobic drugs are encapsulated in the hydrophobic bilayers of the shell [5,8,11]. The main components of liposomes are natural or synthetic phospholipids, which are biodegradable and biocompatible because of their similarity to the lipids found in cell membranes [8]. Phospholipids are composed of a hydrophilic head and non-polar hydrophobic tails (two fatty acid sequences with 10–24 carbon atoms) [13]. Phospholipids that are used to produce liposomes include: phosphatidylethanolamines (PEs), phosphatidylserines (PSs), phosphatidylcholines (PCs), phosphatidic acid (PA), and phosphatidylglycerols (PGs) [8,14]. They are typically chosen based on how they affect pharmacodynamics, encapsulation, drug stability, pharmacokinetics, and release [8]. Also, they can determine the liposome's surface charge (neutral, anionic, or cationic) [15]. Cholesterol is another crucial component that provides stability to these structures [7,13]. Because of the biocompatibility of liposomes, ease of production, stability in biological environments, high drug loading, and safe ingredients (reduced drug toxicity [11]), they are an important drug delivery system [6]. If these nanocarriers display changes in their organization with pH or temperature, they may become reactive. For example, in healthy tissues, pH-sensitive liposomes remain stable, but in tissues with a pH lower than 7.4 they become unstable (absorbed bioactive material will be released) [13]. Liposomes have some disadvantages such as limited stability and short circulation times. To overcome these limitations liposomes can be modified by adding anti-fouling polymers, e.g., polyethylene glycol (PEG) [8,12], which can increase the blood half-life of a liposome drug up to 45 h (regardless of dose) [15]. Although PEG has a long-established record of pharmaceutical utility and general safety, immediate-type hypersensitivity reactions to PEG and PEG-containing products have been documented for several decades [16,17]. A comprehensive review identified 37 reported cases of immediate-type PEG hypersensitivity between 1977 and 2016 [17], indicating that clinically recognized PEG hypersensitivity is uncommon relative to the widespread exposure to PEG-containing products. Thus, PEG hypersensitivity should be considered a rare but potentially serious reaction in susceptible individuals rather than a general limitation of PEGylated formulations [16,17]. Importantly, PEGylated liposomal formulations remain well-established drug-delivery systems with several clinically approved products and are generally well tolerated, although infusion-related hypersensitivity reactions may occur in a subset of patients [18]. These considerations have encouraged the investigation of alternative surface-modifying materials, including polysialic acids, glycoproteins, zwitterionic polymers, and polysaccharides [8]. Liposome formulations have been used in studies for gene delivery, treatment of malaria, several types of cancer, including chemotherapy applications, depression, and many other disorders [11,15].

2.1.2. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are usually made of one or more lipids which are solid both at room and body temperature [6,7,10,19]. These nanoparticles can be divided into three categories: solid solution type (homogenous matrix); drug-enriched shell model; drug-enriched core model [5,6,19]. Cold homogenization, in which a solid drug is evenly distributed throughout a lipid matrix without the use of surfactants, creates the solid solu-

tion model of SLNs. In the drug-enriched shell model, the drug is encapsulated within a core–shell structure created by thermal homogenization. During cooling and recrystallization, a lipid core forms, causing the drug to migrate into the lipid phase. The drug-enriched core model is formed by dispersing drug in melted lipid, leading to supersaturation upon cooling. As the lipid recrystallizes, it forms a membrane-like shell around the drug-rich core [19]. For the synthesis of SLNs, steroids, waxes, free fatty alcohols or acids, and (mono-, di- or tri-)glycerides are frequently used [12,20]. The active substance may be integrated into shell, core, or matrix [12]. These nanoparticles have several advantages, including small size, controlled release, very good drug protection, improved physical stability of hydrophobic drugs, tunable properties through modification of lipid composition) [6,8], low cost and non-toxicity (less toxic than polymeric nanocarriers) [10]. Compared to liposomes, these particles have better physical stability because of their solid lipid core matrix, which is stabilized by surfactants [7,20] (in concentrations from 0.5% to around 5% [19]) or polymers (hybrid polymer–lipid nanoparticles) [10]. Due to variations in formulations, preparation methods, and manufacturing temperatures, solid nanoparticles may have different characteristics [19]. Schematic representation of solid lipid nanoparticles and their target-specific interactions is shown on Figure 2.

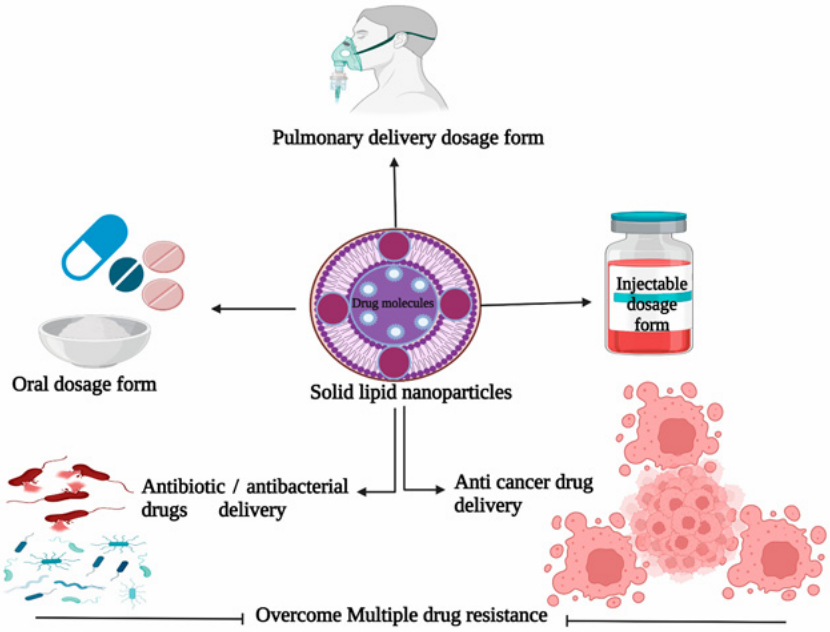


Figure 2. Schematic representation of solid lipid nanoparticles and their target-specific interactions [19].

One of the main problems with this type of lipid nanoparticle is limited drug loading capacity, and low long-term drug retention (polymorphic transition resulting in drug expulsion from the structure). In order to eliminate these problems and improve stability, part of the solid lipids were replaced with liquid lipids or solubilizers. As a result of this modification, nanostructured lipid carriers were formed [6–8], which are discussed in the section below. SLNs have been extensively studied for use in gene transfer, antibacterial, anticancer, and vaccine applications [11].

2.1.3. Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are drug delivery systems that are made with improved features, by changing part of the solid lipid component of SLNs with liquid lipids (oils) in different proportions [5,6,10,19]. For this purpose, different types of lipids are used, including fatty acids, steroids, triglycerides, partial glycerides, and waxes [6]. Their

models are divided based on the arrangement of lipids and drugs within the structure: imperfect type (mixing of spatially different lipids); amorphous type (structureless solid matrix); multiple type (drug contains oil) [5,6,13,19]. Liquid lipids cause structural flaws in solid lipids, resulting in a less ordered crystalline arrangement [19]. Therefore, while polymorphism and lipid crystallinity problems in SLNs have been mostly eliminated, NLCs exhibit larger loading capacities, better stability, and better drug retention [6,7,11]. Nanostructured carriers are known as platforms of both water-soluble and lipid-soluble substances [13]. Despite their important qualities, NLCs have also been linked to cytotoxic effects, limited stability, irritation, and surfactant sensitization [16].

2.2. Polymeric Nanocarriers

Polymeric nanoparticles (PNCs) are colloidal particles made from natural or synthetic materials, monomers, or preformed polymers (which enable a wide range of PNC shapes and properties) [15,21]. Natural PNCs are protein-based or polysaccharide polymers, e.g., gelatin, collagen, albumin, alginate, chitosan, agarose, and hyaluronic acid (HA) [15]. On the other hand, examples of synthetic polymers include PEG, chitosan, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(dimethylsiloxane) (PDMS), poly(caprolactone) (PCL), and poly(ortho esters) (POEs) [15,21–23]. Compared to natural polymeric nanocarriers, synthetic polymers are more appealing for drug delivery systems because they are more repeatable and exhibit lower batch-to-batch variation in molecular weight (MW) [15]. It is possible for active substances to be attached to the PNC surface (by drug adsorption), chemically conjugated to the polymer, trapped in the polymer matrix, or encapsulated within the core [21,24]. This makes it possible to deliver a variety of drugs (hydrophilic, hydrophobic), but also substances with varying molecular weights, e.g., biological macromolecules, vaccines, proteins, and small molecules. They are biocompatible and relatively straightforward to prepare (relatively simple formulation requirements). The loading efficacy and release kinetics of polymeric nanoparticles can be carefully regulated by composition, stability, responsiveness, and surface charge. PNCs are water soluble, stable during storage, biocompatible, biodegradable, and biomimetic. The main disadvantages of these carriers are increased risk of aggregation and toxicity [21]. Several methods, including emulsification, nanoprecipitation, ionic gelation and microfluidics are used to produce them [15,21]. Polymeric nanocarriers can be divided (based on how they are prepared) into nanocapsules (spaces with a polymeric shell/membrane surrounding them) and nanospheres (solid matrix systems) [15,21,24].

2.2.1. Polymeric Micelles

Polymeric micelles consist of a hydrophilic (polymeric) core and a hydrophobic coating, which makes them different from lipid micelles (hydrophobic core) [15,21]. This structure improves drug circulation time and is particularly beneficial especially for hydrophilic drugs (better protection) [21]. Micelles are relatively small; their sizes are usually between 20 and 100 nm [15]. Poly(ethylene glycol) (PEG) is the most widely used hydrophilic polymer because it provides effective protection against biological degradation and offers surface stabilization [15]. Polymeric micelles are capable of loading a wide range of molecules, from small molecules to large proteins [21]. Polymeric micelles exhibit improved properties compared with traditional surfactant micelles, e.g., more stability, longer blood circulation time. They are also characterized by increased drug bioavailability across barriers, high drug loading capacity, targeted delivery and controlled and sustained drug release [15]. Polymeric micelles can be loaded with drugs by physical and chemical (covalent attachment) methods [20].

2.2.2. Dendrimers

Dendrimers are highly branched, tree-like nanoparticles made up of three key components: central core, several branches and terminal groups providing a modifiable surface (which overall creates a complex 3D structure) [20,21,25,26]. The inner and outer layers are very similar and structurally repetitive [25]. Each successive step of branching defines a new dendrimer generation (G), with increasing generation number resulting in distinct structural and functional properties. Lower generations (G1–G3) exhibit greater accessibility but lower diffusion, whereas higher generations (G4–G6) have a large loading capacity [27]. Figure 3 shows schematic representation of dendrimer structure and drug loading strategies.

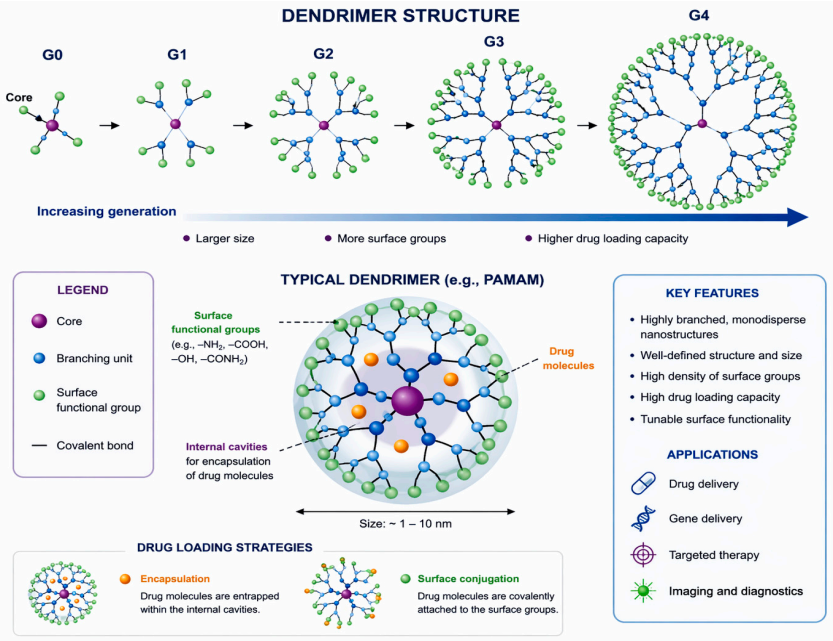


Figure 3. Schematic representation of dendrimer structure and drug loading strategies.

The mass, size, shape, and surface chemistry of dendrimers can be manipulated in order to obtain structures with selected properties [21]. Additionally, they have a high surface/volume ratio, and the capacity to contain a significant amount of drug (or contrast agents) inside or on their surface [22], because of functional groups on the outside [21]. They can increase bioavailability and solubility of hydrophobic medications [26]. One of the primary obstacles is controlling dendrimer size and morphology, which can impact pharmacokinetics and distribution and may also influence toxicity and possibility of interactions with the immune system [22]. Drug delivery systems consisting of dendrimers can deliver nucleic acids and small molecules, for which poly(ethylenimine) (PEI) and poly(amidoamine) (PAMAM) are often used [20,21]. Additionally, they are used in delivery of genes, molecular sensors, bioimaging, and enzyme mimics [26].

