Chapter 9

Nanomaterials in Pharmaceuticals

Tahmina Foyez1,2*, and Abu Bin Imran3

1Department of Hematology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
2Department of Pharmaceutical Sciences, School of Health and Life Sciences, North South University, Dhaka 1229, Bangladesh
3Department of Chemistry, Bangladesh University of Engineering and Technology, Dhaka-1000, Bangladesh

* tfoyez@unc.edu, tahminafoyez@gmail.com

Abstract

Nanotechnology is a relatively new but fast-expanding field that uses nanoparticles as analytical tools or as a controlled delivery system for pharmaceuticals. The unique properties of nanomaterials, including thermodynamic, electrical, structural capabilities, and optical make them intriguing options for pharmaceuticals, which substantially impact drug quality. Pharmaceutical nanotechnology, with its nano-engineered tools, is now well-established for drug delivery, diagnostics, prognosis, and disorder therapy. It has the potential to improve materials and medical devices as well as help to introduce new technologies in areas where traditional technologies have reached their limits. The present review focuses on nanomaterials and their applications in pharmaceuticals.

Keywords

Pharmaceutical, Nanomaterials, Polymer, Nanotechnology, Drug Delivery, Diagnosis, Nanomedicine

Contents

Nanomaterials in Pharmaceuticals .................................................................218
1. Introduction ............................................................................................219
2. Application of nanomaterials in pharmaceutical .....................................221
   2.1 Application of nanomaterials in the delivery of drugs .........................222
   2.1.1 Lipid nanomaterials in the delivery of drugs ...................................222
1. Introduction

Nanotechnology is a fast developing science that produces and uses nanosized particles measured in nanometers. It has revolutionized the distribution of drugs, diagnosis, and manufacture of biomaterials for medical applications, which led to new therapeutic approaches. The outstanding characteristics and specifications of nanoparticles make them more versatile and are expected to have a broad spectrum impact on existing technologies such as drug delivery, health sciences, therapies, and pharmaceuticals. Novel approaches to drug delivery systems are required to ensure drug efficacy and reduce adverse effects by delivering them to the targeted sites in the body. As a result, the pharmaceutical industry will develop its technology to meet the demands of patients. Pharmaceutical nanotechnology is one of the most comprehensive technologies where nanomaterials that are between 1 and 100 nanometers in size ranges are used [1, 2]. The Food and Drug Administration (FDA) advises that while evaluating the efficacy, public health impact, safety, or regulatory status of nanotechnology finished goods, any distinguishing characteristics that the use of nanotechnology may impart be properly considered [3]. The presence of a nanomaterial is characterized by three key aspects: size of particles, surface area of particles, and particle size distribution (PSD) [4, 5]. Pharmaceutical nanomaterials are manufactured using both top-down and bottom-up approaches. The top-down method includes the mechanical or chemical breakdown of a large materials into smaller pieces. In contrast, the bottom-up technique allows the precursor particles to increase in size by chemical reaction starting from atomic or molecular species [6, 7]. These two manufacturing processes result in various primary particles, aggregates, and agglomerates.
(Fig. 1) [8]. The drug nanoparticles improve solubility and bioavailability, as well as the potential to cross the blood-brain barrier, enter the pulmonary system, and be absorbed via the tight connections of skin endothelial cells owing to their small particle size and large surface area [9]. Nanotechnology can be used in two ways: to incorporate drugs into nanocarriers and fabricate drug-contained nanoparticles from various materials with a huge surface area and consistent porous interior [10]. Nanoparticles utilized in pharmaceutical nanotechnology include polymeric nanoparticles, dendrimers, polymeric micelles, liposomes, polymer and drug conjugates, antibodies, and drug conjugates. System types commonly employed include stimuli sensitive, sustained and regulated delivery of drugs, bioactive, multifunctional and site-specific targeted delivery, biosensory and diagnostic, multifunctional delivery systems, and so on [11-19].

Figure 1. Schematic illustration of particle types. The figure has been reproduced with permission from [6]

The recent breakthroughs in nanomedicine, commercialization of pharmacological nanotools, and worldwide interest shown by academia and governmental organizations all suggest that nano-based drug carriers have immense potential and scope (Fig. 2).
This chapter discusses the applications of nanomaterials in pharmaceutical research and industry to cure diseases with minimal side effects. The problems and prospects for the future development of nanomaterials for the pharmaceutical industry are also discussed.

