Review Article

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Approved and marketed nanoparticles for disease targeting and applications in COVID-19

Abstract: Nano-based systems can be used to transport active medicinal products to specific parts of the body. Most challenges with drug delivery, such as low water solubility and poor bioavailability, can be solved using nanotechnology. In addition, nanoparticles can overcome various physiological obstacles to increase load distribution to desired sites. Nanoparticles can carry a load of medication or therapeutic agent, such as a DNA-related substance, to enhance distribution time and deliver the drug to the target site in either a nonspecific (through enhanced permeability and retention (EPR)) or specific (through binding specific target receptors) manner. Moreover, nanoparticle drug delivery systems have been employed in the clinic since the early 1990s. Since then, the field of nanomedicine has developed with growing technical needs to improve the delivery of various medications. Over these past decades, newer generations of nanoparticles have emerged that are capable of conducting new delivery activities that could enable therapy *via* innovative therapeutic modalities. This review highlights different types of approved and currently marketed nanoparticles, such as nanocrystals, liposomes, lipid nanoparticles, PEGylated polymeric nanoparticles, protein-based nanoparticles, and metal-based nanoparticles. Furthermore, it explores the use of vaccine-loaded nanoparticles for COVID-19 prophylaxis.

Keywords: nanoparticle, approved marketed drugs, liposome, polymeric nanoparticles, nanocrystal nanoparticles, protein-based, formulated vaccines

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1 Introduction

In pharmaceutical research and clinical settings, nanoparticulate pharmaceutical drug delivery systems (NDDSs) are commonly used to increase the efficacy of medicines [1]. Liposomes, polymers, micelles, metal nanoparticles, carbon nanotubes, solid lipid nanoparticles, noisomes, and dendrimers are various types of nanoparticles that can be used to deliver drugs and target diseases. Drug-related problems such as low water solubility, poor bioavailability, and off-target delivery can be solved using NDDSs. NDDSs have been used to improve drug stability, to improve distribution time, and to target specific sites in the body [2–4].

NDDSs have been developed to overcome various physiological obstacles and distribute loads to specific target sites [5–8]. Characteristics of multifunctional NDDSs include carrying an adequate load of therapeutic substance, enhancing distribution time, and reaching specific target receptors [4]. In addition, multifunctional NDDSs may be developed to react to various stimuli that are characteristic of the pathological location, by adding elements that respond to irregular pH, temperature, oxidation, and overexpression of some biological molecules. Multifunctional NDDSs can also react to external stimuli, such as ultrasound or magnetic fields. The addition of an imaging contrast moiety can allow the monitoring of distribution, target accumulation, or therapy effectiveness [1,4].

In the last few years, the number of newly developed drugs with considerable lipophilicity, high molecular weight, and low water solubility has increased. Approximately 40% of the market-approved drugs and almost 90% of discovery pipeline molecules have poor water solubility [4]. Much of the failure of newly developed medicines is due to the poor solubility of the drugs in water. It is known that low solubility and poor dissolution can lead to lower bioavailability and sub-optimal drug delivery. Nanoparticle-based formulations, lipid-based drug delivery systems, prodrugs, amorphous solid dispersions, salt formation, co-crystals, and cyclodextrin complexes are widely used to increase the dissolution rate of these molecules [4,9–12].

The preparation of drugs in the nanoparticle form improves the dissolution rate of many medications. Drug-loaded nanoparticles have a greater surface area and a higher overall coefficient of transfer of solution than their micron-scale counterparts. In addition, ultrafine particles tend to display excellent saturation solubility, particularly those less than 100 nm. This phenomenon is described by the Ostwald–Freundlich equation [13]. According to the Noyes–Whiney equation [14], the dissolution rates are also improved. This enhances the bioavailability of the drugs. Other benefits of drug-loaded nanoparticles include improved safety of dosage escalation and increased efficacy and tolerability profiles. In addition, they can improve solubility and dissolution rates, leading to improved bioavailability [15].

Nanoparticle-loaded medications may be formed by three different methods (top-down, bottom-up, and combinative techniques). Top-down methods include high-pressure homogenization (HPH), stirred media milling, and ball milling. This technique involves high shear-impact forces to decrease coarse particle drug crystals to the nanometer scale [16]. Bottom-up methods include particle build-up liquid antisolvent precipitation (LASP), dissolved molecule precipitation, and supercritical fluid precipitation. Melt emulsification is another example of a bottom-up methodology and is used for medicines with low melting points [17]. In this method, the drug is distributed and heated to melt the crystals in an aqueous stabilizer solvent, followed by flash cooling to generate nanoparticulate medications. Combinative methods include a combination of bottom-up and top-down approaches [15]. This review classifies nanoparticles and highlights their applications, with a focus on marketed and approved nanoparticles. Furthermore, we discuss the use of vaccine-loaded nanoparticles in the prevention of COVID-19.