2.3. Inorganic Nanocarriers

Inorganic nanocarrier materials are used in various drug delivery applications (e.g., anticancer, antibacterial, antioxidant [23]), photothermal therapies, and imaging applications [21]. They are used in inorganic components like silica, calcium phosphate, iron, silver, titanium, zinc, and gold [21,28]. They can be further divided into three categories, i.e., magnetic (iron oxide, gold, silver), ceramic (silica, titanium oxide, alumina), and semiconductor (zirconium dioxide, zinc oxide) [23]. To obtain these particles, various substances are used, both of natural and synthetic origin, depending on the synthesis method. In the

case of chemical methods, they require substances such as dimethyl formamide and sodium borohydride (at high temperature). By contrast, safer and less toxic natural substances include plant parts or microorganisms (bacteria and fungi), which make a natural method of preparation simpler, faster, more stable, and more environmentally friendly than other ones [28]. Furthermore, due to the properties of the base material, inorganic nanocarriers can demonstrate catalytic, thermal, physical, electrical, radioactive, plasmonic, magnetic and optical capabilities [21,29]. The majority of them are stable, small (so they can penetrate membranes both physiological and biological, which are typically impermeable to other macromolecules [28]), and exhibit higher loading capacity [21,22,29]. However, low solubility and toxicity issues, particularly in formulations, including heavy metals, restrict their clinical use [21]. To improve performance of metal nanoparticles, they are coated with PEG or their surface is functionalized by substances that give them targeting properties (e.g., in tumor treatment). These nanocarriers can be synthesized by various methods including microemulsion, polyol method, laser ablation, chemical reduction, and sol-gel [28].

2.3.1. Gold Nanoparticles

Gold nanoparticles (AuNPs) can have a variety of shapes, which are divided by dimensions, including: nanorods, nanowires (1D), nanoplates (2D), nanostars, and nanopods (branched structures) [21,22,29]. Gold nanodrugs have photothermal and imaging (optical) capabilities because of their free electrons (on the surface with a large surface-to-volume ratio [30]) that continuously oscillate at a frequency which depends on their size and shape [21,22]. They are also easily functionalized and can be loaded with targeting and/or imaging agents (e.g., MRI agents, fluorophores [30]), but also with chemotherapeutics, peptides, proteins, siRNAs, and pharmaceuticals [21,28,30]. Applying modifications can give them additional delivery properties, which is advantageous in diagnostics, treatment, and targeting (even simultaneously with real-time monitoring) [21,30]. Unfortunately, they may cause side effects due to unwanted interactions with biological molecules despite being known for their biocompatibility. In order to minimize the toxicity of nanocarriers, scientists add biocompatible polymers or proteins [30].

2.3.2. Magnetic Nanoparticles

Magnetic nanoparticles are known for their potential (at specific sizes) as drug delivery systems (DDSs), contrast agents, thermally mediated therapies and in cancer diagnostics [18,27]. They are composed of iron oxide, i.e., hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) [21,29]. In the case of paramagnetic nanoparticles, iron oxide is put into the core, while other substances (e.g., silica, gold, phospholipids, peptides, fatty acids, surfactants, and polymers) may be used as coatings [26]. Magnetic nanocarriers can be transported using an external magnetic field that is directed to specific anatomical sites [22]. They are also characterized by ease of functionalization, biodegradability, low-cost synthesis, and antibacterial properties [23]. Nevertheless, these nanocarriers have major limitations, e.g., toxicity and being unable to accumulate in high enough concentrations for efficient imaging or drug delivery. These problems can, however, be mitigated by the addition of stimuli-responsive agents and surface modification. These modifications make iron nanoparticles stable and biocompatible, but more importantly, they can act directly and in a controlled manner on cancer cells while reducing systemic toxicity [30,31]. Potential applications of magnetic nanoparticles are presented on Figure 4.

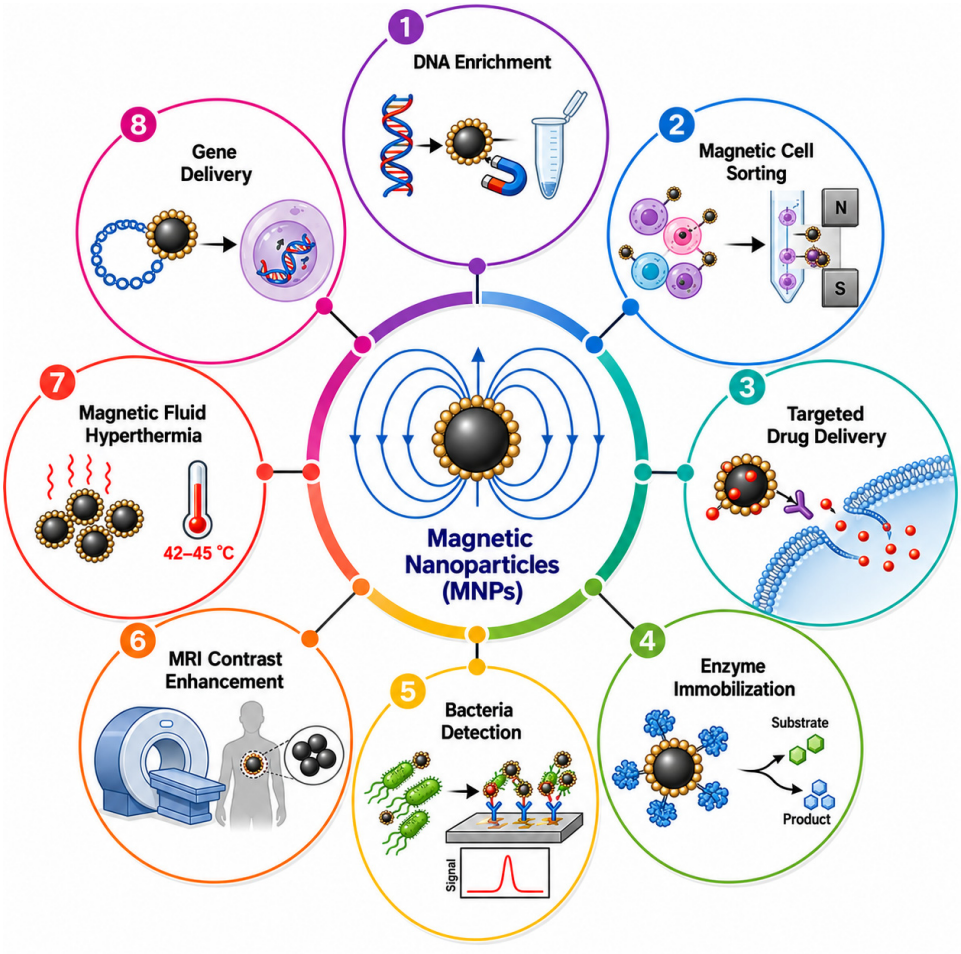


Figure 4. Applications of magnetic nanoparticles [31].

2.3.3. Carbon-Based Inorganic Nanocarriers

Carbon-based nanomaterials (CBNs) are a distinct class of inorganic nanocarriers, characterized by unique allotropic structures, nanoscale dimensions and exceptional physicochemical properties. Materials in this class include carbon nanotubes (CNTs), graphene, fullerenes and related derivatives. They have attracted considerable interest in the field of nanomedicine thanks to their potential as efficient drug delivery systems. These materials are composed of sp^2-hybridized carbon atoms arranged in ordered nanostructures, which distinguishes them from classical organic or polymeric carriers and supports their classification as inorganic systems. The diversity of carbon allotropes allows for the development of nanocarriers with adjustable morphology and functionality, making them suitable for use in biomedicine [32]. Carbon nanotubes (CNTs) are among the most extensively studied carbon-based nanocarriers. Structurally, CNTs are cylindrical nanostructures formed by rolling graphene sheets into seamless tubes with nanometer-scale diameters. They are classified into single-walled (SWCNTs) and multi-walled (MWCNTs) depending on the number of graphene layers [33]. Figure 5 shows carbon nanotube structure. (a) Single-walled CNTs. (b) Multi-walled CNTs.

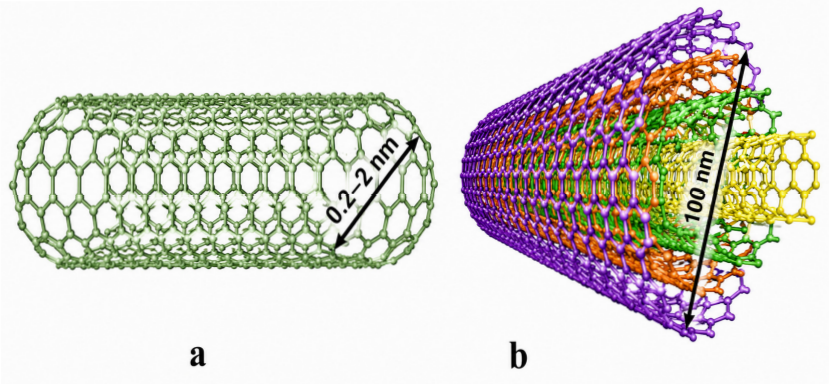


Figure 5. Carbon nanotube structure. (**a**) Single-walled CNTs. (**b**) Multi-walled CNTs [34].

CNTs exhibit exceptional mechanical strength, electrical conductivity, and thermal stability due to their unique carbon–carbon bonding and one-dimensional structure [35]. Their extremely high surface-to-volume ratio provides a large interface for molecular interactions, which is essential for drug loading [36]. CNTs can adsorb drugs through π–π stacking interactions, hydrophobic interactions, and electrostatic forces, enabling the loading of both small molecules and biomacromolecules such as nucleic acids. This high loading efficiency enhances cellular uptake and facilitates intracellular delivery [37]. Additionally, CNTs have demonstrated the ability to penetrate cellular membranes and, when appropriately functionalized, cross biological barriers such as the blood–brain barrier. Carbon-based inorganic nanocarriers also exhibit multifunctional properties that extend beyond conventional drug delivery. Their intrinsic optical and electronic characteristics allow their use in theragnostic applications, combining drug delivery with imaging and therapeutic modalities. CNT-based systems have been applied in cancer therapy to enhance drug accumulation at tumor sites and improve therapeutic efficacy while reducing systemic toxicity [37]. Furthermore, their ability to enable controlled and stimuli-responsive drug release makes them promising platforms for advanced therapeutic strategies [38]. Despite these advantages, the clinical translation of carbon-based nanocarriers is limited by several challenges. Their potential cytotoxicity and long-term biocompatibility are important concerns as these properties depend on size, shape and surface chemistry. The formation of a protein corona in biological environments can also affect biodistribution, cellular uptake and the immune response [34]. When nanoparticles are exposed to biological fluids, proteins adhere to their surface to form a dynamic protein corona, which can alter their surface properties and biological identity. The composition of the protein corona has been associated with changes in blood circulation time, biodistribution, cellular uptake and intracellular localization [39]. Protein adsorption can also affect the effective particle size. Corona formation is commonly manifested by an increase in mean nanoparticle diameter due to the deposition of a protein layer on the particle surface [40]. Protein-mediated aggregation can also increase the hydrodynamic radius under specific conditions, depending on protein concentration, identity and ionic strength [41]. Importantly, corona formation can interfere with ligand-mediated targeting. In antibody-conjugated liposomes, both in vitro- and in vivo-formed coronas significantly reduced receptor binding and cellular internalization, though the in vivo corona did not completely abolish targeting [40]. Similarly, Zhang et al. found that the targeting capacity of ligand-modified nanoparticles was lost after in vitro plasma incubation but was partially retained after in vivo corona formation, and that the composition of the in vitro and in vivo coronas differed [42]. These observations suggest that results obtained with an in vitro corona cannot necessarily be extrapolated directly to an in vivo situation [40,42].

Surface modification can reduce protein adsorption. PEGylation is widely used for this purpose and can reduce nonspecific protein adsorption, although it does not completely

suppress it. Zwitterionic coatings provide another antifouling strategy. In the model system studied by Debayle et al., sulfobetaine-coated nanoparticles showed no detectable hard or soft protein corona, whereas phosphorylcholine- and carboxybetaine-coated nanoparticles showed reversible protein adsorption or partial aggregation [43]. Zwitterionic modification of ultrasmall iron oxide nanoparticles has also been shown to strongly reduce serum protein corona formation in vitro [44]. Biomimetic approaches, including cell membrane decoration, endogenous protein coatings, and biomolecule modification, have additionally been investigated as strategies for controlling protein-corona formation or composition [45]. Therefore, evaluation of protein-corona formation under biologically relevant conditions, including consideration of differences between in vitro and in vivo environments, is important when assessing the biological performance of nanocarriers [40,42]. Furthermore, ensuring the safety and efficacy of carbon-based nanocarriers requires careful design and surface modification to prevent aggregation and persistence in biological systems.