2. **Application of nanomaterials in pharmaceutical**

Adverse and therapeutic effects should be addressed when designing novel medicines using nanomaterials. The use of nanotechnology in medicine, diagnosis, image analysis, and biosensing could greatly affect people's health [20]. Three factors, characterization, safety, and environmental impact, are crucial components of nanoparticles in pharmaceuticals that must be regulated. Solid lipid nanoparticles, different metallic nanoparticles, antibody-based products, and polymeric drug/protein conjugates are all lipid-based nanoparticles approved by the FDA [21]. Nanomaterials impact pulmonology, ophthalmology, immunology, oncology, cardiology, endocrinology, targeting CNS, targeting cancerous cells, and vaccine formulations [20, 22]. Nanoparticles may increase pharmacokinetics and bioavailability by inhibiting phagocytic cell uptake. They recognize biomacromolecules on their surfaces as artificial receptors, which could be used to control cellular and extracellular processes in a variety of biological applications such as diagnostics, drug administration, therapy, and biosensing (Fig. 2). However, there are some drawbacks to use nanotechnology in pharmaceuticals, such as increased aggregation in a living system due to low solubility, biocompatibility, and high surface energy. In addition, low half-life due to rapid scavenging by the host immune system, site-specificity, and safety issues are not expected [10, 20].
2.1 Application of nanomaterials in the delivery of drugs

Low solubility, low selectivity, quick elimination, and degradation rate hinder drug delivery to cells. Nanomaterials in drug delivery bring up new frontiers because of their ability to pass through microvascular capillaries, high surface area, and high loading capacity [23]. They have increased stability, biodegradability, long-circulating, and effectiveness without higher doses [24]. Drugs are incorporated into nanoparticle delivery systems in two ways: during nanoparticle formation and by incubating the carrier with a drug solution [23, 25]. Drug solubility, absorbed drug clearance, drug dispersion, delivery route, and degradation mechanisms affect drug release patterns [25, 26]. The size of nanoparticles, drug solubility, surface charge, stability, permeability, biocompatibility, biodegradability, and toxicity must be addressed when choosing matrix materials. Liposomes, polymers, carbon based nanomaterials, nanogels, dendrimers, metal nanoparticles etc. increase the pharmacological and therapeutic effects of traditional medicines [10, 23, 24].