2 Types of therapeutic nanoparticles

Nanoparticles can be classified into four major categories: nanocrystalline, polymeric, nonpolymeric, and lipid-based
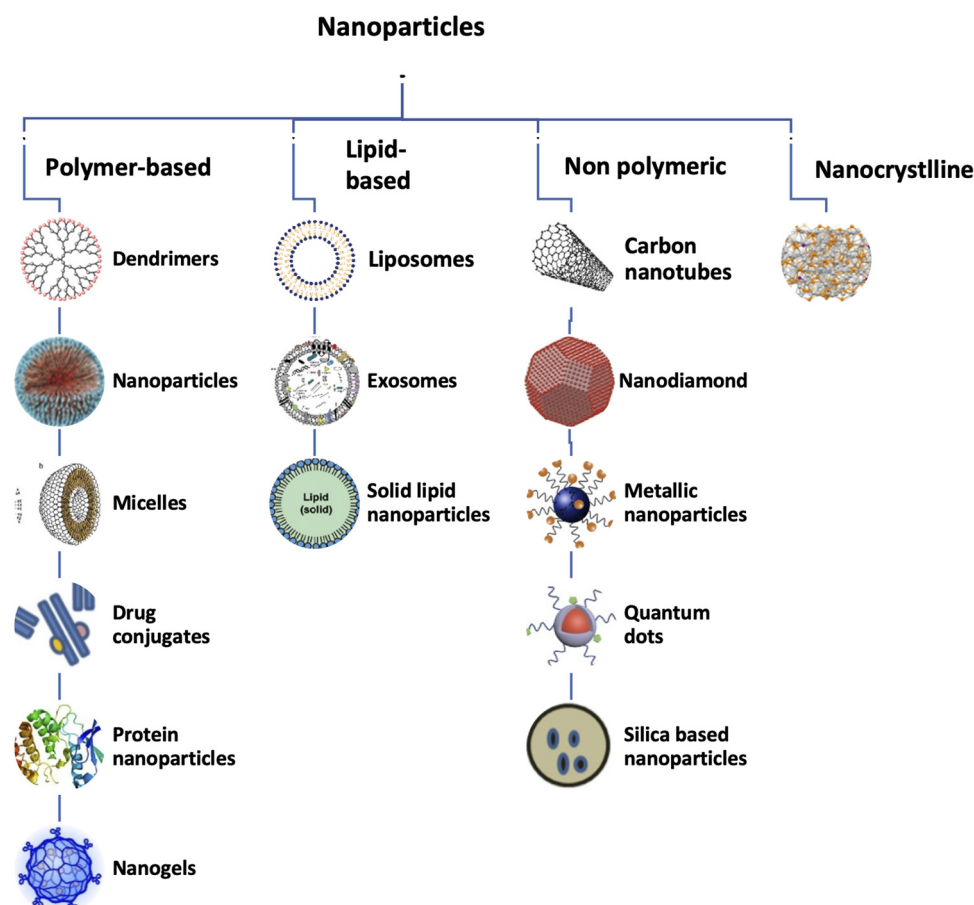
Figure 1: Schematic diagram representing the different types of nanoparticles due to varying types of formulations.

nanoparticles (Figure 1). Micelles, drug conjugates, gels, protein nanoparticles, and dendrimers are polymer-based nanoparticles. Nanodiamonds, silica, quantum dots, carbon nanotubes, and metallic nanoparticles are nonpolymeric nanoparticles. Lipid-based nanoparticles include liposomes and solid lipid nanoparticles (SLNs) [18]. Crystalline nanoparticles are formulated by mixing therapeutic agents in the crystal state. In this section, we briefly summarize various kinds of therapeutic nanoparticles and their medical applications, as well as their delivery techniques, in difficult pathophysiological situations [19,20] (Figure 1).

2.1 Polymeric-based nanoparticles

2.1.1 Dendrimers

Owing to their hyperbranched, compartmentalized design and large monodispersity, dendrimers are widely used in medical practice. By tweaking the number of branches, the dimensions of the particles can be reduced to a minimum (1–5 nm). They can be made by spherically shaped polymerization, which results in the production of cavities within the dendrimer particle [21,22]. High entrapment efficiency was found with high-generation dendrimers. For example, dendrimers that contain over 64 surface groups were compared with relatively small dendrimers. These can be used for the delivery of medications. Dendrimers have free end groups that can be easily swapped with biocompatible conjugate molecules to improve their limited cytotoxicity and permeability. Moreover, surface improvements can enhance the delivery of therapeutic agents to specific target sites. Designing dendrimers through encapsulation or complexation makes them attractive vehicles for simultaneous delivery to target sites. Biological molecules such as genes, drugs, vaccines, and mono-polymers or co-polymers such as chitin, polyethyleneimine, polyamidoamine, and poly(propyleneimine) are currently used to form dendrimers [22,23].

2.1.2 Polymer-based nanoparticles

Polymer-based nanoparticles are either synthetic or natural. They offer an alternative approach for medicinal applications such as biocompatibility, nonimmunogenicity, nontoxicity, and biodegradability [24]. Polyester formulations are used to reduce the immunogenicity and toxicity of synthetic polymers. Natural polymer-based nanoparticles such as chitosan, gelatin, albumin, and alginate appear to solve toxicity problems and offer a significant increase in efficacy compared to traditional approaches. On the basis of their structure, they may be classified as nanocapsules or nanospheres [25]. A multitude of polymeric nanoparticle preparation techniques can be used to tweak the release characteristics of integrated therapeutic agents, allowing the concentration of agents at the target site. Specific recognition ligands that enhance the drug specificity in targeted tissues may easily alter and functionalize the surface of polymeric nanoparticles [26–31].