2.4. Hybrid Systems

To improve nanomaterials—i.e., overcome limitations or increase carrier multifunctionality—hybrid nanoparticles were created [5]. Polymer–lipid nanocarriers (PLNs) are classified according to their structural configurations, which include different lipid and polymer combinations [6]. They consist of three main components [46]. The best-known configuration of them is made of an exterior layer of PEG lipid and interior layer of lipid that surrounds a polymeric core [5,46]. PEG stabilizes and protects PLNs from immune system-mediated degradation. The middle monolayer protects the core and acts as a molecular barrier and can reduce drug leakage [46]. They combine the properties of both lipids and polymers and are characterized by higher biocompatibility, bioavailability, excellent physical stability, extended release (and circulation time), and higher permeability through membranes [5,6,46]. Both hydrophobic and hydrophilic medications can be delivered with hybrid PLNs [46]. Lipid-coated silver nanoparticles (lipid-AgNPs), liposome–gold nanoparticles, and lipid–aluminum nanoparticles are a few examples of hybrid lipid–inorganic nanoparticles. The combination of metals and lipids in nanoparticles increase biocompatibility, stability, and endocytosis efficiency [5]. Among the more advanced hybrid nanocarrier systems developed for drug delivery applications are virus-based platforms and carbon dots (CDs), particularly carbon–organic hybrid systems.

2.4.1. Viral Carriers

Viral nanocarriers are a type of hybrid nanocarrier derived from naturally occurring viruses or engineered virus-based systems. Examples include viral nanoparticles (VNPs) and virus-like particles (VLPs). These structures consist of self-assembled protein capsids that form highly ordered, monodisperse nanostructures with a defined size and geometry. VLPs are non-infectious due to their lack of a genome, while still maintaining the structural features required for cargo delivery [47]. A key characteristic of viral nanocarriers is their innate capacity to transport biological cargo; viruses have evolved to naturally deliver nucleic acids into host cells. This capability is exploited in nanomedicine for the delivery of drugs, proteins and nucleic acids. Cargo can be encapsulated within the capsid, adsorbed onto its surface or chemically conjugated to the functional groups present on the protein shell. This enables a variety of loading strategies. Viral nanocarriers exhibit several properties that make them well-suited to biomedical applications. These include biocompatibility, biodegradability and structural uniformity, which result from genetically encoded assembly. Their multivalent protein surfaces allow targeting ligands to be attached, enabling site-specific delivery to selected tissues or cells [47,48]. Furthermore, viral capsids can be modified through genetic engineering or chemical functionalization to improve targeting efficiency and therapeutic performance. An important subgroup of viral nanocarriers are

viral vectors used in gene therapy. Examples include adeno-associated viruses (AAVs), lentiviruses and adenoviruses. These systems enable highly efficient gene delivery and can achieve long-term expression of therapeutic genes in target cells. AAV-based vectors in particular are widely used due to their low pathogenicity, broad tissue tropism and ability to sustain transgene expression, making them one of the most successful platforms in clinical gene therapy [49,50].

2.4.2. Carbon Dots

Carbon dots (CDs) are a class of zero-dimensional, carbon-based nanomaterials typically measuring less than 10 nm. They are characterized by a carbonaceous core composed of sp^2/sp^3 hybridized carbon, as well as a surface rich in functional groups such as carboxyl, hydroxyl and amino moieties [51,52]. This core–shell structure determines their physicochemical and biological behavior, as the functionalized surface governs interactions with biomolecules and enables further chemical modification [51]. Due to their abundant surface functional groups and carbon-based composition, CDs exhibit high water solubility, low toxicity, and good biocompatibility [52,53]. The surface chemistry of CDs allows them to be extensively functionalized and conjugated with therapeutic agents, targeting ligands and biomolecules. This supports their use as nanocarriers [51,53]. Their small size and high surface-to-volume ratio facilitates efficient cellular uptake and drug loading, and functionalized systems enable targeted, controlled drug delivery. Furthermore, CDs can act as multifunctional platforms, combining drug transport with real-time imaging thanks to their fluorescent properties [53].

2.5. Supramolecular Molecular Containers

In addition to lipid-, polymer-, inorganic- and hybrid-based nanocarriers, supramolecular systems containing defined molecular cavities are another type of structure that has been investigated for drug encapsulation and delivery. These systems generally rely on host–guest recognition, whereby a guest molecule is accommodated within a pre-organized cavity via non-covalent interactions. Depending on their molecular architecture, such hosts can be cyclodextrins, cucurbiturils, calixarenes, pillararenes, cavitands, carcerands or self-assembled molecular capsules [54–59]. Unlike conventional nanoparticles, individual molecular containers are not necessarily nanoparticles themselves. However, they can form host–guest complexes directly with pharmaceuticals or participate in the formation of larger supramolecular assemblies used as drug delivery systems [54–56,59].

The accessibility and degree of enclosure of the internal cavities of molecular containers differ substantially. Cavitands have open-ended cavities that can bind complementary molecules and ions, whereas carcerands have more enclosed cavities with portals that strongly restrict the exchange of guests. Hemicarcerands have comparatively larger portals, and self-assembled molecular capsules form enclosed cavities through the reversible non-covalent association of two or more molecular subunits [54]. Consequently, molecular container architectures can range from relatively open, concave, bowl-shaped receptors to capsules that substantially surround the guest molecule. The dimensions, shape, and chemical environment of the cavity determine which guest molecules can be accommodated, and how easily they can be released [54].

2.5.1. Calixarenes

Among macrocyclic molecular containers, calixarenes are bowl- or cone-shaped hosts composed of phenolic units connected by methylene bridges. Their cavities can form inclusion complexes with suitable guests through several non-covalent interactions, including hydrophobic interactions, hydrogen bonding and π–π interactions. Drugs can be associated

with calixarene-based systems through host–guest complexation, encapsulation, solubilization or adsorption. Functionalized calixarenes can also participate in the formation of larger structures, including micelles, vesicles, hydrogels and other nanoscale assemblies. Therefore, the macrocyclic cavity can represent one drug-binding site, while additional loading regions may become available after supramolecular self-assembly [55,56].

2.5.2. Pillararenes

Pillararenes constitute another family of synthetic macrocyclic hosts. Their relatively rigid, electron-rich and hydrophobic cavities allow reversible accommodation of various guest molecules, including pharmaceutical compounds. Pillararene-based delivery systems can be produced through direct host–guest complexation as well as through self-assembly of supramolecular amphiphiles and amphiphilic supramolecular polymers. Such assemblies can generate larger structures, including vesicles, micelles and nanoparticles. Chemical modification of the pillararene framework can alter properties such as water solubility and amphiphilicity and can introduce components responsive to environmental conditions. Systems described in the literature have been investigated for the delivery of different types of cargo, including anticancer drugs, antibiotics, siRNA and insulin [57,58]. Drug release from particular pillararene-based systems has also been designed to respond to conditions such as changes in pH, reactive oxygen species, enzymes, thiols or light; however, these mechanisms depend on the chemical design of the individual carrier [58].

2.5.3. Cucurbit(n)urils

Cucurbit(n)urils [CB(n)] are rigid, macrocyclic hosts that are made up of glycoluril units which are connected by methylene bridges. They contain a hydrophobic cavity and carbonyl-lined portals, which enable the formation of host–guest complexes with a variety of neutral and positively charged compounds. Different homologues, including CB(5), CB(6), CB(7), CB(8) and CB(10), have cavities of different dimensions. Due to their ability to bind pharmaceutical molecules, cucurbiturils have been investigated as molecular containers for drug delivery and controlled release [59,60].

Experimental evidence supporting this application has been obtained for CB(7). Hettiarachchi et al. examined CB(5), CB(7), and several related CB(n)-type molecular containers in cell-based experiments. The investigated containers exhibited high cellular tolerance at concentrations of up to 1 mM in the tested kidney-, liver- and blood-derived cell lines. CB(7) was internalized by macrophages and ethambutol encapsulated within CB(7) retained activity against intracellular mycobacteria that was comparable to that of the unbound drug under the investigated conditions. These observations provided proof of concept that a drug bound within a cucurbituril container can subsequently become available to its intracellular target [59]. However, these findings relate to specific experimental systems and should not be generalized to all cucurbituril derivatives or therapeutic compounds.

Another application of cavity-containing supramolecular hosts is the in vivo sequestration of pharmaceuticals and toxic compounds. This approach differs conceptually from conventional drug delivery methods. Rather than transporting a therapeutic compound to its target, the host binds a circulating compound, thereby reducing its freely available concentration. Cyclodextrins, calixarenes, acyclic cucurbiturils and pillararenes have been investigated for this purpose. Reported targets include neuromuscular blocking agents, anesthetics, illicit drugs, heparin, and selected toxic compounds [60,61]. Host–guest complexation can influence sequestration-relevant parameters, including the distribution, circulation and elimination of the bound compound. Therefore, supramolecular sequestration is a pharmacokinetic strategy that uses molecular recognition to alter the availability of an unwanted guest rather than antagonizing its biological receptor directly [60].

The development of supramolecular antidotes demonstrates the potential of this concept for translation into practice, although the degree of advancement in experiments and clinical trials varies considerably between individual systems. Cyclodextrins, cucurbiturils and their acyclic derivatives, as well as calixarenes and pillararenes, have all been evaluated as hosts for potentially harmful molecules [60,61]. Consequently, cavity-based supramolecular systems can be considered a complementary approach to conventional nanocarriers. Depending on their structure and application, host–guest interactions can be used to either encapsulate and deliver therapeutic molecules or sequester undesirable compounds. However, their suitability for biomedical use depends on host–guest affinity and selectivity, aqueous solubility, guest-exchange behavior, biocompatibility, and the pharmacokinetic properties of the free host and the resulting host–guest complex [59–61].

3. Nanoparticle Bioavailability Enhancement

3.1. Bioavailability Determinants

Bioavailability is an important factor affecting the performance of pharmacological therapy because it influences the amount of the drug that is delivered to systemic circulation (in an unchanged, active form) from the selected drug delivery system (topical, oral, rectal, parenteral) [62–64]. Several factors influence overall pharmaceutical bioavailability, namely the chemical and physical properties of the selected drug, the mode of transport (including the drug-delivery platform), interactions with other substances (both in the drug formulation and in the body), absorption, distribution, metabolism, and final excretion [63,64]. Bioavailability is the degree to which absorption of the drug occurs (passive, facilitated and active diffusion, as well as endocytosis) [62,65]. The drug needs to pass, e.g., through the gastrointestinal tract (GI tract), skin or respiratory system into the bloodstream [63]. Passive diffusion is a movement of particles from a region of higher concentration to one of lower concentration. The penetration of drugs with hydrophilic properties through biological membranes is very limited (in contrast to hydrophobic substances). In facilitated diffusion, movement is driven by an electrochemical gradient, and proteins are involved as carriers. Active diffusion is a movement against gradient, and drug molecules need to be selected very specifically for this type of transport [62]. After the drug is absorbed into the systemic circulation, the next stage begins, which is distribution (dispersion of the substance to appropriate locations, such as tissues and organs). Next, because of enzymes mostly in the liver, drug metabolism occurs, transforming drugs into more soluble metabolites, and elimination of the substances from the body follows [63]. Drug formulation (such as added excipients and formulation methods), solubility, stability, and hydrophilic or hydrophobic properties are a few examples of drug characteristics crucial to their bioavailability [63]. Additionally, drug absorption is also influenced by physiological factors such as organ blood flow, intestinal microflora, and biological barriers, including the blood–brain barrier (BBB) [11,29,32]. Other factors that can reduce bioavailability include, for example, the quantity of hydrogen donors, heavy atoms, drug-molecule interactions (which result from the reaction or formation of complexes and aggregates), and certain compounds, such as tetrazoles, benzoquinones, and aminopyridines. On the other hand, factors that may increase bioavailability include the quantity of hydrogen acceptors, small atoms (with minimal molecular weight), and substances (azide, salicylic acid, or amide groups) [62]. One of the very important points to address when increasing bioavailability is the use of nanoparticles, described in the section below.

3.2. Nanocarriers for Improving Drug Bioavailability

Conventional drug formulations have relatively low bioavailability, which reduces their overall absorption by the body and ultimately affects their therapeutic efficacy [22]. Many

pharmaceuticals are rejected because of their unfavorable physiochemical properties [15]. Currently, nanocarriers provide an attractive substitute for conventional drugs by addressing various issues related to drug administration [6]. Many of these systems are considered to exhibit improved properties due to their unique physicochemical characteristics, small size and potential for targeted delivery [22]. Drug delivery systems use nanocarriers to prolong drug absorption, drug solubility in blood (and water), and to reduce drug degradation, inactivation and eliminate drug aggregation [9]. An ideal delivery system based on nanocarriers should have a number of essential features. First, it should maximize drug bioavailability while maintaining controlled and predictable release kinetics. Equally important is the ability to selectively target specific tissues, which enhances efficacy and reduces off-target effects. The system should also minimize immunological responses to ensure safety and compatibility within the body. It must also support good patient compliance and have an adequate drug loading capacity. Lastly, an optimal system should be able to deliver a variety of treatments, including complex biomolecules and substances that are usually challenging, such as lipophilic and amphiphilic molecules [66,67]. Some nanocarriers can enter the smallest biological compartments because of the remarkable high surface-area-to-mass/volume ratio. The high surface-to-volume ratio and small size of nanoparticles can facilitate their penetration into small tissue compartments and promote their accumulation in tumors through the enhanced permeability and retention (EPR) effect [15]. However, certain nanocarriers exhibit limited ability to cross cell membranes [22]. Table 1 presents collected information regarding types of nanoparticles, their advantages, including effects on bioavailability, and limitations.