2.1.1 Lipid nanomaterials in the delivery of drugs

Lipid-based nanoparticles may be an alternative to traditional carriers in targeted drug delivery. They may protect their contents from deteriorating physiological conditions by using lipid nanoparticles. They may be used to deliver medications that aren't soluble in water. Lipid bilayer-encased vesicles, known as liposomes, have an aqueous core and an outer lipids coating. The liposome is used as a delivery method because it has biocompatibility and encapsulating ability [27, 28]. Phospholipids such as phosphatidylglycerol, phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine are fabricated into liposomes, which are tiny vesicles. Food, cosmetics, and pharmaceutical industries have employed these phospholipids [29-31]. Generally, three varieties of liposomes are utilized by their size and number of bilayers: small unilamellar vesicle (SUV) (20 to 100 nm), large unilamellar vesicle (LUV) (100 to 800 nm), and multilamellar vesicle (MLV) [32]. Liposomes can be designed to treat various medical conditions, including cancer and skin disease, through multiple routes of administration. Depending on lipid bilayers, liposomes may include one or more therapeutic compartments, with lipophilic compounds incorporated into the lipid membrane and hydrophilic compounds integrated into the aqueous core. Liposomes, solid lipid nanoparticles (SLNs), lipid nanoparticles (LNPs), lipid nanoemulsions (LNEs), and nanostructured lipid carriers (NLCs) are the different types of lipid-based nanoparticles (Fig. 3) [33]. Because liposomal lipids resemble biological membranes, they are biocompatible and biodegradable [34].
The advantages of liposomal formulations include improved cellular penetration, pharmacokinetics, drug release, decreased side effects, and toxicity [32]. Liposomes are used in vaccine adjuvants, medical diagnostics, and analytical biochemistry. The usage of organic solvents, instability, sluggish payload release after administration and expensive cost of liposomes motivated researchers to create SLNs and NLCs [36-38]. SLNs are solid-at-room-temperature lipid nanocarriers. They may accept drugs or other molecules between fatty acid chains. They have considerable promise in pharmaceutical nanotechnology because of their particle size after drug incorporation, biocompatibility, biodegradability, and enhanced efficiency. High initial release, coupled with homogeneity and cheap cost/ease of scaling up, increases the effect of drugs [39]. Since SLNs have limitations such as drug leakage through the matrix and reduced loading efficiency, a new generation of NLCs have been designed [33, 40]. In these NLCs formulations, mixing solid lipids with small amounts of liquid lipids to induce rearrangements of the matrix structure increased their qualities while preserving the original benefits of SLNs [28, 41]. SLNs have European Medicines Agency (EMA) and FDA approval and are commercially available for intravenous, dermal, and oral delivery [34]. Lipid-based nanoparticles drug delivery systems can carry drug molecules to target cells with a regulated release, making them
ideal for various pharmaceutical companies. Almurshedi and colleagues explored pH-sensitive afatinib (AFT) liposomes for lung cancer. They discovered AFT-loaded liposomes induced cell death with a massive inhibitory effect on cancer cells. They also investigated that pH-sensitive liposomes release AFT quickly at pH 5.5, while cationic liposomes release AFT slowly at pH 7.5 [42]. The researchers also discovered that Turmeric-loaded NLC exhibited more excellent antioxidant activity than turmeric extract alone. NLC-turmeric has a higher antibacterial effect than free turmeric extract [43]. Lipid nanoemulsions (LNEs) are aqueous solutions containing submicron lipid droplets stabilized by surfactants. Therapeutic LNEs are plant-based lipid droplets 500nm in size maintained by phospholipids. LNEs are also employed to transport anesthetics, cancer treatments, and vitamins [44]. Whereas LNPs are similar to liposomes, except they enclose RNA and DNA. Pfizer and Moderna COVID-19 vaccines employ LNPs as mRNA carriers, making them the most frequently used non-viral gene delivery technology. LNPs lack the outer phospholipid bilayer structure of liposomes and instead contain genetic material in a micelle-like structure of cationic lipids. Surface functionalization of LNPs allows exact binding to target cells and boosts therapeutic effectiveness [45].

2.1.2 Carbon-based nanomaterials (CBNs) in drug delivery

CBNs are cylindrical structures produced from inorganic elements, including carbon, titanium, and metals like gold and silver (Fig. 4). CBN-based drug delivery systems provide higher efficiency, decreased toxicity, greater biodistribution, and enhanced patient compliance. Its drug delivery efficacy is impacted by shape, number of layers, size, and catalyst removal after synthesis [46, 47]. Examples of CBNs that have been extensively studied for drug delivery applications include CNTs, nanodiamonds, carbon nanohorns, carbon nanodots, and graphenes. It is possible to use SWNTs, MWNTs, and C60 fullerenes for drug administration because of their small size, geometry, and surface characteristics [46, 48]. CNTs have a huge surface area and unique surface chemistry, making them a good option for drug loading. CNTs-based drug delivery offers various benefits, including their tiny size (10 to 40 nm), ability to build a rod-like scaffold, and increased capacity to transport pharmaceuticals and transfer medications to the nucleus [46, 49, 50]. Liu et al. created chemically functionalized SWNTs and conjugated paclitaxel (PTX) to the PEG chain on the surface of the SWNTs. They then examined the suppression of cell proliferation in a murine breast cancer model. PTX had a tenfold increase in uptake due to the longer circulation time. They concluded that employing nanotubes as a drug delivery vehicle is effective for therapy with few adverse effects and low drug doses [51]. Treatment becomes more challenging in the central nervous system because drugs capable of crossing the blood-brain barrier are exceedingly limited. However, it has been demonstrated that certain functionalized CNT formulations can improve a compound's capacity to pass the blood-brain barrier [52]. Different carbon nanomaterials are shown in Fig.4 [53].
Figure 4. Schematic illustration of Carbon-based nanomaterials (CBNs) as an effective drug delivery system. The figure has been reproduced with permission from [53]