2.1.3 Micelles

Micellar solutions are most commonly used to carry low-solubility therapeutic agents. Micelles are approximately $100\,\mu m$ in diameter and form aggregates in the solvent. The constituent molecules of polymeric micelles are structured in a spherical configuration, where a mantle of hydrophilic groups surrounds the hydrophobic centers. The hydrophilic surface offers protection against nonspecific absorption by the reticuloendothelial system, maintaining its high stability within physiological systems [32]. Conversely, water-insoluble hydrophobic therapeutic agents can be mechanically trapped by the hydrophobic centers of polymeric micelles. It is also possible to covalently bind product molecules to this hydrophobic center. The dynamic design of polymeric micelles offers a prominent therapeutic agent delivery mechanism that enables flexible loading, targeted ligand conjugation, and a lower dissolution rate [32–34].

2.1.4 Drug conjugates

For low-molecular-weight agents, conjugation of polymers with drug molecules is common, especially in cancer treatments. The total molecular weight of medications is increased by conjugation, which affects the pharmacokinetic disposition of the cells. Polymer–drug conjugates are highly soluble, stable carriers and improve permeability and retention in cancer cells [35]. For continuous drug release and improved drug capacity, covalently conjugated polymer drugs are highly stable [36]. pH-Sensitive polymeric drug conjugates are formed by the use of pH-responsive polymer–drug chemical bonds. Thus, regardless of the medium acidity, pH-responsive nanoparticles are used for the controlled release of drugs at the tumor site [37,38]. For instance, polymeric conjugation of paclitaxel and doxorubicin, in combination, improved the bioavailability of the drugs [36,39,40].

2.1.5 Protein nanoparticles

Protein nanoparticles, including viruses, enzymes, and virus-like particles, are formed by recombinant activity. The synthesis of materials, drug and gene administration, imaging, and vaccine development benefit from this technology. Viruses are natural carrier systems for transporting genetic material encapsulated by capsid proteins. Virus-like particles (VLPs), a type of protein nanoparticle, are classified as nanocarrier systems with a morphologically similar, virus-isolated structure but do not contain viral genetic material [41,42]. Caged proteins (CPs) are nano-formulation systems of self-assembled proteins that are morphologically similar to viruses but are not derived from them. VLPs and CPs are enticing nanocarrier structures that can cause antigen-specific immune responses against cancer cells to develop cancer vaccines [43]. Protein nanoparticles that are isolated proteins of animal or plant origin, such as gelatin, silk, albumin, elastin, collagen, and soy, are formed by self-assembling protein polymers. Protein polymers are self-assembled into usable drug delivery carriers by genetic modification, with polymer-based nanoparticle benefits [44,45]. Abraxane is a protein nanoparticle drug approved by the Food and Drug Administration (FDA) that enables the delivery of paclitaxel by albumin. Another example, an HIV vaccine made from VLPs, has contributed to significant development, accelerating research into protein nanoparticles for clinical use [46,47].

2.1.6 Nanogels

Gels are colloidal or polymeric nonfluid networks that swell when in contact with a fluid. Nanogels are defined by the International Union for Pure and Applied Chemistry (IUPAC) as gel particles with these properties but with a diameter of less than 100 nm [48]. The swelling properties of flexible scale and elevated water concentration of nanogels are the outcomes of physically or chemically cross-linked natural or synthetic polymers [49,50]. Physically cross-linked amphiphilic polysaccharides have been physically cross-linked to prepare the first recorded nanogel, where cholesterol-bearing pullulans were self-assembled (by hydrophobic interactions) into water nanogels [51,52]. Compared to other nanocarrier structures, nanogels provide many benefits, such as reduced untimely medication leakage, encapsulation of multiple therapeutic molecules in the same formulation, and simple administration by parental or mucosal routes. Nanogels have been used in various applications, including biochemical separation, cell culture, bio-catalysis, drug delivery, antitumor therapy, and biosensors. Among these, the most commonly researched uses of nanogels are the delivery of therapeutics such as nucleic acids, antibiotics, cytokines, and nasal vaccines [49–51].

2.2 Nonpolymeric nanoparticles

2.2.1 Carbon nanotubes

Carbon nanotubes are tubular structures based on carbon that are 1 nm in diameter and 1–100 nm in thickness [53]. Such structures are obtained by wrapping a single layer of graphite, called graphene, into a smooth cylinder. Single-walled nanotubes (SWNTs), multiwalled nanotubes (MWNTs), and C60 fullerenes have been used in carbon nanotube configurations. Carbon nanotubes are an appealing nonpolymeric transporter for therapeutic agents because of their size and stable geometric form. In addition, the internal diameters of SWNTs and C60 fullerenes are 1–2 nm, which is approximately half the average diameter of the DNA helix [54]. Through endocytosis or direct entry *via* the cell membrane, SWNTs and MWNTs may reach the cell. Fullerenes vary in their graphite cylinder arrangement and the central structure of a high number of conjugated double bonds. Fullerene studies have demonstrated their use in supply therapeutics as antiviral, anticancer, and antibiotic agents [55–58]. In addition, by providing free radicals, they can support damaged mitochondria [59]. This approach enables selective targeting of mitochondria to deliver drug molecules [60].