Table 1. Comparative overview of nanocarrier systems and their effects on bioavailability, including advantages and limitations.

Type of Nanoparticle	Factors Contributing to Enhanced Bioavailability	Other Positive Factors	Disadvantages
Liposomes	• Ability to encapsulate both hydrophobic and hydrophilic drugs [22,23,30] • Controlled and precise targeting to specific tissues/cells [14,23,30] • Protection from enzymatic degradation [14,22] • Ease of functionalization [22,23]	Biocompatibility [22,23,30], biodegradability [22,23], low toxicity [30], ability to carry large molecules [14]	High production cost, short half-life [14], low stability, relatively low encapsulation efficiency [29,68] (depending on formulation), high cost [68,69]
Lipid-based (SLNs, NLCs)	• Ability to encapsulate both hydrophobic and hydrophilic drugs [23,70] • Enhanced stability [23,68] and bioavailability [22] • Prolonged blood circulation (ligand-based targeting) [22,70] • Surface modifications [12,23]	Biocompatibility, biodegradability, easy functionalization, controlled release, stimuli-responsive behavior [23], loading capacity [22], non-toxic [29], safer, low cost [68]	Potential cytotoxicity [70], low drug incorporation efficiency, risk of gelation [68]
Polymeric (nanospheres, nanocapsules)	• Surface functionalization (e.g., targeting ligands) [25,26,70]; • Carrier for hydrophobic and hydrophilic drugs [22,69,70]; • Controlled and sustained release of drug [22,69]; • Protection from degradation [22,70]	Biodegradability, biocompatibility [22,70], ease of modification, high stability [69], intracellular release [71], water solubility [72]	Self-aggregation [70], unpredictable drug release in bloodstream [68], scalability issues [71], risk of degradation [72], toxic monomer accumulation [21]

Table 1. *Cont.*

Type of Nanoparticle	Factors Contributing to Enhanced Bioavailability	Other Positive Factors	Disadvantages
Dendrimers	• Targeted delivery (passive and active) [72]; • Surface functionalization [69]; • Carrier for hydrophobic, hydrophilic drugs [72]; • High water solubility [72]	Well-defined structure (size and shape), can be produced for specific applications, tunable architecture [69], high loading capacity [71]	High production cost [69], complex synthesis, limited clinical use [71]
Polymeric micelles	• Increased solubility of hydrophobic drugs (core-shell structure) [71]; • Targeted delivery (ligand-based) [69]; • Prolonged circulation time [69].	Non-toxic [29], ease of synthesis and reduced side effects [69]	Potential increase in systemic toxicity [69], low drug loading, instability in circulation [71]
Gold (AuNPs)	• Surface functionalization improving targeting and accumulation [69]; • High surface/volume ratio [69,72].	Small size [70], optical properties [22], ease of functionalization [29], multiple forms [23]	Limited biocompatibility [29] (depending on size and surface chemistry)
Iron (Fe_2O_3; Fe_3O_4)	• Targeted delivery through surface ligands or external magnetic field [22,69]; • Easily functionalized [29]; • Large surface area [69,72].	Improved magnetic properties, multiple forms [23], high stability [29], small size [70]	Cellular toxicity, low biodegradability [29]

3.2.1. Physical Properties of Nanocarriers

Size, surface properties, targeting, accumulation and shape of nanocarriers play an important role in increasing bioavailability [22,73]. The size, shape and possible surface modifications of nanocarriers are presented in Table 2. Nanocarriers are characterized by their small size and high mobility, which allows them to reach hard-to-access places, e.g., by penetrating through many biological barriers that were previously inaccessible to traditional drugs [26,74]. Additionally, physical properties affect drug load and release, as well as stability [26]. The smaller the particles, the greater the surface/volume ratio, which leads to significantly faster release of the active substance from the carrier [26,75]. One of the negative aspects of smaller nanocarriers is the possibility of aggregation [24,26]. Size affects many factors, such as enzymatic degradation, targeted distribution throughout the body, cellular uptake, and sustained drug release [75]. Surface charge (zeta potential) of nanocarriers affects their adsorption, stability, and biodistribution [26], but also aggregation [75]. The negatively charged surface of nanocarriers affects, among other things, longer circulation and better targeting. On the other hand, positively charged nanocarriers have very strong interactions with membranes and a support biocompatibility [26,74]. Surface modifications are also widely used, mainly utilizing polymer materials [75]. Zwitterionic/polymer coatings improve biocompatibility, stability, and circulation time. PEG coatings on the surface of nanocarriers create a hydrophilic barrier, reduce interactions with other substances and can extend blood circulation time [26]. Chitosan coating improves the solubility of a drug at pH-sensitive sites and releases the drug in a controlled manner [74]. Those kinds of coatings can also promote accumulation in tumor tissue, which is important in cancer therapy [26].

Table 2. Key physical characteristics of nanocarriers (based on data available in [76]).

Nanomaterials	Composition	Size [nm]	Shape	Possible Surface Modifications
Polymeric	Biodegradable polymers (e.g., PLGA)	20–50	• Spherical • Nanocapsules (core-shell) • Nanospheres (solid)	PEGylation, targeting ligands, functional groups, hydrogel coatings, stimuli-responsive modifications (pH, temperature)
Dendrimer	Branched polymers	1–10	• Spherical (high symmetry) • Branched, tree-like structures	
Organic, lipid-based	Solid or liquid lipids	50–1000	• Spherical (core–shell) • Irregular	PEGylation, targeting ligands, hydrophobic or hydrophilic modifications, functional groups
Liposomes	Phospholipid bilayer	50–1000	• Spherical (core–shell); • Uni/multilamellar	
Inorganic, metallic	Metals (e.g., gold, silver)	20	• Divided by dimensions, e.g., nanostars, nanorods	PEGylation, silica coatings, ligands, stabilizing polymers

3.2.2. Solubility, Stability and Protection from Degradation

Over 70% of recently developed drugs are water insoluble [15]. The solubility of a drug is an important parameter that determines the bioavailability of the drug on the absorptive surface or membrane [62] and further biodistribution [15]. Low solubility usually causes low bioavailability and medications with poor solubility may need higher doses to reach therapeutic levels (which can raise toxicity) [64]. Improving the solubility of a medicine is especially crucial for substances whose absorption profile is closely related to solubility [62,64]. Its improvement affects the increase in the rate of absorption of the active substance, e.g., in intestinal environments, thereby enhancing the quality of therapy [62]. Drugs can penetrate biological membranes in ionized forms, which depends on solubility and local pH [62,63]. Local pH can be very different and in the GI tract ranges from acidic (stomach, pH 1–3) to neutral and alkaline. To overcome these problems, carriers with coatings are being created to protect the drug from degradation caused by different pH levels, primarily in the gastric environment [64]. In general, ionized pharmaceuticals are more hydrophilic [62].

Managing drug solubility is particularly important for oral administration because a drug must dissolve in the gastrointestinal tract before it can be absorbed into the bloodstream. Advanced formulations, including surfactants, prodrugs, and nanocarriers, can be used to improve the solubility of poorly soluble drugs [64]. Nanoparticle-based formulations can increase the effective surface area available for dissolution, thereby improving drug solubility in biological fluids and potentially enhancing absorption and therapeutic efficacy [63,64].

Nanoparticles can be produced using either a top-down or a bottom-up approach. Top-down methods involve reducing larger particles to the nanoscale and include processes such as high-pressure homogenization and high-energy wet milling. By contrast, bottom-up methods involve forming nanoparticles from molecules or dissolved drug species. Examples of these methods include the hydrosol method, freeze-drying, supercritical-fluid technology and gas recrystallisation [24].

Encapsulation of the drug by nanocarriers, apart from increasing solubility, can protect the drug from degradation in, e.g., the GI tract (with respect to previously mentioned pH changes) [64,65]. A common example of this phenomenon is liposomes, which, thanks to their spherical core–shell structure, can protect both hydrophilic and hydrophobic substances from environmental factors [64]. It is also notable that the size of the nanoparticle affects its rate of degradation. The smaller the particle, the greater the likelihood of en-

zymatic degradation due to the larger surface area, and consequently, the drug may be released more quickly [75].

3.2.3. Targeting Strategies and Drug Loading in Nanocarrier

Targeted delivery to specific tissues, organs, and cells is achievable using nanocarriers by functionalization of their surface with ligands. These ligands attach only to the appropriate receptors located on the surface of a given cell, such as a cancer cell, thereby improving the therapeutic value of the drug and its bioavailability [64]. Targeting removes the drug's interaction with healthy cells, reducing systemic toxicity and side effects [64,65]. Passive targeting focuses on properties of DDSs and the characteristics of the target site. On the other hand, active targeting is related to changes on the surfaces of nanodrugs. Such changes involve, e.g., the attachment of ligands or antibody–antigen interactions [31]. A large drug-loading capacity is essential for an efficient delivery system. Higher drug loading enables a greater amount of the therapeutic agent to be incorporated into the delivery system, potentially increasing the amount available for delivery to the target site per administered dose [26]. Some nanocarriers can have limited drug loading because of their smaller size [24]. Typical drug loading for polymeric nanoparticles ranges from 5% to 20%, for lipid-based nanocarriers it is 1–5% and for lipid–polymer hybrids it is 5–15% [71]. Two loading approaches are commonly used. In the first approach the drug is included during the creation of the nanoparticle (incorporation method). In the second approach, the drug is adsorbed onto or loaded into the nanocarrier after production. The degree to which the drug dissolves in the nanocarrier matrix determines the effectiveness of drug loading. As a result, choosing the right polymer is crucial, e.g., PEG [26].

3.2.4. Drug–Nanocarrier Interactions and Their Role in Carrier Selection

The physicochemical properties of a therapeutic compound and its interactions with the carrier matrix are important considerations in nanocarrier formulation because they influence drug loading, retention, and release. In non-covalent delivery systems, drug association with nanocarriers can involve hydrophobic, electrostatic, hydrogen-bonding, van der Waals, and steric interactions, and the balance between these forces contributes to the stability of the drug–nanocarrier complex. Accordingly, drug hydrophobicity, charge, and compatibility with the carrier material should be considered when selecting the composition and loading strategy of a nanocarrier [77,78]. Hydrophobicity is particularly relevant when it comes to incorporating drugs into polymeric nanocarriers that contain hydrophobic domains. Experimental studies with PLGA/PLA nanoparticles have shown that the solid-state solubility of hydrophobic drugs in the polymer depends on the composition, molecular weight and end-group chemistry of the polymer, as well as on drug loading and release [79]. Using dexamethasone and flutamide as model drugs, Panyam et al. found that polymers providing greater solid-state drug–polymer solubility generally produced higher drug loading, whereas greater solubility was associated with lower cumulative drug release [79]. For instance, flutamide loading was higher in hydrophobic PLA than in PLGA with a 50:50 lactide-to-glycolide ratio (11.0% ± 0.6% versus 7.1% ± 0.3%, respectively). These observations were attributed to the drug partitioning between the polymer matrix and the external aqueous phase; greater affinity for the polymer reduces partitioning into the release medium [79]. However, hydrophobicity alone does not determine loading capacity. Wilkosz et al. investigated itraconazole as a model hydrophobic drug in PEG–PLGA nanoparticles and identified drug–polymer compatibility as an important determinant of drug loading [80]. Despite the hydrophobic character of itraconazole, experimental measurements and molecular dynamics simulations indicated limited miscibility with the PLGA core. Itraconazole preferentially localized at the water–PLGA interface rather

than throughout the hydrophobic PLGA core, which limited the volume available for drug accumulation [80]. The authors related this behavior to the molecular charge distribution of itraconazole and the absence of direct hydrogen bonding between itraconazole and PLGA, while its interfacial localization allowed hydrophobic groups to avoid water and electronegative groups to participate in hydrogen bonding with water molecules [80]. Thus, classification of a drug as hydrophobic is not, by itself, sufficient to predict its affinity for a hydrophobic carrier domain.

Drug–carrier interactions also influence release kinetics. In haloperidol-loaded PLGA/PLA nanoparticles, polymer hydrophobicity, particle size, and surface coating were identified as major determinants of the in vitro release profile [81]. Increasing polymer hydrophobicity reduced the initial burst and prolonged release; for 220 nm particles, the initial burst was 46% from PLA compared with 70% from PLGA, while cumulative release after 35 days was 70% and 90%, respectively [81]. The comparatively low diffusivity of haloperidol in PLA was attributed to strong hydrogen-bonding interactions between haloperidol and carboxylic acid groups, illustrating that specific drug–polymer interactions can substantially modify release independently of hydrophobicity alone [81]. These findings also indicate that rapid or burst release should not be attributed simply to "drug–carrier incompatibility," because release is jointly determined by drug–polymer interactions and carrier properties, including polymer hydrophobicity, particle size, and surface characteristics [81].