2.1.3 Polymeric nanomaterials in drug delivery

Polymeric nanoparticles provide substantial benefits over conventional drug delivery, including improved solubility in water, less antigenic activity, lower deactivation potential, and lowered toxicity [54]. It has been shown that stimuli-responsive, antibacterial, antioxidant, anticancer, and anti inflammatory activities are the most significant features of cationic polymeric nanosystems [55, 56]. In nature, biopolymers derived from living organisms can be found in abundance. They have the following benefits over traditional nanomaterials for drug delivery: they are nontoxic, biodegradable, biocompatible, and inexpensive. Albumin, gelatin, chitosan, dextran, cyclodextrin, HA, and starch are all examples of biodegradable polymeric nanoparticles [57]. Polysaccharides, a family of natural polymers, are particularly important. In terms of structure and pharmacokinetics, polysaccharides have a diverse molecular weight, polydispersity, electric charges, and chemical components. They have excellent biocompatibility, nontoxicity, biodegradability, nonimmunogenicity, and biological activity [58]. When it comes to hydrophilic drug delivery systems, chitosan is a good choice. It has garnered substantial interest as a carrier in innovative bioadhesive drug delivery nanosystems because of its reactive capabilities, ease of breakdown by enzymes, polycationic nature, and nontoxic degradation properties [55]. Drugs are chemically conjugated with chitosan derivatives such as N-Succinyl chitosan, glycol chitosan, and carboxymethyl chitosan. Cyclodextrins are polysaccharides that are used as nanocarriers [58-60]. The main benefits of cyclodextrins are sites where cationic or cell-targeting moieties can be added [55, 61]. HA
nanosystems are used to make gels that deliver drugs to the eye. This is done so that insulin from eye drops can be absorbed through the cornea when HA is present. So, the gel keeps the medicine from being washed away by tears and gives it a long time to work at the site of action [62]. Peptides and polypeptides are the two main types of biopolymer type nanomaterials that have emerged as a vehicle for therapeutic molecular delivery to fight against cardiovascular disease, aging, and diabetes, as well as various chronic metabolic syndromes, cancer, and many degenerative disorders [63]. Albumin is a protein nanoparticle that disintegrates naturally and is not toxic or immunogenic. It is a great way to give a drug as it is easily absorbed by the tumor tissue and dissolves in water, making it easy to inject [57]. In drug delivery systems, protein nanoparticles have many disadvantages compared to nanoparticles made of inorganic materials or synthetic polymers. They are usually made from microorganisms, and making and purifying protein nanoparticles takes a long time [58, 64]. Using various synthetic polymers, polymeric prodrugs have been developed. Poly(L-glutamic acid) (PGA), poly(L-aspartic acid) (PAA), Polyethylene glycol, PEI, dendrimer, and some amphiphilic block copolymers like PEG-b-PAA, PEG-b-PGA, and N-(2-Hydroxypropyl) methacrylamide (HPMA) are all examples of polymeric prodrugs [58, 62]. PEI can be changed chemically into linear and branched forms with different molecular weights, which gives it beneficial physical and chemical properties [55, 65, 66]. Poly-L-lysine (PLL) has a lot of amines on its surface, and it can interact with negatively charged molecules [55].

2.1.4 Drug delivery based on nanogel

Polymer gels, which are 3D networks of synthetic or natural polymers, have attracted much interest as polymeric nanocarriers [67, 68]. These nanosized cross-linked structures have properties like controlling their size, having a large surface area for bioconjugation, being low in toxicity, being able to swell and de-swell quickly, responding to multiple stimuli, and having a large mesh size [69-72]. To make nanogels, there are two main routes: making nanogels from polymer precursors or making nanogels through heterogeneous polymerization of monomers. Physical and chemical cross-linking is often used to connect polymer precursors [73, 74]. The physical interaction between polymers in nanogel makes it possible to encapsulate hydrophobic drugs [75]. Nanogels solve some problems with drug delivery systems, such as being able to deliver the right amount of drug to the right place, keeping the drug in the blood longer and allowing the target cell to accept it in, breaking down slowly, being biocompatible, being able to be made into targeted drug delivery nanosystems, and having low cytotoxicity [69, 76]. Because of their hydrophobic/hydrophilic repeating units change depending on the pH, nanogels are considered a great way to carry drugs. They take positively charged drugs through electrostatic interactions at alkaline pH. When the pH is acidic, the drugs are released. Also, when the pH is acidic, the low polarity makes drug molecules go into the hydrophobic core of the nanogel and come out when the pH is neutral. In general, nanogels transport drug molecules through physical entrapment, covalent, and noncovalent interactions [69, 77].
Drug release from nanogels can be controlled by diffusion, swelling, or active chemicals [76, 78].