2.2.2 Nanodiamonds

Nanodiamonds (NDs) are components of carbon-based nanoparticles that are less than 100 nm. They come in two distinct facet forms, formed by different techniques, such as chemical vapor deposition (CVD), detonation, and high-temperature/pressure techniques [61,62]. The detonation process of nanodiamonds involves triggering a controlled explosion on carbon-containing precursors in a closed chamber, the oldest and most widely used nanodiamond preparation technique. Nanodiamonds prepared by this technique normally include sp^2 carbon on the surface, and the electrostatic potential of the surface depends on the form and the composition of the NDs [63–66]. To deposit NDs on diverse substrates, such as thin films, the CVD form is preferable. With few defects,

nanodiamond thin films are high quality [67]. Nanodiamonds have special features, such as electrostatic surface properties, low chemically inert core cytotoxicity, and low photobleaching. They immobilize various biomolecules, making them exceptional for medical applications such as magnetic resonance imaging (MRI), contact lens synthesis, and drug delivery. Furthermore, nanodiamonds can be coupled with gadolinium (Gd)(III) as a contrast agent for MRI. The signal produced from this complex is superior to that of other contrast agents based on Gd(III) [61–63].

2.3 Metallic nanoparticles

Metallic nanoparticles are 1–100 nm in size and are often composed of gold, cobalt, nickel, iron, and their respective oxides such as chromium dioxide, maghemite, cobalt ferrite, and magnetite. They can be easily synthesized and modified, which allows them to be decorated with different molecules, including medicinal agents and biological molecules such as DNA, proteins, and peptides [68–73]. As carriers, they are stable, biocompatible, and have unique characteristics such as magnetic properties. Magnetic nanoparticles may be guided to a particular location in the body using an external magnetic field. A significant parameter for their medical use is magnetic susceptibility, defined as the ratio of the induced magnetization to the area applied. Superparamagnetic iron oxide nanoparticles (SPIONs) have a high magnetic susceptibility and are commonly used as contrast agents for MRIs in hospitals [74]. Similarly, superparamagnetic properties promote the secure distribution of therapeutic agents to the body and proper accumulation in the target tissue, providing a reproducible and safe approach [57,75]. They can create heat in a process called magnetic hyperthermia, as metallic nanoparticles are affected by an alternating magnetic field, which allows them to be used in the ablation of tumors [76].

Gold nanoparticles (AuNPs) are used in the diagnosis and treatment of cancer. This is due to the unique optical and localized surface plasmon resonance (LSPR) and lower cytotoxicity resulting from the inert nature of gold. Because of the LSPR, when light with the proper wavelength is provided to gold nanoparticles as an external stimulus, they undergo photo-thermal transition. They target tumor tissues in a heat-specific manner to kill cancer cells. Gold nanoparticles are also used to deliver drugs, with light irradiation triggering drug release at the targeted site [73,77–81].

2.3.1 Quantum dots

Quantum dots (QDs) are tiny semiconducting particles or nanocrystals with a size range of 2–10 nm. These particles are composed of an inorganic core semiconductor, such as CdSe, and an organic-coated aqueous shell, such as ZnS [70,82]. Quantum dots fluoresce with distinctive colors that are partially the product of exceptionally high surface-to-volume ratios. The color produced is determined by the core structure of quantum dots, while the outer aqueous shell may be used to conjugate biomolecules such as peptides, proteins, and DNA [83–85]. A cap can also be borne by QDs, which increases their solubility in aqueous buffers. Quantum dots can be used to detect therapeutic agents inside cells/tissues because of their narrow emission, light fluorescence, and high photostability. Their surface's flexible bioconjugation, adaptable photophysical features for multiplexed detection, and superior stability for longer examination times make them outstanding candidates compared to other fluorescent substances. However, the medicinal use of QDs is still controversial [86,87].

2.3.2 Silica-based nanoparticles

Silica-based nanoparticles provide significant advantages in nanomedicine owing to their applicability to modeling complex structures and their cost-effectiveness. Their particular surface properties, porosity, and functionalization characterize them as appealing therapeutic delivery tools [88]. The broad surface area of silica nanoparticles is protected by polar silanol units, which are favorable for water adsorption and enhance the stability of therapeutic agents. Furthermore, nanoparticles based on silica can interact with nucleic acids, allowing them to be used as targeted delivery vehicles [89]. In addition, therapeutic agent encapsulation inside silica-based nanoparticles offers a solid agent distribution medium. The pores of silica nanoparticles can be capped with different stimulus-responsive molecules to enhance drug release in the desired target tissue. Mesoporous silica nanoparticles capped with β-cyclodextrin were used to release the encapsulated drug into acidic tumor tissue. In biological systems, nanoparticles are combined with contrast agents such as silver, iron oxide, organic dyes, gold, and quantum dots [90]. In addition, these nanoparticles are used in pharmaceutical processing as additives to enhance the mechanical characteristics and biocompatibility of the substance.

2.4 Lipid-based nanoparticles

2.4.1 Liposomes

Liposomes are particles formed by hydrating dried phospholipids. They are made with lipid particles and surface adjustment to produce particles of various shapes, compositions, scales, and versatility. Liposomes have the significant benefit of being able to fuse with the cell membrane and spill their contents into the cytoplasm, making them appropriate carrier systems for selective delivery. The simplest liposomes are composed of a lipid bilayer surrounding a hollow center of 50–1,000 nm. Therapeutic molecules can be loaded into this hollow center [91–93]. Liposomes are categorized into three specific forms based on the number of bilayers: large unilamellar, multilamellar, and small unilamellar. Multilamellar particles are composed of multiple bilayers of lipids that are separated by aqueous spaces. Unilamellar vesicles, by comparison, are composed of a single bilayer covering the trapped aqueous area. They can carry both hydrophobic and hydrophilic particles owing to their structural properties. In the liposome's aqueous interior, hydrophilic particles can be stored, and in lipid membrane hydrophobic particles, they can be dissolved [94].