Alternative loading strategies may be required for charged hydrophilic compounds because formulation methods optimized for hydrophobic therapeutics do not readily translate to hydrophilic molecules [78]. One such strategy is hydrophobic ion pairing (HIP), which involves the ionic association of a charged hydrophilic therapeutic with an oppositely charged counterion containing a hydrophobic domain. The resulting complex has reduced aqueous solubility due to charge masking and the incorporation of hydrophobic groups, allowing it to be encapsulated using approaches developed for poorly water-soluble compounds [78]. Taken together, these studies show that when selecting and formulating nanocarriers, it is important to consider not only broad classifications such as hydrophilic or hydrophobic character, but also drug charge, polymer–drug miscibility and specific non-covalent interactions. This is because these parameters can affect loading efficiency, localization within the carrier and subsequent release behavior [77–81].

3.3. Overview of Nanocarrier Types and Their Biomedical Applications

Currently, considerable experimental research is being conducted on the development of nanocarriers, mainly in the pharmaceutical sector, but also in the food sector. Improvement in drug bioavailability using nanocarriers primarily concerns increasing the solubility and stability of nanostructures. Mainly, polymeric and hybrid nanocarriers are chosen, which combine the properties of different types of nanocarriers, e.g., polymer–lipid nanoparticles (where often the core is lipid and the outer shell is polymer–PEG or chitosan). Notably, the vast majority of scientific papers dealing with bioavailability focus on the oral delivery of drugs, as shown in Table 3.

Table 3. Overview of nanocarrier types, administration routes, compositions, and applications.

Nanocarrier Type	Main Components	Active Substances	Bioavailability Enhancement	Route of Administration/Application	Ref.
Polymeric–lipid nanoparticles	Lecithin; chitosan	Simvastatin; Coenzyme Q10	Solubility	Oral; treating hypercholesterolemia	[82]
Polymer-based	Gliadin; pectin	Amphotericin B	Controlled release, improved oral bioavailability	Oral; fungal infections	[83]

Table 3. *Cont.*

Nanocarrier Type	Main Components	Active Substances	Bioavailability Enhancement	Route of Administration/Application	Ref.
Nanostructured lipid carriers	Gelucire 44/14; Miglyol 829	Loteprednol	Targeting, drug loading, encapsulation efficiency	Ocular; ocular inflammation	[84]
Polymer-based	Chitosan; PEG	Resveratrol	Stability, solubility, antioxidant capacity	Antioxidant activity in food and supplements	[85]
Inorganic nanoparticles	Dendritic mesoporous silica	Carvedilol; Indomethacin; Magnolia officinalis extract	Stability, solubility, drug capacity, specific surface	Oral; therapeutic applications	[86]
Polymeric–lipid nanoparticles (+ SLNs)	Lipid core (stearyl alcohol); chitosan shell	Sorafenib	Solubility in water, sustained drug release, better bioavailability	Oral; antitumor activity	[87]
Polymer-based nanoparticles (micellar)	Disodium glycyrrhizinate; protamine; hyaluronic acid	Decoquinate	Solubility, targeted biodistribution, drug release, dissolution	Oral; anti-parasitic DDSs	[88]
Inorganic, gold nanoparticles	Gold (core); PEG, TNFα, NHS/PAMAM (coatings)	-	Tissue distribution studies, toxicity, accumulation, clearance, size and surface chemistry	Nanoparticle model in research	[89]
Protein–lipid nanoparticles	Casein; lecithin (liposomes)	Curcumin	Thermal and storage stability, solubility in water, protection from pH	Nutraceutical in food, supplement, pharmaceuticals	[90]
Polymeric nanoparticles	PLGA	Edaravone	Drug stability, half-life, brain bioavailability, reduction in systemic exposure, targeted drug delivery	Nasal; treatment of amyotrophic lateral sclerosis (ALS)	[91]

3.4. Routes of Administration

To deliver the drug quickly (especially at the beginning) and in the largest possible quantity, many types of drug delivery systems have been created [28]. Drug absorption and, consequently, bioavailability depend on the drug administration route and the intended application [28,29]. Table 4 presents the main groups of nanocarriers and their applications.

Table 4. Nanocarrier systems and their applications.

Type of Nanocarrier	Applications
Liposomes	DDSs [14,23,26,30], cancer therapy [14,26], diagnostic imaging [30], gene therapy [23,30], cosmetics, food preservation, wound healing [32]
Lipid-based (SLNs, NLCs)	DDSs, cosmetics [22,23,26], food preservation, anticancer agents [19,23], genetic therapy [21], delivery of antibiotic [19], wound healing, tissue engineering [23]
Polymeric (nanospheres, nanocapsules)	DDSs [21,22,24], cancer therapy, diagnostics [21], imaging, gene therapy [22], wound healing, tissue engineering, food preservation, food packaging [23]
Dendrimers	DDSs, gene therapy, imaging diagnostics [22,26,69]
Inorganic, metal nanocarriers	DDSs [14,19,26], imaging, diagnostics [21,22], photothermal therapy, gene delivery, cancer therapy [30], biosensors [22], tissue engineering, cosmetics, food packaging, bioimaging [23]

Parenteral administration routes can be divided into, e.g., intravenous (invasive, avoids first-pass metabolism, rapid increase in drug concentration), intramuscular, intraarticular, subcutaneous, and transdermal (more patient friendly, longer release of medication, administered through the skin) [19,28]. Transdermal drug delivery systems avoid metabolism, gastrointestinal irritation and are usually more acceptable for patients because of their non-invasive properties. On the other hand, intravenous administration is suitable when a drug cannot be injected into tissues and is characterized by complete bioavailability of drug (direct injection of drug into circulation, without an absorption phase) [28,62]. The main barrier in oral administration is the gastrointestinal epithelium. The absorption of drugs through this route through the GI tract is complex and highly dependent on the properties of the DDS, but also on enzyme activity, thickness of mucosa and surface area [75]. Most experiments focus on improving the bioavailability of orally administered drugs [62]. Delivery through inhalation is very beneficial, e.g., large absorption surface area and non-invasive action [92]. The amount of active substance delivered by a given DDS platform and the amount of drug that enters the systemic circulation are often different, with the exception of intravenous administration, which is characterized by 100% bioavailability [62,63]. Table 5 summarizes routes of administration, including their absorption rates and site, factors affecting absorption and possible impact of nanocarriers on bioavailability.

Table 5. Routes of drug administration, absorption characteristics, and impact of nanoparticles on bioavailability.

Route of Administration		Absorption Rate and Site [63]	Factors Affecting Absorption [62,93]	Possible Nanoparticle Impact on Bioavailability, e.g.,
Oral		Slow; gastric mucosa or intestinal	Blood flow to GI tract, surface area of absorption, gastric emptying time, pH of GI tract, gender, emesis, digestive enzymes (drug stability, dissolution time), intestinal flora, properties of drugs	Improve solubility; protect drug from acidic degradation in stomach; reduce first-pass metabolism; enhance intestinal absorption.
Injection	Intravenous	Very quickly; -	-	No absorption needed (100% bioavailability); enable controlled drug release; targeted delivery; prolong circulation time (e.g., PEGylation).
	Subcutaneous	Quickly; subcutaneous (or adipose) tissue	Blood flow at injection site, vasoconstriction, local pH, properties of the drug, e.g., size (the larger the size, the lower the bioavailability) and complex composition	Controlled/sustained drug release; improved lymphatic uptake. Reduced degradation at injection site.
	Intramuscular	Very quickly; muscle tissue	Blood flow to muscle, gender, drug properties, muscle mass and activity	Prolonged release at injection site; improved stability of drug; enhance absorption depending on particle size.
Inhalation		Very quickly; mucous membrane of the lungs	Lung surface area, disease of the lung (lower perfusion and ventilation), drug properties (particle size)	Improved deposition in lungs; enhanced absorption; targeted delivery to respiratory tract; reduced systemic side effects.

Table 5. *Cont.*

Route of Administration	Absorption Rate and Site [63]	Factors Affecting Absorption [62,93]	Possible Nanoparticle Impact on Bioavailability, e.g.,
Transdermal	Quickly; stratum corneum; epidermis; dermis	Skin hydration and blood flow, skin barrier function, thickness of stratum corneum, drug lipophilicity, drug formulation	Enhanced skin penetration. Overcome barrier of stratum corneum; controlled drug release; improved bioavailability of poorly permeable drugs.
Rectal	Quickly; mucous membrane of the rectum	Rectal blood flow, drug formulation, pH of fluids	Improved drug stability; enhanced mucosal absorption; prolonged local or systemic effect.

Patient compliance, the medication's physicochemical characteristics (e.g., solubility, bioavailability), the target site's accessibility, and overall therapeutic efficacy are all important considerations when choosing a drug delivery method [28]. More than 50% of the lipid-based nanocarriers are delivered by parenteral routes [67] (most effective when a drug has low bioavailability), but they can also be administered as pellets, powders, tablets (after lyophilization and spray-drying), and gelatin capsules. Macromolecules such as proteins and peptides (when given orally) are very susceptible to enzymatic degradation [19]. Liposomes can be delivered to the lungs (as aerosols, inhalation), topically to the skin and orally. Oral administration of liposomes is very limited because of the gastric environment (in this case there is no difference in conventional and liposomal drug formulations) [14]. Inorganic, particularly metallic, nanoparticles can be administered by inhalation, injection, transdermal, or oral routes [28]. Polymer nanoparticles are delivered via injections, oral, pulmonary, and transdermal administration [92].

4. Nanoparticles for Improving Bioavailability: Case Studies

4.1. Case 1: Curcumin Nanoformulation

Curcumin is a hydrophobic polyphenol with considerable therapeutic potential; however, its clinical application is substantially limited by its extremely low oral bioavailability. This poor bioavailability is primarily attributed to low aqueous solubility, limited gastrointestinal absorption, and extensive intestinal and hepatic metabolism, resulting in minimal systemic exposure even following high oral doses. Clinical studies have shown that administration of doses of 8–12 g of conventional curcumin results in undetectable or minimal plasma concentrations in most participants [94]. These limitations have been addressed by developing nanoformulation strategies to enhance solubility and absorption. Nanoparticle-based formulations such as THERACURMIN reduce particle size and improve aqueous dispersibility, leading to significantly increased systemic exposure. Human studies have shown that THERACURMIN achieves measurable plasma concentrations (C_{max} up to 275 ng/mL) at doses as low as 150–210 mg, whereas conventional formulations at gram-scale doses remain largely undetectable [95]. Similarly, micellar and micronized delivery systems substantially enhance bioavailability by improving dissolution and gastrointestinal solubilization. In a controlled human study, micellar curcumin increased systemic exposure by up to 185-fold, while micronized formulations resulted in bioavailability up to nine times higher than that of native curcumin [96]. Overall, these findings demonstrate that nanocarrier-based approaches effectively overcome the intrinsic physicochemical and pharmacokinetic limitations of curcumin by primarily increasing the dissolution rate

and enhancing solubilization, as well as partially protecting the compound from rapid metabolic degradation.

4.2. Case 2: Paclitaxel Nanoformulations

Paclitaxel is a highly effective anticancer agent; however, its clinical use is significantly limited by its extremely poor solubility in water, which necessitates its formulation with toxic solvents such as Cremophor EL and ethanol. These solvents are associated with severe hypersensitivity reactions, altered pharmacokinetics and impaired drug distribution due to micelle formation. This can entrap paclitaxel in circulation, reducing its delivery to tumor tissues [97]. To overcome these limitations, a solvent-free formulation of paclitaxel bound to albumin (nab-paclitaxel, ABI-007) was developed. This nanocarrier system uses albumin to enhance the transport of the drug and its delivery to tumors via natural biological pathways, including receptor-mediated transcytosis and increased endothelial transport. Preclinical studies have demonstrated that nab-paclitaxel is transported across endothelial cells approximately four times more effectively and accumulates in tumors more efficiently than conventional formulations [97]. Clinically, nab-paclitaxel has demonstrated significantly improved therapeutic performance. In a phase III trial, nanoparticle-based paclitaxel produced higher overall response rates (33% versus 19%) and prolonged time to tumor progression (23.0 vs. 16.9 weeks) than conventional paclitaxel, despite a substantially higher delivered dose [97]. Notably, the incidence of severe neutropenia was significantly reduced (9% vs. 22%), and no hypersensitivity reactions occurred without premedication [98]. These findings demonstrate that, in addition to overcoming solubility limitations, nanocarrier-based delivery improves pharmacokinetics, enhances tumor targeting and reduces formulation-related toxicity, resulting in a significantly improved therapeutic index.