### 2.1.5 Drug delivery based on metal nanomaterials

Scientists have focused on metal nanoparticles with unique physical and chemical properties in biomedical research. Metal-based nanoparticles have a high drug load and overcome the first-pass metabolism, photothermal behavioral potential, electrostatic charge, and surface chemistry of the molecules. Nanoparticles of silver, nickel, gold, iron, platinum, zinc, silica, gadolinium, and titanium dioxide (TiO₂) are often used in drug delivery systems [79-81]. Silicon nanoparticles work well as nanocarriers for a wide range of drug molecules. Mesoporous silica nanoparticles (MSN) with large surface areas resulted in high entrapment of either hydrophobic or hydrophilic drugs [81]. Noncrystalline drug entrapment in the mesoporous, high dispersibility with a large surface area, and an increase in the hydrophilic surface of MSN improve the drug's dissolution in water and bioavailability [82, 83]. Gold nanoparticles can also be considered promising pharmaceutical vehicles because of their chemical and physical properties. For example, they are easy to make in a wide range of sizes and shapes, from up to 100 nm, including spheres, hollows, nanoshells, rods, prims, and diamonds. They also absorb and scatter light strongly, have a high photothermal conversion rate, are biocompatible, and easily coat with different molecules. Lee et al. showed that gold nanoparticles could be used to deliver drugs for cancer therapy [84, 85]. TiO₂ is also used in the biomedical field because it is stable, biocompatible, and isn't toxic. It can destroy pathogenic substances like bacteria, viruses, fungi, and cancerous cells [86, 87].

### 2.1.6 Drug delivery based on dendrimer

Drug delivery is one of the most promising applications of dendrimers, which are monodisperse, hyperbranched macromolecules with 3D structures [88, 89]. While classical nanomaterials and polymers may have higher cellular absorption, monodispersity, synergistic or multivalence effects, and good cellular uptake; the globular shape and well-defined surface functionalities of dendrimers make them superior for drug delivery systems [90, 91].

### 2.2 Nanomaterials in gene delivery

In order to influence the expression of a specific gene and the biosynthesis of related proteins implicated in the onset of disease, nucleic acids are delivered to the target cell or tissue and used as a gene therapy technique. Positive charges can be added to carbon nanomaterials by either covalently or non-covalently changing the carbon surface, allowing the negatively charged DNA and siRNA to be delivered to the cells [46]. To make electrostatic complexes with the negatively charged siRNA, tiny groups with distal ammonium functionalities were covalently incorporated into SWNTs. Even at very high concentrations, carbon nanoparticles used for gene therapy do not hurt cells as much as commercial gene transfection methods do. Using transporters made of carbon
nanomaterials to deliver genes dramatically lowers the dose needed and improves cell absorption [46]. Dendrimers have received a lot of attention as gene delivery because their structures are flexible, their topologies have a lot of branches, and they are cationic, which allows binding to DNA at physiological pH [12]. A new way to get genes into the brain uses a serine-arginine-leucine (SRL) functionalized polyamidoamine (PAMAM) dendrimer [92]. Lipidic nanomaterials also seem to be a good choice for a gene delivery nanosystem because they are stable in storage, easy to make, and simple to sterilize, lyophilize, and pack [21]. Nanogel's cross-linked structure gives it better properties in gene delivery nanosystems. This made it possible to encase small fragments of nucleic acid like miRNA and siRNA in a stable way. Gene silencing has also been done successfully with polysaccharides like dextran and HA, and nanogels. Designing nanogels that can be disrupted by extracellular stimuli like light, ultrasound, temperature, or biological pH changes leads to fast disintegration and/or swelling [12, 77, 78, 93-104].