Furthermore, more than one form of the drug may be loaded in liposomes in two compartments (lipid and aqueous) or in the multiple aqueous layers of multilamellar liposomes. They also enable the release of various drug molecules through the dissociation of layers from the outer shell to the inner center [95]. Compared to large, unmodified liposomes, neutral or positively charged smaller liposomes have a better circulation time [96]. Surface modifications, such as coating with a functionalized polymer or PEG chains, facilitate specific target distribution and improve circulation time in biological systems. Liposomes have been studied for a broad range of therapeutic uses, including tumor detection and treatment, antibacterial therapy, immunization, and brain-targeted drug delivery [93,97].

2.4.2 Exosomes

Exosomes are normally shaped and secreted by different cell types. They are extracellular vesicles originating from endosomes with a scale of 30–150 nm that are typically present in various body fluids such as blood, urine, saliva, and breast milk [98]. Exosomes are lipid bilayer vesicles that are cell membrane-like and contain diverse compounds, including DNA, glycolipids, RNA, and proteins [99,100].

Transmission of different compounds to physiological pathways such as neural connectivity, immune response, and antigen presentation can help in conditions such as cardiovascular disease, diabetes, cancer, and inflammation. Exosomes are essential for intracellular communication [98,101]. Allogenic exosomes benefit the immune system. These vesicles can be separated from body fluids and used to effectively shield cargo from accelerated clearance and enhance drug distribution to the targeted sites [102]. Exosomes are being studied for their potential as drug carriers for tumors and autoimmune diseases and as diagnostic biomarkers for tumors and even for tissue regeneration [103,104].

2.4.3 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are aqueous colloidal dispersions that contain a solid lipid matrix at room and body temperatures. Surfactants improve their stability, while the particular lipid used has an impact on the drug delivery characteristics. SLNs range in size from 10 to 1,000 nm, depending on the manufacturing method [105]. SLNs are a type of lipid carrier that can encapsulate large amounts of lipophilic, hydrophilic, and nucleic acids, making them a versatile drug delivery vehicle [106,107]. Antibodies, magnetic nanoparticles, and pH-sensitive lipids/polymers are among the various moieties that can be loaded onto SLNs to modulate targeted delivery and stimuli-responsive drug release [108,109]. They have been demonstrated to be efficient carriers for tumor, pulmonary, and oral drug delivery [110,111].

2.4.4 Nanocrystalline particles

Nanocrystalline spheres (nanocrystals) have a crystallite dimension of only a few nanometers, and they are carrier-free drug particles. As a highly cost-effective solution, nanocrystal products are commonly used for poorly water-soluble drugs, which would normally have low bioavailability and absorption [112–114]. Size reduction is usually an effective method to increase the bioavailability of drugs, in which the rate-limiting stage is the dissolution velocity. The crystal structure results in a larger total surface area, which increases the dissolution velocity. This trait increases solubility, particularly when the agent's therapeutic index is reduced because of difficulties with absorption. Owing to their rapid breakdown, nanocrystalline particles allow the rapid absorption of therapeutic agents, providing a benefit for agents that rely on rapid

action. The sustained or selective release can be accomplished by changing the nanocrystal structure, enabling therapeutics to be used at smaller concentrations, and reducing adverse effects [115].

2.5 Viral vector vaccines

Despite the fact that the use of viral vectors for therapeutic purposes began in the late 1990s, the application of these vectors for disease treatment was mostly overtaken by the death of Jesse Gelsinger, who died after receiving an adenoviral vector for adenovirus infection [116], and leukemia in children with severe combined immunodeficiency (SCID) who were treated with retroviral vectors [117,118]. Although significant progress has been made in the development of viral vector vaccines in recent years, the results have been encouraging with regard to dendritic cells, and an increasing number of studies have begun to focus on the use of different viral vectors, including RNA (retroviral and lentiviral), adenoviral, and AAV vectors [119–122]. In viral vector vaccines, the immunogenicity-causing antigen is cloned in a pseudovirus that cannot proliferate or transfer in dendritic cells, creating higher immune stimulation than recombinant proteins [123].

2.5.1 Retrovirus and lentivirus-based vectors

Retroviruses contain a single-stranded RNA genome that encodes all replication-related proteins [124]. MMLV-based vectors are among the most efficient engineered vectors, with high transduction efficiency in dividing cells, and good integration and expression of transgenes [125]. Retroviral expression vectors can carry up to 8 kb genes and use a variety of envelope proteins to package them. These envelope proteins can be modified to recognize only mouse and rat cell receptors (ecotropic) or be amphoteric, allowing targeting of a wide range of mammalian cell receptors. Encapsulating envelope proteins from other virus strains, such as the broad-spectrum tropism VSV-G protein (VSV-G), can also be used to pseudotype retroviral vectors [126]. Retroviral vector therapy is effective in treating X-linked SCID (SCID-X1), chronic granulomatous disease (CGD), and adenosine deaminase-deficient SCID [127–130]. Nonintegrating lentiviral vectors (NILVs) [131] can express transgenes transiently in dividing cells or episomes into nondividing cells and can be introduced into diverse cell types. With relation to

COVID-19 infections, the Shenzhen Geno-immune Medical Institute recently produced two lentiviral vector-based vaccines (Covid-19/aAPC and LV-SMENP-DC) [132]. These vectors have been engineered to express several viral genes as antigens, including conserved structural, structural, and protease protein domains.