4.3. Case 3: Amphotericin B Nanoformulations

Amphotericin B (AMB) is a potent, broad-spectrum antifungal agent. However, its clinical use is severely restricted due to its poor aqueous solubility and significant, dose-dependent toxicity, particularly nephrotoxicity. The conventional formulation (Fungizone®), which uses deoxycholate micelles, is associated with infusion-related reactions and renal damage, which restricts its therapeutic use despite its strong antifungal efficacy [99]. To address these limitations, lipid-based nanoformulations such as liposomes and lipid complexes were developed. These systems incorporate AMB into nanoscale carriers (e.g., AmBisome®, Abelcet®, Amphotec®), altering its distribution and interaction with biological membranes. Liposomal AMB consists of small (~80–100 nm), stable phospholipid vesicles that retain the drug within the bilayer, reducing its interaction with mammalian cell membranes while preserving antifungal activity [100]. This modification significantly decreases toxicity while enabling targeted delivery, including preferential accumulation at infection sites and within phagocytic cells. Clinically, nanoformulated AMB demonstrates comparable or improved efficacy with a markedly enhanced safety profile. Liposomal AMB has been shown to be at least as effective as conventional formulations while significantly reducing nephrotoxicity and infusion-related adverse effects. This modification significantly decreases toxicity while enabling targeted delivery, including preferential accumulation at infection sites and within phagocytic cells. Clinically, nanoformulated AMB demonstrates comparable or improved efficacy with a markedly enhanced safety profile [99,100].

4.4. Case 4: Fenofibrate Nanocrystals

Fenofibrate is a lipophilic, lipid-lowering agent used to treat hypercholesterolemia and dyslipidemia. However, its clinical performance is limited by its extremely poor aqueous

solubility. This results in dissolution-limited absorption and a strong dependence on food intake. Conventional formulations exhibit significantly higher bioavailability under fed conditions, with absorption increasing by up to 35% compared to fasting due to enhanced solubilization by dietary lipids [101]. To overcome these limitations, nanocrystal formulations of fenofibrate (e.g., Tricor®) have been developed, which use particle size reduction to the nanometer range. This increases the surface area, dissolution velocity and apparent solubility of the drug without altering its chemical structure. Consequently, nano-sized fenofibrate achieves improved dispersion in gastrointestinal fluids and enhanced absorption, independent of external solubilizing factors, such as food intake [96]. Clinically, this formulation eliminates the variability observed with conventional products under fed and fasted conditions, resulting in bioequivalent plasma levels under both conditions [101]. The improved dissolution behavior enables consistent systemic exposure and more predictable pharmacokinetics. These findings demonstrate that nanocrystal technology effectively overcomes the absorption limitations of fenofibrate due to its low solubility by enhancing the dissolution rate and apparent solubility, thereby improving bioavailability independently of food intake.

4.5. Case 5: Doxil® (Doxorubicin) Nanoformulation

Doxorubicin is a highly effective, broad-spectrum anticancer agent. However, its clinical use is significantly limited by severe, dose-dependent toxicity, particularly cardiotoxicity, and rapid distribution and non-specific tissue exposure. These limitations restrict the maximum tolerated dose and reduce therapeutic selectivity. To address these challenges, PEGylated liposomal doxorubicin (Doxil®) was developed as a nanocarrier-based formulation. This system consists of ~100 nm sterically stabilized liposomes that encapsulate doxorubicin via remote loading, enabling high and stable drug retention. PEGylation prolongs circulation time by reducing recognition and clearance by the reticuloendothelial system, while the nanoscale size allows passive tumor targeting via the enhanced permeability and retention effect. Clinically, Doxil® demonstrates markedly altered pharmacokinetics, with prolonged circulation half-life (~90 h) and detectable drug levels for over 350 h, enabling enhanced tumor accumulation compared to conventional (non-liposomal) doxorubicin [102]. This results in improved therapeutic index, primarily through reduced systemic toxicity, particularly cardiotoxicity, while maintaining anticancer efficacy. These findings demonstrate that nanocarrier-based delivery of doxorubicin effectively modifies drug distribution, prolongs systemic exposure, and enhances tumor targeting, thereby overcoming key limitations of conventional formulations.

5. Pharmacokinetics and Pharmacodynamics of Nanocarrier Drug Delivery Systems

Nanocarrier-based drug delivery systems significantly influence both pharmacokinetics (PKs) and pharmacodynamics (PDs), thereby improving the therapeutic performance of active pharmaceutical ingredients. While conventional formulations are primarily limited by poor absorption and rapid clearance, nanocarriers enable modulation of drug behavior at multiple stages of the ADME process. These systems enhance drug exposure, alter biodistribution profiles, and enable controlled and sustained drug release.

5.1. Absorption Enhancement

Nanocarrier-based drug delivery systems can significantly improve the absorption of drugs by overcoming the physiological and biochemical barriers that are associated with conventional formulations. Poor oral bioavailability is primarily due to drug instability in the gastrointestinal tract, limited permeability across biological membranes and extensive first-

pass metabolism. Nanoparticles address these limitations through multiple complementary mechanisms. One of the primary mechanisms of absorption enhancement is protection of active pharmaceutical ingredients from degradation in the GI environment. The acidic pH of the stomach and the presence of digestive enzymes can lead to premature drug degradation, thereby limiting the amount that is available for absorption. Nanocarriers, including lipid- and polymer-based systems, provide a protective matrix that shields drugs from these harsh conditions, thereby increasing their stability and effective concentration at the absorption site [103,104]. This protective effect is particularly important for sensitive molecules, such as peptides and proteins, and for poorly soluble compounds.

In addition to improving stability, nanocarriers facilitate the transport of drugs across biological barriers. The mucus layer and the intestinal epithelium are major obstacles to oral drug delivery. Nanoparticles can be engineered to minimize interactions with mucus and facilitate diffusion through the mucin network. Studies have shown that particle size plays a critical role in this process, with particles measuring less than 200–300 nm in diameter exhibiting improved permeability through mucus and epithelial layers [73]. Furthermore, surface properties such as hydrophilicity and a near-neutral charge reduce adhesion to mucus components and promote more efficient transport [103]. These characteristics enable nanoparticles to reach the epithelial surface and increase the likelihood of absorption.

Nanocarriers also facilitate alternative uptake pathways that are inaccessible to conventional drug formulations. These include transcellular transport via enterocytes, paracellular transport through tight junction modulation and uptake via specialized M cells located in Peyer's patches. Additionally, receptor-mediated transport mechanisms involving bile acid transporters or Fc receptors can be exploited through the functionalization of nanoparticle surfaces [103,104]. Importantly, some nanocarrier systems facilitate lymphatic transport, enabling drugs to bypass first-pass hepatic metabolism and significantly increase systemic bioavailability [104]. These mechanistic advantages translate into measurable pharmacokinetic improvements. Comparative in vivo studies have demonstrated that nanoparticle-based formulations can increase systemic exposure, as reflected by higher area under the concentration–time curve (AUC), and prolong circulation half-life relative to conventional drug forms [105]. Such enhancements are particularly pronounced for lipophilic and poorly soluble drugs, where dissolution and permeability are the primary limiting factors.

5.2. Distribution Modification

Nanocarrier-based drug delivery systems can significantly impact drug distribution, a critical factor in determining therapeutic efficacy and toxicity. Unlike conventional small-molecule drugs, which typically distribute non-specifically across tissues, nanoparticles exhibit distinct biodistribution patterns that are governed by their physicochemical properties, including size, surface charge, composition and surface functionalization [106,107]. A key feature of nanoparticle-mediated distribution is their preferential accumulation in specific organs. Quantitative analyses of over 2000 datasets have demonstrated that, following systemic administration, nanoparticles predominantly accumulate in the liver (approximately 17.6% ID/g) and spleen (approximately 12.1% ID/g), with significantly lower distribution to other tissues (generally less than 5% ID/g). This phenomenon is largely attributed to uptake by the reticuloendothelial system (RES), particularly by macrophages in these organs that recognize and internalize nanoparticles coated with serum proteins (opsonins) [107,108]. Surface modification strategies, particularly PEGylation, have been extensively developed to modulate nanoparticle biodistribution. PEGylation reduces protein adsorption and macrophage recognition through steric hindrance, thereby decreasing RES uptake and prolonging systemic circulation [107,109]. Experimental studies have demonstrated that PEGylation can reduce RES uptake by up to threefold, increase plasma

exposure by around sixfold, and enhance tumor accumulation by up to threefold. These changes directly reflect altered tissue distribution patterns and improved delivery efficiency to target sites.

Another critical mechanism influencing nanoparticle distribution is the enhanced permeability and retention (EPR) effect. Due to the leaky vasculature and impaired lymphatic drainage in tumor tissues, nanoparticles can preferentially extravasate and accumulate within tumors while being largely excluded from healthy tissues [107]. However, the magnitude and reliability of EPR-mediated accumulation can differ considerably between experimental tumor models and human cancers [110,111]. Conventional xenograft models may overestimate EPR-mediated delivery as they do not accurately replicate the structural and biological complexity of human tumors. Experimental murine tumors typically develop within weeks and frequently exhibit relatively high tumor blood flow. In contrast, human tumors develop over substantially longer periods and can display poorer perfusion, greater genetic diversity and more complex tumor–stroma interactions. Differences in tumor-to-body weight ratio and the use of immunodeficient animals can also contribute to discrepancies between experimental and clinical conditions [110]. In human tumors, EPR-mediated delivery is additionally influenced by substantial inter- and intra-patient heterogeneity, including differences in vascularization and vascular permeability, extracellular matrix density, interstitial fluid pressure, hypoxia and tumor blood flow [110–112]. Clinical imaging provides direct evidence of this variability. For example, in a study of 19 patients with HER2-positive metastatic breast cancer, PET imaging of ^{64}Cu-labeled HER2-targeted PEGylated liposomal doxorubicin revealed a 35-fold variation in tumor accumulation, ranging from 0.52% to 18.5% ID/kg 24–48 h after administration [108]. Therefore, the extent of nanoparticle accumulation observed in preclinical tumor models cannot be assumed to occur uniformly in patients. These limitations have increased interest in strategies that do not rely exclusively on passive EPR-mediated accumulation, including alternative trans-endothelial transport mechanisms [110]. Active targeting is also being investigated to improve interactions of nanocarriers with target cells; however, ligand-mediated targeting does not necessarily increase the overall amount of nanomedicine accumulating within tumors and may instead improve intratumoral distribution and cellular uptake [112]. Consequently, the heterogeneity of EPR-mediated tumor targeting should be considered when evaluating the translational potential of nanocarrier-based therapies [110,112,113]. Schematic illustration of the enhanced permeability and retention (EPR) effect is shown on Figure 6.

This selective accumulation depends on both nanoparticle properties and tumor microenvironment characteristics, including vascular permeability and interstitial pressure. Physicochemical parameters play a decisive role in determining biodistribution profiles. Particle size is particularly important: nanoparticles must be large enough to avoid renal filtration (with a cutoff of <5.5 nm), yet small enough (typically ~100 nm) to evade splenic filtration and enable tumor penetration [107]. Similarly, surface charge has a strong influence on distribution: highly charged nanoparticles (positive or negative) are rapidly cleared due to enhanced protein adsorption and macrophage uptake, whereas near-neutral particles exhibit prolonged circulation and reduced non-specific accumulation [107]. Surface composition and hydrophobicity also modulate protein binding and subsequent biodistribution behavior.

Importantly, nanocarriers can enhance tissue selectivity and reduce off-target exposure. Encapsulation within nanoparticles protects drugs from rapid metabolism and renal clearance, enabling prolonged circulation and increasing the likelihood of accumulation in target tissues [108]. At the same time, the controlled modification of nanoparticle properties enables a reduction in drug distribution to non-target organs, thereby minimizing systemic toxicity and improving the therapeutic effect.

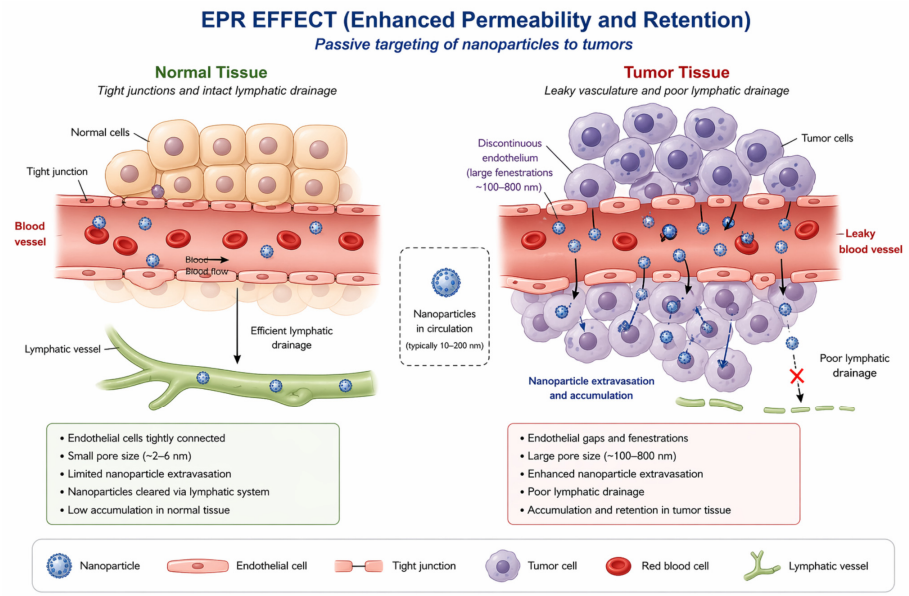


Figure 6. Schematic illustration of the enhanced permeability and retention (EPR) effect, depicting the preferential accumulation of nanoparticles in tumor tissue due to leaky vasculature and impaired lymphatic drainage. This representation is simplified; in vivo EPR effects are highly heterogeneous and often limited in clinical tumors.