2.3 Nanomaterial in co-delivery systems

As nanomaterials can transport multiple therapeutic drugs, they can be used as an excellent way to make treatments more effective and have the best synergistic effect [105]. MSNs are metal-based nanomaterials used extensively as a co-delivery system [106]. Lipidic nanoparticles are better at encapsulating and incorporating drugs and genes. The formulations are an excellent way to deliver water-soluble or insoluble drugs while keeping side effects to a minimum and maximizing the delivery of active agents [21]. To treat Parkinson's disease, Cortesi and his team made NLCs with four types of levodopa. The results show that NLCs are attributed to a controlled drug release [107]. Using the appropriate nanosystem and dendrimer, researchers have been able to deliver genes and drugs to cells simultaneously, causing a synergistic effect at the target site of action [105, 108]. Hyperbranched structures and large holes in dendrimers enable the delivery of low molecular weight drugs via a co-delivery nanosystem, that is effective in delivering both drugs and nucleic acids to the same cell [109]. Co-treatment is considered an effective delivery system for polymeric nanoparticles because of their biocompatibility, stability, high efficiency in cellular uptake, and the ability to bind to genes. On the other hand, hydrophobic drugs can be encapsulated in hydrophobic polymer cores [106, 110]. SN38 anticancer medicines were successfully encapsulated in chitosan/CMD nanoparticles [111]. In nanotherapy, one of the most significant problems is the development of medication and gene delivery systems that selectively target specific cells without causing damage to normal healthy cells or tissues. Targeted therapy has the potential to improve efficacy while reducing adverse effects, which has led to the development of increasingly customized nanomedicines. Additionally, nanomedicine is promised in the local or targeted delivery of drug molecules, which results in the free dispersion of drug molecules throughout the body [112]. The steric hindrance of PEG allows it to be employed in the manufacture of stealth nanoparticles with limited absorption by the RES system and the creation of hydrophilic protective layers on the nanoparticles' surface [58, 77]. Targeting moieties such as aptamers, peptides, proteins carbohydrates folates, antibodies, vitamins, tiny molecules on nanomaterials may also boost treatment efficacy and selective
accumulation in the targeted area [77, 113]. Nucleic acid, protein, and peptide-grafted CBNs have garnered interest too. Biomedical applications are constrained by the potential for functionalized CNTs to be turned into hazardous materials. Using CBNs as co-delivery systems for active targeting of overexpressed receptors on cells, specific targeting ligands may be chemically bonded to CBN surfaces [46]. Engineered nanotechnology has proven improved biocompatibility and multimodality to improve therapeutic results. Han and colleagues administered doxorubicin (DOX) and major vault protein (MVP) siRNA to human breast cancer MCF-7/ADR cells using a polyamidoamine (PAMAM) dendrimer linked with hyaluronic acid (HA) polysaccharide as an active target, lowering MVP expression and increasing DOX chemotherapeutic impact. Co-delivery of MVP siRNA and DOX significantly reduced MCF-7/ADR cell drug resistance [114]. Camptothecin (CPT) and 3,30-diindolylmethane (DIM) are two anticancer medicines that may be delivered via chitosan cross-linked with graphene oxide nanoparticles. Co-treatment of CPT and DIM boosted anticancer efficacy and prevented the harmful impact of CPT in vivo [115]. Imran et al. reported Ag nanoparticles incorporated hydrogel with antibacterial, biocompatibility, and wound healing capability [116].