2.5.2 Adenovirus-based vectors

Adenoviruses are nonenveloped, double-stranded DNA viruses with a diameter of 90 nm. They have been found to infect humans, birds, reptiles, fish, amphibians, and non-human primates [133–135]. Adenoviruses cause respiratory infections, conjunctivitis, and gastroenteritis in humans [133,136]. The linear double-stranded DNA of the virus measures between 25 and 48 kb and contains noncoding inverted terminal repeats (ITRs) at both ends and genes encoding approximately 35 proteins. The early genes are involved in host cell gene regulation and virus replication, while the late genes encode structural proteins required for capsid assembly [136]. Preclinical and clinical studies have shown that human adenovirus serotype 5 (AdHu5) is effective in inducing immune responses as well as in gene therapy applications [137–140]. Recently, a new COVID-19 vaccine was developed using an adenovirus-based vector [132]. The use of adenovirus-based vectors has a number of advantages, including enhanced transgene expression and immune responses *via* induction of innate immunity, scalability, and purification and safety for human application. In addition, they can be delivered mucosally or systemically [141–143].

2.5.3 Adeno-associated virus vectors as a platform for vaccination

Adeno-associated viruses (AAVs) are tiny nonenveloped viruses in the Parvoviridae genus *Dependovirus* [144–146]. The genome structure [147–150], infection latency [151–154], replication/transcription, and virion assembly [155–157] were all described throughout the ensuing 20 years of study [158]. The AAV virion is a 4.7 kb single-stranded particle encased in a 25 nm capsid [144]. The AAV genome has an ITR at each end that serves as a replication and packaging origin. There is one replication gene (rep4) that encodes four proteins (Rep4, Rep52, and Rep68), one capsid gene (cap) that encodes three subunits *via* differential splicing and translation and one assembly activating protein (AAP) that promotes virion assembly [159,160]. Several preclinical and clinical trials for the treatment of genetic disorders,

including hemophilia, spinal muscular atrophy, hereditary retinal disease, and lipoprotein lipase deficiency [161–163], have demonstrated the effectiveness and safety of rAAVs in delivering genes to target cells [164,165]. Recent research has focused on creating an AAV-type COVID-19 vaccine [132].

2.5.4 RNA-based vaccines and nanoparticle formulations

RNA-based vaccines are the latest advancement in the quest for safe and effective immunization. The poor stability of RNA has been one of the primary obstacles to its application in immunization. Because RNA is only transiently expressed and negatively charged, it requires extra substrates to enter cells. RNA-based techniques are now among the most efficient methods of immunization due to recent developments in mRNA stability and RNA transport into cells. However, because mRNA is negatively charged, its transfection efficiency is typically very low, necessitating the use of alternative substrates to facilitate mRNA delivery into cells, of which lipid nanoparticles (LNPs) are one of the most widely used [166,167]. The first COVID-19 vaccine to start clinical testing was an RNA-based vaccine, which was expected to make a significant contribution to the ongoing pandemic struggle [168]. In addition, it was discovered that administering 50 ng of taRNA to mice resulted in the development of antibodies against the influenza hemagglutinin antigen [169]. These vaccines have shown promise in clinical studies against the Ebola virus using saRNA viral vectors. RNA-based vaccines can be generated in a few weeks, with clinical trials starting in a few months depending on the gene sequence. A wide range of NP methods can also be used to promote RNA transport within cells, thereby extending therapeutic possibilities. Given the urgency of the need for an effective COVID-19 vaccine, RNA-based vaccines appear to be the most viable option available [170].

2.6 Biomimetic nanoparticles

Molecular biomimetics is a new area in which hybrid technologies are being produced by combining the capabilities of molecular biology with nanotechnology to create new applications. Polypeptides may now be genetically designed to precisely attach to chosen inorganic compounds, allowing them to be used in nanotechnology and biotechnology applications. These advances are based on biological principles [171,172]. It is becoming increasingly common to use biomimetic NPs, which combine the functionality of biological materials with the flexibility of synthetic materials to achieve effective navigation and interfacing in complex biological systems. Biomimetic NPs are a new class of particles that combine the functionality of biological materials with the flexibility of synthetic materials to achieve efficient navigation and interfacing in complex biological systems. Biomimetic systems, such as cell membrane-coated NPs, combine the functionality of cell membranes with the ability of synthetic core structures to transport imaging reporters and medicinal cargo [173]. It mainly referred to the development of any new substance or technology that resembles or is derived from nature. Biomimetic NPs are a new type of nanoparticle that aims to overcome the existing difficulties in nanomedicine by mimicking the biomimicry of natural cells. Research in this area provides a wide range of NPs, ranging from such mimicking blood cells, to immunologic cells, and even tumor cells. Traditional NP platforms may now leverage the characteristics of natural cells to accomplish particular functions while preserving the enhanced delivery capabilities of a synthetic NP due to the application of these biomimetic methods [174]. Biomimetic nanoparticles can be designed and built through the use of interaction forces to move lipid accumulation from bilayers onto the spherical solid cores. Nanoparticles, such as polystyrene nanospheres, silica particles, and hydrophobic drug aggregates, have been coated with lipid bilayers, yielding functional hybrid assemblies. Many uses have been developed including biomolecular recognition, drug delivery, and vaccine development [175].