5.3. Controlled Release Kinetics

Nanocarrier-based drug delivery systems enable precise control over drug release kinetics. This is a critical factor that influences both pharmacokinetic behavior and therapeutic efficacy. Unlike conventional formulations, which often result in rapid and uncontrolled drug release, nanocarriers provide sustained release profiles mediated by diffusion or degradation. These profiles can be tailored through material selection and structural design. One of the fundamental mechanisms governing the controlled release of drugs from nanocarrier systems is diffusion-driven release. In polymeric nanoparticles, drugs are usually either encapsulated within the polymer matrix or adsorbed onto it and are then released via diffusion or desorption processes [66]. The rate of release depends on factors such as the composition of the polymer, the interactions between the drug and the polymer, and the structure of the nanoparticle. For instance, encapsulated drugs can gradually diffuse from the carrier into the surrounding environment, enabling prolonged exposure of the target site to the drug [66]. Another key mechanism is degradation-controlled release, which is particularly prevalent in biodegradable polymer systems, such as poly (lactic-co-glycolic acid) (PLGA). These materials undergo hydrolytic degradation into monomeric units under physiological conditions, enabling the sustained release of encapsulated drugs over time [65,109]. The rate of degradation—and thus the rate of drug release—can be modulated by adjusting the properties of the polymer, such as its molecular weight and copolymer ratio. This provides a high degree of control over the release kinetics [66,109].

Nanocarriers also enable sustained release through their structural and physicochemical design. For example, nanoemulsion-based systems deliver drugs over a prolonged period due to their small droplet size, large interfacial area and interaction with biological membranes, facilitating gradual transport of drugs across tissues. These systems can maintain drug levels over extended periods, reducing the need for frequent dosing and improving therapeutic consistency. Furthermore, nanoemulsions demonstrate high stability and resistance to coalescence, resulting in controlled and predictable release behavior [114].

The release kinetics of nanocarriers can be further influenced by surface and structural modifications. For example, functionalization with polymers or surface coatings can

modulate drug diffusion rates and interaction with biological environments. For instance, dendrimer- and polymer-modified systems have been demonstrated to reduce drug release rates and enhance stability, enabling more precise and prolonged therapeutic delivery [58]. Similarly, lipid-based and polymer-coated nanoparticles provide structural barriers that slow drug release and enhance retention within the carrier system.

Controlled release is also closely linked to improved drug stability and bioavailability. Nanocarriers protect encapsulated drugs from premature degradation and enable gradual release into the systemic circulation, thus maintaining drug concentrations within the therapeutic window. In the case of nanocrystal-based systems, the increased surface area enhances dissolution kinetics while enabling prolonged drug exposure due to improved interaction with biological membranes [115].

Stimuli-Responsive Nanocarriers and pH-Triggered Drug Release

Stimuli-responsive drug delivery systems are designed to alter their properties or release their cargo in response to either endogenous stimuli, such as pH, redox conditions or enzymes, or exogenous stimuli, such as temperature, light, ultrasound or magnetic fields [116]. Of these endogenous triggers, pH has been the subject of extensive investigation due to the occurrence of pH gradients between physiological and pathological or intracellular environments [117,118]. For instance, while the physiological pH value in the extracellular environment is around 7.4, the pH value along the endocytic pathway is much lower, ranging from 5.5–6.0 in endosomes to 4.5–5.0 in lysosomes [117]. pH-responsive nanocarriers can exploit these differences through ionizable groups or acid-labile chemical bonds. The protonation or deprotonation of ionizable groups can alter polymer swelling or phase behavior, while the cleavage of acid-labile linkages can promote carrier disassembly or drug release [118]. Acid-sensitive functionalities investigated for controlled drug release include hydrazone, acetal, orthoester and related linkages [117–119]. Hydrazone bonds generally undergo accelerated hydrolysis under acidic conditions and have been incorporated into polymer–drug conjugates, micelles, liposomes and other nanocarriers [119]. Acetal linkages are similarly tunable: Gillies et al. demonstrated pH-dependent hydrolysis of structurally different acetals, with substantially faster cleavage at pH 5.0 than at pH 7.4 [117]. These mechanisms provide a means of coupling drug release to changes in the local biological environment.

However, clinical translation remains limited. NC-6300 (K-912) is a polymeric micelle that has been investigated in clinical trials, in which epirubicin is conjugated through an acid-labile hydrazone linkage [120]. In a first-in-human Phase I study involving 19 patients with advanced or recurrent solid tumors, the maximum tolerated dose and the recommended Phase II dose were both found to be 170 mg/m^2. One patient achieved a partial response, while ten experienced stable disease [120]. While these findings demonstrated clinical feasibility, they did not establish therapeutic superiority.

The broader clinical experience highlights the challenges involved in translating stimuli-responsive systems. A 2026 analysis reported that only a small proportion of such therapeutics had progressed to clinical trials, identifying material complexity, tissue penetration, economic constraints, and difficulties in clinical implementation as important barriers. HermoDox, a heat-triggered liposomal doxorubicin formulation, reached Phase III evaluation; however, the OPTIMA trial did not demonstrate a significant improvement in progression-free survival. Therefore, successful translation requires stimulus-responsive release, predictable activation, formulation stability, reproducible manufacturing and practical clinical implementation [117].

5.4. Pharmacodynamics Implications

Nanocarrier-based drug delivery systems can significantly impact pharmacodynamic (PD) outcomes by altering drug exposure at the target site, thereby enhancing therapeutic efficacy and reducing systemic toxicity. These effects arise from changes in pharmacokinetics, biodistribution and cellular interactions mediated by nanoparticles, which collectively determine the biological response to treatment [105,121].

One of the primary PD advantages of nanocarriers is improving therapeutic efficacy by enhancing drug accumulation in target tissues. Nanoparticles can be engineered to deliver drugs selectively to diseased sites, such as tumors, resulting in higher local concentrations of the drug compared to conventional formulations. For instance, the liposomal encapsulation of doxorubicin has been demonstrated to increase tumor accumulation and cytotoxicity, while simultaneously reducing cardiotoxic side effects and improving overall therapeutic outcomes [22]. This selective delivery enhances the action of the drug at the target site while minimizing damage to healthy tissues. Nanocarriers contribute to an improved therapeutic index by balancing efficacy and toxicity. Conventional drugs often exhibit dose-limiting toxicity due to non-specific distribution. However, nanoparticle formulations reduce off-target exposure and enable more controlled drug release. Consequently, higher effective doses can be administered without increasing systemic toxicity, thereby enhancing the safety profile of the treatment [105]. The relationship between nanoparticle-mediated targeting and reduced adverse effects is central to their pharmacodynamic benefit. Another important implication is their ability to interact directly with biological systems and modulate cellular processes. Unlike conventional drug carriers, nanocarriers are not necessarily inert; they can influence biological pathways by interacting with proteins, cell membranes and the immune system. In addition to serving as drug carriers, some nanomaterials may interact with proteins, cell membranes, and immune cells, thereby influencing biological responses [105]. These additional mechanisms can enhance treatment outcomes, particularly in complex diseases such as cancer and chronic inflammatory conditions.

The physicochemical properties of nanoparticles play a critical role in determining these responses. Parameters such as size, surface charge and composition influence protein corona formation, cellular uptake and tissue targeting, thereby affecting drug efficacy. For example, nanoparticles that are optimized for prolonged circulation and reduced immune recognition can accumulate more effectively at target sites, leading to enhanced pharmacological effects [105,121]. Similarly, modifying nanoparticle properties has been associated with improved tissue penetration and therapeutic response. Importantly, the pharmacodynamic effects of nanoparticle systems cannot be fully predicted by traditional pharmacokinetic measurements alone. Plasma drug concentration does not necessarily reflect local drug activity, especially when nanoparticles enable targeted delivery and localized release. Therefore, to gain a comprehensive understanding of nanoparticle-mediated pharmacodynamics, it is necessary to integrate tissue distribution data, cellular interactions and local drug activity [105].

Nanocarrier-based drug delivery systems allow for the effective modulation of pharmacokinetics and pharmacodynamics. They enhance absorption by improving stability and permeability and alter distribution through controlled biodistribution and targeted accumulation. Furthermore, nanocarriers provide sustained and controlled release profiles, ensuring stable drug exposure over time. These pharmacokinetic improvements directly translate into pharmacodynamic benefits, including increased drug efficacy, reduced systemic toxicity and an improved therapeutic index. Overall, nanocarriers offer an integrated approach to optimizing drug performance by linking physicochemical design with biological outcomes.

6. Challenges, Opportunities and Future Perspectives

Despite significant advances in nanocarrier-based drug delivery, major challenges remain related to safety, long-term toxicity, and translational predictability, highlighting the need for mechanism-driven design, standardized evaluation frameworks, and integration of computational approaches.

6.1. Safety and Toxicity Considerations

Despite significant progress in nanocarrier-based drug delivery, safety and toxicity remain key barriers to its clinical application. The physicochemical properties that provide therapeutic benefits, such as nanoscale size, a high surface area and adjustable surface chemistry, also pose potential biological risks. Due to their small size, nanoparticles can cross biological membranes efficiently and accumulate in tissues and organs, leading to increased systemic exposure and potential long-term toxicity [122].

The toxicity of nanoparticles is strongly dependent on their physicochemical characteristics, including size, surface charge, shape and composition. Smaller nanoparticles are more easily internalized by cells and are more reactive, which can significantly increase cytotoxic responses. The surface charge is particularly important as positively charged nanoparticles strongly interact with negatively charged cell membranes, thereby promoting membrane disruption and intracellular damage [123]. These interactions trigger key molecular mechanisms of toxicity, including the generation of reactive oxygen species (ROS), mitochondrial dysfunction, DNA damage, inflammatory signaling and apoptosis [123,124]. Figure 7 shows nanoparticle toxicity mechanisms.

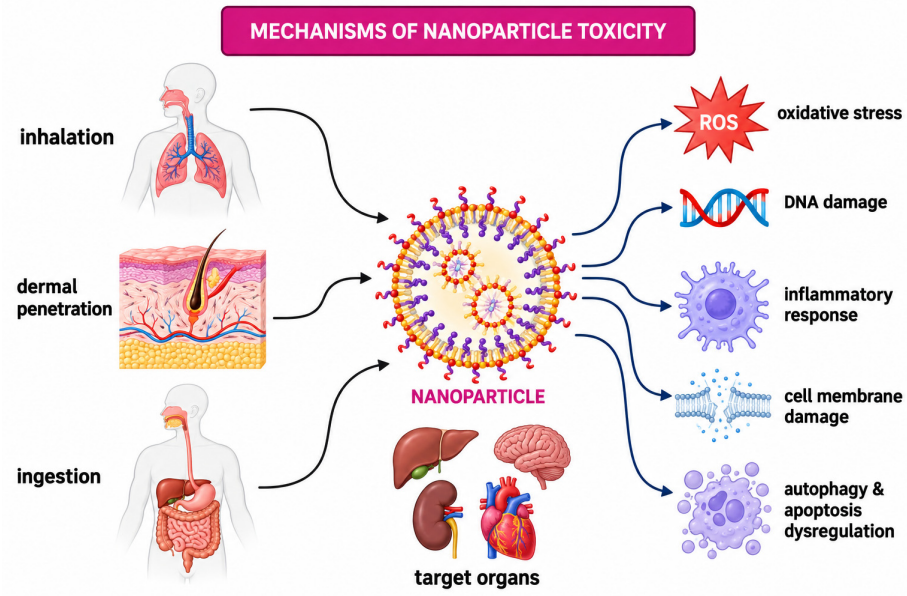


Figure 7. Nanoparticle toxicity mechanisms [123].

Quantitative evidence highlights the magnitude of these effects. Meta-analytical data have demonstrated significant nanoparticle-induced toxicity in metabolic organs, including increased hepatic oxidative stress (standardized mean difference, SMD = 1.42; 95% CI: 1.10–1.75), renal tubular apoptosis (SMD = 1.27; 95% CI: 0.94–1.61), and pancreatic β-cell dysfunction (SMD = 1.18; 95% CI: 0.88–1.49) [125]. These findings provide strong evidence for organ-specific toxicity and confirm that nanoparticle exposure can result in measurable biological damage.