3. **Approved pharmaceutical therapeutic nanosystems**

Preclinical evaluation (clinical trial phases I, II, and III) and premarketing evaluation (phase IV) are required for FDA approval of nanoparticle-based delivery systems [117]. Approximately 70% of phase I evaluated drugs are considered for phase II, and the primary reason for phase I study termination is safety failure. In phase II, drugs are evaluated on a homogeneous patient population. Based on phase II results, drugs can proceed to the phase III study. About 33% of phase II drugs fail to progress to phase III due to inefficiency. Phase III is completed on a large patient population to ensure long-term safety. Only 25%–30% of phase III evaluated drugs are submitted to the FDA for approval [118]. Phase IV, or postmarketing, evaluation of the product occurs after it has been approved for sale. During this time, nanosystems drugs' efficacy and long-term safety are examined in populations that were not included in the phase III study. Phase IV of clinical trials is critical for nanoparticle delivery systems because of the efficiency and toxicity issues [119]. Many nanoparticles formulations have problems making it to the clinic because of how their studies were set up from biological, technological, and other perspectives. Biodistribution and controlling how nanoparticles move across the cell membrane are two examples of physical barriers. Increasing target site accumulation and reducing off-target activity or adverse effects is difficult in clinical application of the delivery system. Scaling up synthesis, improving performance, and anticipating performance are the major technical obstacles for nanoparticle-based drug carriers in clinical applications [118, 120, 121]. In the pharmaceutical industry, nanoparticle delivery systems already on the market or in clinical trials make up 15% of the market. The FDA-approved products can be given orally, topically, or systemically, depending on where they are meant to work and how the nanoparticle delivery system is being used [117]. Liposome nanocarriers, polymer drug conjugates, polymer protein conjugates, monoclonal antibody products, and some polymeric drugs are all FDA-approved nanomaterials (Table 1). Over 12 drug delivery
systems that use liposomes are in different stages of clinical trial approval. Doxil is the first liposome-based drug delivery system that the FDA has approved. This product reduces the toxicity of DOX and makes it work better by putting the drug inside a unilamellar liposome that is linked to PEG to keep the drug stable in the bloodstream for a long time so that it can reach its target site [122]. The visudyne liposome is a drug that works when exposed to light. It can be used to treat people with neovascularization [121].

Table 1. FDA-approved nanomaterials-based pharmaceuticals [123-127]

<table>
<thead>
<tr>
<th>Nanomaterial</th>
<th>Drug</th>
<th>Disease</th>
<th>Approval year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxil</td>
<td>Multiple myeloma, cancer of the ovary</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>DaunoXome</td>
<td>Kaposi's cancer</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>AmBisome</td>
<td>Infections by fungus</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Curosurf</td>
<td>Respiratory Distress Syndrome</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td>Visudyne</td>
<td>Macular degeneration, myopia</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Marqibo</td>
<td>Leukemia</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>Onivyde</td>
<td>Cancer of pancreas</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Vyxeos</td>
<td>Myeloid leukemia</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>Onpatro</td>
<td>Amyloidosis</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>BNT162b2 vaccine</td>
<td>coronavirus disease</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>mRNA-1273 vaccine</td>
<td>Prevention of coronavirus disease</td>
<td>2020</td>
</tr>
<tr>
<td>Polymer Nanoparticles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adagen</td>
<td>Immunodeficiency disease</td>
<td>1990</td>
</tr>
<tr>
<td></td>
<td>Oncaspar</td>
<td>Lymphoblastic leukemia</td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td>Copaxone</td>
<td>Multiple sclerosis</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>Renagel</td>
<td>Chronic kidney disease</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Peglntron</td>
<td>Hepatitis C infection</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>Eligard</td>
<td>Prostate cancer</td>
<td>2002</td>
</tr>
<tr>
<td></td>
<td>Neulasta</td>
<td>Neutropenia, chemotherapy-induced</td>
<td>2002</td>
</tr>
<tr>
<td></td>
<td>Somavert</td>
<td>Acromegaly</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Macugen</td>
<td>Macular degeneration, neovascular age-related</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>Abraxane</td>
<td>Breast cancer, lung cancer, pancreatic cancer</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>Mircera</td>
<td>Anemia</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Cimiza</td>
<td>Ankylosing spondylitis, Crohn's disease, psoriatic arthritis, rheumatoid arthritis,</td>
<td>2008</td>
</tr>
</tbody>
</table>
4. Nanomaterial in vaccine technology