Current nanoparticle platforms have the potential to be considerably improved and enhanced using biomimetic design methodologies. Many of the distinct capabilities performed by different cell types are largely due to the composition of cell membranes. Several alternative techniques for using the cell membrane as a source of inspiration for nanoparticle development. These include the use of protein and glycans, and also its derivatives, and the use of natural cell membranes as nanocarriers or as a coating material for synthesized nanoparticulate cores [176]. Recently, researchers throughout the world are becoming interested in biomimetic nanoparticles because they can combine the benefits of both synthetic nanomaterials and natural materials, allowing for molecular imaging and precise drug delivery *via* a biomimetic approach [177].

3 Approved nanoparticles in the global market

3.1 Lipid-based nanoparticles

3.1.1 Doxorubicin (Doxil)

In 1995, the FDA-approved doxorubicin (Doxil), also known as Caelyx. It is a nanodrug used to treat multiple cancers, ranging from metastatic ovarian cancer to Kaposi sarcoma (KS) associated with AIDS. A doxorubicin (adriamycin) mixture is enclosed in unilamellar liposomes coated with PEG (polyethylene glycol) and are known as "PEGylated liposomes." The sizes of these structures vary between 80 and 90 nm. This DDS increases the half-life of circulation, leading to a boost in the bioavailability of medications. The first company to develop injectable Doxil was an Indian pharmaceutical company called Sun Pharma Global FZE, which obtained FDA approval in 2013. Doxil has two distinct mechanisms of action: intercalation into the DNA molecule, causing topoisomerase and DNA repair destruction, and intracellular production of reactive oxygen species and free radicals, causing lipid peroxidation and destruction of cell membranes. The second-generation PEGylated liposomal doxorubicin (Doxil or Lipobox) works by a passive targeting technique to enhance the EPR effect of tumors. The other main advantage of liposomal doxorubicin is its ability to reduce adverse drug effects, which can be toxic to several parts of the body, especially the skin and heart (Table 1) [178,179].

3.1.2 Daunorubicin (DaunoXome)

Liposomal daunorubicin, commercially known as DaunoXome, was approved by the FDA in 1996. DaunoXome, another anthracycline drug, is used to treat cancer and HIV-associated Kaposi's sarcoma (KS). In addition, different clinical trials have demonstrated the applicability and efficacy of daunorubicin for various types of leukemia. Because of its potency and lower side effects compared with alternative cytotoxic drugs, such as adriamycin, bleomycin, and vincristine, DaunoXome has been approved as a first-line cytotoxic therapy in advanced KS. The liposomes have an approximate diameter of 45 nm and consist of cholesterol and distearoyl phosphatidylcholine compound lipid bilayers with a molar ratio of 1:2. In DaunoXome, the lipid-to-drug weight ratio is 18.7:11 (lipid:daunorubicin). Although the exact mechanism of DaunoXome specificity is not known, it is thought to be the consequence of enhanced permeability of tumor neovasculature (EPR effect). In pre-clinical studies, DaunoXome has been shown to increase the concentration of daunorubicin in tumors while reducing its concentration in the brain, liver, spleen, and intestine, compared to the treatment with free daunorubicin. However, myelosuppression, which can cause fever, nausea, and vomiting, is a primary toxic effect of DaunoXome (see Table 1) [178,180].

3.1.3 Irinotecan (Onivyde)

Onivyldan was approved by the FDA in 2015 as an irinotelatinoid nanoform (MM-398) derivative. Liposomal irinotecan has also been shown to exhibit synergistic effects with other anticancer agents. Irinosuccinate, 5-fluoracylinic acid, folinic acid, and oxalate folinamide treatment showed superior outcomes in patients with advanced pancreatic cancer. Nanoliposomal formulations have improved circulation time, passive tumor targeting, and fewer side effects due to tumor overexpression. However, there are still some side effects of Onivyde, including diarrhea, vomiting, stomach pain, and alopecia (Table 1) [178,181].

3.1.4 Cytarabine (DepoCyt)

DepoCyt was authorized under accelerated approval regulation in 1999. It is a cytarabine liposomal formulation that is produced using Depofoam technology. In 2007, the FDA approved it for the treatment of a life-threatening condition called lymphomatic meningitis. In this case, liposomal medicine was only delivered intrathecally into the spine. The liposomal formulation comprises dioleoyl phosphatidylcholine, dipalmitoyl phosphatidylglycerol, triolein, and cholesterol. This special liposomal preparation has a half-life 40 times longer than that of normal cytarabine. DepoCyt is a sustained-release formulation intended for immediate administration into the cerebrospinal fluid. This antineoplastic agent can affect cells during S-phase cell division and inhibit DNA polymerase (Table 1) [178,182].