In addition to metabolic toxicity, nanoparticle-based systems may induce application-specific adverse effects. For instance, nanoparticle-mediated therapies have been associated

with cardiotoxicity, driven by oxidative stress, endothelial dysfunction, immune activation, and off-target accumulation in cardiac tissue [126]. Experimental studies further demonstrate that different nanoparticle types can elicit distinct immune responses and biodistribution patterns, with variations in T-cell activation and inflammatory markers depending on nanoparticle composition [127].

A critical translation challenge is the persistence and incomplete clearance of nanoparticles. Inefficient elimination may lead to prolonged retention in tissues, resulting in chronic inflammation and cumulative toxicity [125]. This issue is compounded by the lack of standardized toxicity assessment protocols and regulatory frameworks. Current models often fail to capture nanoparticle-specific biological interactions, while variability in synthesis and characterization leads to inconsistent and non-reproducible results [128]. These limitations significantly hinder the reliable translation of nanocarrier systems into clinical practice.

6.1.1. Regulatory and CMC Considerations

Regulatory assessment of nanomedicines requires consideration of both conventional pharmaceutical requirements and nanomaterial-specific characteristics. The FDA guidance for drug products containing nanomaterials recommends a risk-based approach that considers material structure and complexity, physicochemical properties, stability, in vivo release, manufacturing maturity, and the effects of manufacturing changes on critical quality attributes (CQAs) [129]. Chemistry, manufacturing, and controls (CMCs) are particularly important because nanomedicine quality, safety, and efficacy can be sensitive to process conditions and production scale. Consequently, CQAs should be identified during development so that appropriate process controls and control strategies can be established [129,130]. For liposomal products specifically, FDA guidance identifies particle size and size distribution, morphology, surface characteristics, zeta potential, drug encapsulation/loading, in vitro drug release, leakage, and stability-related properties among relevant characterization and quality considerations [131]. Clinical translation nevertheless remains challenging because promising preclinical performance may not be maintained during development. Reported barriers include difficulties in reproducible manufacturing and scale-up, inadequate or non-standardized characterization, biological instability, safety concerns, disease heterogeneity, limitations of predictive preclinical models, and regulatory complexity [132,133].

6.1.2. Biocompatibility and Immunological Assessment

Biocompatibility evaluation of nanocarriers should account for interactions with both hematological and immune systems. Relevant endpoints include hemolysis, thrombogenicity, complement activation, cytokine release, phagocyte activation, oxidative burst, and antigenicity [132]. These assessments are important because the multicomponent nature and altered biodistribution of nanomedicines can produce biological interactions that differ from those of the free active pharmaceutical ingredient, and specialized immunotoxicity testing may therefore be required [132]. Standardization frameworks also provide guidance for biological evaluation of nanomaterials. ISO/TR 10993-22 [134], developed within the ISO 10993 framework for the biological evaluation of medical devices, addresses nanomaterials used in medical devices and discusses aspects of cytotoxicity, genotoxicity, carcinogenicity, reproductive toxicity, immunotoxicity, irritation, sensitization, and hemocompatibility [135]. However, ISO 10993 should not be interpreted as a universal pharmaceutical testing standard for all nanomedicines; testing requirements depend on the type, intended use, exposure, and risk of the nanomaterial [135].

6.2. Economic Considerations

Economic feasibility is an important consideration in the clinical translation of nanomedicines because increasing formulation complexity can increase material, manufacturing, characterization, and development requirements [133,136]. Agrahari and Agrahari emphasize that cost-effectiveness should be considered during scale-up and that the cost–benefit ratio of a nanomedicine should be evaluated relative to available conventional treatments [133]. Similarly, Hua et al. identified cost–benefit analysis as a potential limitation to clinical translation, particularly when a more complex and expensive nanomedicine is compared with an existing therapy; economic value may arise through improved therapeutic efficacy, improved quality of life, reduced toxicity, or reduced requirements for other medical interventions [136]. However, higher manufacturing complexity does not necessarily imply higher overall clinical-development costs. A systematic analysis of 37 nanomedicines approved by the FDA Center for Drug Evaluation and Research between 2011 and 2023 found that the median estimated cost of pivotal trials for nanomedicines was 47% of that for biologics and new molecular entities approved during the same period [137]. Therefore, economic evaluation of nanomedicines should consider both additional formulation and manufacturing costs and potential savings or clinical benefits across the broader development and treatment pathway [136,137].

6.3. Opportunities and Future Perspectives

Despite the challenges involved, nanocarrier systems present significant opportunities for improving drug delivery and precision medicine. A key area of research is the development of targeted, multifunctional nanoparticles that can deliver drugs selectively. Functionalization strategies enable enhanced accumulation at disease sites through passive mechanisms such as the enhanced permeability and retention effect, as well as active targeting approaches. This reduces off-target toxicity while improving therapeutic efficacy [138]. Nanocarriers also enable precise modulation of intracellular signaling pathways. For example, nanoparticle-based systems improve the delivery of therapeutics targeting the PI3K/AKT/mTOR pathway, allowing regulation of autophagy and tumor progression while overcoming limitations of conventional therapies such as poor specificity and systemic toxicity [139]. These capabilities establish nanomedicine as a vital tool for overcoming drug resistance and enhancing treatment outcomes.

Future developments are increasingly focused on the rational design of nanocarriers to balance efficacy and safety. Strategies include using biodegradable and biocompatible materials, optimizing size and surface properties to reduce immune recognition and developing stimuli-responsive systems that enable controlled drug release in response to physiological triggers [138,139]. These approaches aim to mitigate toxicity while preserving therapeutic performance.

For the clinical translation of stimuli-responsive nanocarriers, future research should focus not only on optimizing stimulus responsiveness and therapeutic efficacy but also on ensuring manufacturability, reproducibility, and stability under physiologically relevant conditions. Despite their potential for controlled and targeted drug release, several technical barriers remain, particularly those related to in vivo stability, scalable and reproducible manufacturing, and reliable drug delivery. Key limitations include insufficient reproducibility of drug delivery, premature drug release during systemic circulation and inadequate accumulation of nanocarriers at the target site [140]. Therefore, stimuli-responsive systems must maintain structural and functional stability during circulation while preserving their ability to release the payload in response to the intended stimulus, whether endogenous or exogenous. Stability assessment should extend beyond conventional storage conditions to include studies in biological media at temperatures representative of the biological envi-

ronment. It should also include the assessment of interactions with biological components, the degradation of the encapsulated drug and drug-release testing in physiologically and clinically relevant media [141]. It is important to note that currently available regulatory approaches are not fully standardized across different nanocarrier systems, which highlights the need for more harmonized characterization strategies and stability assessment criteria [130,141,142].

Reliable physicochemical characterization is essential for evaluating the quality and reproducibility of nanocarriers because particle size, size distribution, morphology and surface properties are important characteristics of nanoparticle formulations [143–146]. Dynamic light scattering (DLS) is a common technique for determining the size of particles in a dispersion based on Brownian motion. It provides a hydrodynamic diameter, whereas transmission electron microscopy (TEM) enables direct visualization of the size and morphology of nanoparticles [143,144]. These techniques provide complementary information and should not be considered interchangeable. Differences between DLS and TEM measurements can arise from factors including particle concentration, shape, aggregation, scattering angle dependence, size weighting and experimental or data analysis procedures [143]. Scanning electron microscopy (SEM) provides additional morphological characterization, particularly with regard to particle surface and structure, and is one of the approaches used in the physical characterization of nanosystems [145]. Surface properties should also be evaluated because they contribute to the behavior and stability of colloidal formulations. Zeta potential (ZP), obtained from electrophoretic mobility, provides information related to the electrokinetic properties of nanoparticles and is commonly used together with DLS during nanoparticle characterization [146]. However, both DLS and ZP measurements are sensitive to experimental conditions, sample preparation, and data interpretation [146]. DLS measurements performed using different instruments or analytical settings can produce significant discrepancies, particularly for dilute, small, polydisperse, or non-spherical particles [143]. Farkas and Kramar further demonstrated that inappropriate interpretation of DLS distributions can produce discrepancies exceeding 15%, depending on sample polydispersity [147]. Consequently, standardized protocols, appropriate reporting of measurement conditions, and complementary analytical techniques are important for improving the reliability and reproducibility of nanomedicine characterization [143,148].

Reproducibility and manufacturing scale-up are important challenges in the clinical translation of nanomedicines. As nanoparticle manufacturing involves multiple material and process variables, maintaining consistent physicochemical and functional characteristics across batches is essential. It is important to identify and control critical quality attributes (CQAs), such as particle size and size distribution, surface charge, morphology, drug loading and encapsulation efficiency, because these properties can influence the performance of nanomedicines [130,148]. In particular, the physicochemical properties of nanomedicines can affect their biodistribution and their interactions with tissues and biological membranes [132]. Batch-to-batch variability has been demonstrated experimentally for PLGA nanoparticles. Haque et al. reported that the preparation of PLGA nanoparticles by emulsification–evaporation using water-immiscible solvents was susceptible to aggregation and non-uniform particle size, resulting in multimodal size distributions. The reproducibility of this process was found to be sensitive to various factors, including the grade and concentration of the PLGA, the concentration of the stabilizer, the conditions of homogenization or sonication, the phase-volume ratio, and the geometry of the mixing vessel [148]. By contrast, their optimized emulsification–solvent diffusion procedure using ethyl acetate produced PLGA nanoparticles with a size range of approximately 50–400 nm and a zeta potential ranging from −30 to +30 mV, demonstrating high reproducibility between batches. Five independently prepared batches were evaluated for each formulation [148]. Garms

et al. [149] further support the importance of process control, showing that PLGA nanoparticle properties are affected by multiple synthesis and isolation variables. The energy source used for emulsification produces particularly pronounced effects on particle size and polydispersity. Processing conditions can also affect drug encapsulation. For instance, surfactant concentration and the procedures employed for particle isolation and characterization can influence the measured properties of PLGA formulations [149]. These findings illustrate that reproducibility requires control of both formulation composition and processing and analytical conditions. This is particularly important during scale-up, when laboratory procedures must be transferred to larger manufacturing processes without unacceptable changes in product quality. Accordingly, translational development requires the identification of critical quality attributes (CQAs) and critical process parameters, appropriate analytical characterization, evaluation of batch-to-batch consistency and demonstration of a reproducible manufacturing process during scale-up [130,149]. Regulatory requirements further complicate translation because nanomedicines are complex products and specific regulatory frameworks remain incompletely harmonized; early interaction with regulatory authorities and implementation of quality-by-design and risk-based approaches have therefore been recommended [141,142]. Standardized manufacturing protocols validated analytical methods, and systematic control of material and process variables are consequently important for achieving reproducible nanomedicine production and supporting progression toward clinical use [130,132,141,142].

Emerging technologies are expected to play a central role in advancing the field. Artificial intelligence and computational modeling provide powerful tools for predicting nanoparticle behavior, optimizing design parameters and reducing experimental variability. Additionally, advanced biological models, such as organoids and organ-on-chip systems, offer more physiologically relevant platforms for evaluating toxicity and efficacy, thereby improving the predictive value of preclinical studies [126,128].

Overall, the future of nanocarrier-based drug delivery lies in the integration of physicochemical design, quantitative pharmacokinetic–pharmacodynamic modeling and advanced toxicity assessment. Overcoming current challenges relating to safety, reproducibility and regulatory standardization is essential for translating nanomedicine from experimental research into routine clinical practice.

7. Conclusions

Nanocarrier-based drug delivery systems offer significant potential for overcoming limitations associated with conventional formulations, such as poor solubility, limited stability, rapid degradation and inadequate delivery to target tissues. However, the benefits of nanocarrier-mediated delivery depend strongly on the composition of the carrier, its size, surface properties, the drug-loading strategy employed, the route of administration and its interactions with biological barriers. It is important to note that increased drug loading or systemic exposure alone is not sufficient evidence of improved therapeutic performance. Meaningful evaluation requires consideration of biodistribution, target-site exposure, pharmacodynamic response and safety.

Despite substantial advances in nanocarrier design, the clinical translation of these systems is still limited by issues such as toxicity and immunogenicity, protein corona formation, unpredictable biodistribution and clearance, formulation instability, variability between batches, and challenges associated with scalable manufacturing and regulatory evaluation. Furthermore, differences between experimental models and human physiology remain a major obstacle to translating promising pre-clinical findings into clinically meaningful outcomes.

Therefore, future research should move beyond optimizing individual formulation parameters and establish quantitative relationships between the physicochemical characteristics of nanocarriers, their biological interactions, pharmacokinetics, pharmacodynamics and therapeutic outcomes. Standardized characterization methods, clinically relevant experimental models, long-term safety assessments and direct comparisons with conventional formulations will be essential in determining whether improvements in bioavailability translate into genuine therapeutic benefits. At the same time, reproducible and scalable manufacturing strategies must be incorporated into nanocarrier development at an earlier stage to facilitate regulatory evaluation and clinical implementation. Ultimately, successful translation will depend not only on maximizing drug delivery, but also on demonstrating consistent improvements in efficacy and safety that justify the added complexity of nanocarrier-based formulations.

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