Nanoparticles outperform conventional vaccines and adjuvants. Solubilizing hydrophobic antigens with nanoparticles improve vaccine safety. They allow for a controlled release of antigens with less volume and dose [128, 129]. Modifying nanoparticles can make them more immunogenic with adjuvant, which helps to carry antigens for multiple pathogens at once securely. Researchers have also developed a spore-based vaccine that is effective against Bacillus subtilis and Clostridium tetani spores [130, 131]. Vaccines are the best way to prevent viruses like SARS-CoV-2. Imran et al., 2022, reviewed recent advances in COVID-19 vaccine development, highlighting the role of nanotechnology in vaccine production [132]. Peptide-based vaccines are the simplest to develop, validate, and prepare [133]. DNA vaccines can produce cellular immunity, including humoral immunity, and are currently the safest one. DNA vaccines encapsulated with specific nanoparticles prevent DNA degradation [134]. PSM-based therapeutic dendritic cell vaccine acts as both antigen peptide carrier and adjuvant. The shape of PSM objects is associated with absorption by circulating dendritic cells. Inguinal lymph nodes and spleens were heavily vaccinated. In contrast, popliteal lymph nodes respond better to intradermal vaccines [135]. Nanotechnology has a high potential for future vaccine development.
5. Application of nanomaterials in imaging

Imaging is being used more to diagnose and make treatment plans for diseases. Imaging data can now be used in clinical trials as objective, noninvasive ways to measure how well a therapy works. Nanotechnology can be used to find clinically significant markets with imaging techniques like magnetic resonance imaging (MRI), ultrasound, single photon emission computed tomography (SPECT), fluorescence microscopy, positron emission tomography (PET), and computed tomography (CT). Liposomes can be made magnetic so MRI can track their movement inside the body. With their nanometer-sized magnetite cores, these magnetic liposomes can be used as biocompatible MRI agents that could be used for both imaging and drug delivery [136]. Different contrast agents and radio-pharmaceuticals can be carried inside liposomes. Using positron emission tomography (PET), liposomes are also used to monitor real-time liposomal trafficking in tumors in mice [137]. Magnetic nanoparticles send drugs and genes to specific cells, separate cells, and label cells. Colloidal iron oxide and dextran [138] are utilized as MRI contrast agents. Iron oxide nanoparticles are widely used because they are biodegradable, safe for living things, superparamagnetic, and suitable for MRI applications. Insulin-coated iron oxide nanoparticles stuck to receptors on the surface of cells, blocking them from going inside the cells and lowering their toxicity [139].

6. Nanotechnology and safety issues

Nanotechnology is a new, promising technology that will significantly affect all industries. Therapeutics that use nanotechnology are becoming increasingly popular in the pharmaceutical industry. But the same new properties and traits that make it easier for drugs to get to where they need to go also pose new risks and toxicity. Some of these unique qualities are unknown or need to be investigated more. The limited information supporting either side makes it difficult to justify. Due to their low toxicity, nanoparticles made from natural or safe components, such as lipids, albumin, or nanoemulsions, appear to have the most potential. Other systems like CNTs show promise, but more research is needed on toxicity. Until then, CNT-based delivery systems for therapies are unlikely.

Conclusions

Nanomaterials can be used to deliver drugs in a controlled way and take images of specific areas. With its nanoengineering tools, pharmaceutical nanotechnology is expected to affect many aspects of diagnosing, predicting, and treating diseases. Many nanoparticles are made to carry substances that improve the pharmacological and therapeutic effects of drugs. Nanocarriers can better distribute active compounds in the body, protect them from disintegrating, and respond to biological barriers. The systems for delivering nanoparticles are being made to treat and cure many diseases. Gene therapy is hard to use clinically because it breaks down and gets rid of itself in the bloodstream, is taken up by cells that aren't the target, escapes from endosomes, and has toxic effects when the immune system is stimulated. Using nanocarriers to deliver a drug and a gene is better than just using
chemotherapy alone. Co-delivery methods still have to deal with many problems, such as capacity, biocompatibility, stability, release kinetics, loading, and the effectiveness of tumor targeting. Many different nanoparticles can be used for bioactive delivery, and each has its benefits, which FDA has clinically approved. In addition to these efforts, many clinical trials are looking into new nanoparticle systems that are better than those already approved. The market for nanopharmaceuticals is growing, and that growth is expected to continue over the next few decades as new delivery systems based on nanoparticles are being made and new therapeutic approaches that need intelligent delivery systems to work.

Acknowledgments

T. Foyez gratefully acknowledges the administrative support received from North South University. A.B. Imran is thankful to the Committee for Advanced Studies and Research (CASR) at Bangladesh University of Engineering and Technology for funding.

References