3.1.5 Vincristine (Marqibo)

In 2012, the FDA-approved liposomal vincristine sulfate, also known as Marqibo. Vincristine is an alkaloid anticancer agent that binds to tubulin and interferes with the cell division. Marqibo is vincristine encapsulated in sphingomyelin/cholesterol liposomes. When administered

Table 1: Approved marketed drug-loaded lipid-based nanoparticle

No.	Drug loaded	Type of nanoparticle	Trade name (company name)	Applications	Approval date	Ref.
1	Daunorubicin	Liposomal daunorubicin	DaunoXome (Galen)	Karposi sarcoma	1996	[307,308]
2	Cytarabine	Liposomal cytarabine	DepoCyt© (Pacira Pharms Inc)	Lymphoma	1999	[307,308]
3	Vincristine	Liposomal vincristine	Marqibo (Acrotech)	Acute lymphocytic blood clot	2012	[309]
4	Irinotecan	Liposomal irinotecan	Onivyde (Ipsen Inc)	Pancreatic cancer	2015	[181]
5	Amphotericin B	Liposomal amphoteric B	AmBisome (Astellas)	Fungal infection	1997	[307,308]
6	Verteporfin	Liposomal verteporfin	Visudyne (Valeant Luxembourg)	Decreased vision, ophthalmic hiscomaplastia	2000	[307,308]
7	Doxorubicin	Liposomal doxorubicin	Doxil (Baxter Hlthcare Corp)	Karposi sarcoma, ovarian cancer, multiple myeloma	1995	[307,308]
8	Amphotericin B lipid complex	Liposomal amphotericin B lipid complex	Abelcet (Leadiant Biosci Inc.)	Fungal infection	1995	[307,308]
9	Poractant Alfa	Liposome-proteins SP-band SP-C	Curosurf (Chiesi USA Inc)	Lung activator for stress disorder	1999	[307,308]
10	Perflutren	Perflutren lipid microspheres	Definity (Lantheus Medcl)	Ultrasound contrast agent	2001	[194]
11	Octocog alfa	Liposome	Advate	Hemophilia A	2004	[310]
12	Mifamurtide	Liposomes	Mepact (Takeda)	Myosarcoma	2009	[311]
13	Propofol	Liposomes	Diprivan/Propofol-Lipuro/ Propofol	Anesthesia	1989	[194]
14	Cytarabine: daunorubicin	Liposomes	VYXEOS (Celator Pharms)	Acute myeloid leukemia	2017	[194]
15	Pfizer-BioNTech	Liposomal nanoparticle	Pfizer-BioNTech	COVID-19	2020 (EUAs)	[170,278]
16	Moderna	Liposomal nanoparticle	Moderna	COVID-19	2020 (EUAs)	[170,278]
17	Patisiran sodium	Lipid nanoparticle	Onpattro	Transthyretin (TTR)-mediated amyloidosis	2018	[194]

EUAs, emergency use authorization; NPs; nanoparticles.

to adult patients with Philadelphia chromosome-negative chronic myelogenous leukemia, Marqibo (2.25 mg/m^2) induced a positive reaction in 35% of the patients. In comparison, conventional vincristine clearance is slower (area under the plasma drug concentration *vs* time curve). Liposomal vincristine offers other benefits, such as increased circulation time and low systemic toxicity. Significant adverse effects include constipation, nausea, weakness, diarrhea, and insomnia (Table 1) [178,182].

3.1.6 Amphotericin B (AmBisome)

AmBisome, the liposomal form of amphotericin B (AmB) or L-AmB, is an antifungal agent administered to treat a broad spectrum of fungal pathogens. Because it does not work through enzyme inhibition, AmB does not lead to the emergence of resistant fungal species, like other antifungal agents do. Fungizone and standard injectable water-soluble AmB have been developed in an attempt to find new formulations that alleviate toxicity. Studies have been carried out on murine models concentrating on particle size, AmB content, physicochemical stability, and toxicity. The final optimized mixture consists of phosphatidylcholine-hydrogenated soybeans, cholesterol, and AmB-containing di-stearoyl phosphatidylglycerol at a molar ratio of 2:1:0.8:0.4. The benefits of liposomal AmBisome include improved pharmacokinetic properties and circulation stability, decreased accumulation in normal uninfected tissue, and decreased mammalian cell toxicity compared to fungal cells, making it far safer than Fungizone. AmBisome allows the drug to cross the liposome membrane and then bind to ergosterol in the fungal membrane, resulting in ion leakage and, ultimately, fungal cell death [178,183].

3.1.7 Daunorubicin: cytarabine (Vyxeos)

Daunorubicin and cytarabine encapsulated in liposomes, known as Vyxeos, received FDA approval in 2017 to treat adults with acute myeloid leukemia resulting from previous therapy or changes in myelodysplasia [178,184]. Cytarabine and daunorubicin were loaded into the liposomal structure in a 5:1 molar ratio. Daunorubicin influences DNA and RNA syntheses by forming complexes with DNA that control gene expression and generate free radicals. Cytarabine decreases DNA synthesis by controlling DNA polymerase. Vyxeos significantly increases plasma exposure and reduces distribution to ordinary tissues. However, it also has side effects such as hyperviscosity, cardiotoxicity, and tissue necrosis (Table 1) [178,184–188].

3.1.8 Amphotericin B lipid complex (Abelcet)

In 1995, another AmB lipid complex, Abelcet, was approved. It is an antifungal medication, similar to AmBisome. It is used to treat severe leishmaniasis and fungal infections such as aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, and cryptococcosis. In a 1:1 drug to lipid molar ratio, Abelcet contains AmB and two phospholipids. It also produces less severe side effects compared with free AmB (Table 1) [178,189].

3.1.9 Verteporfin (Visudyne)

Visudyne is a liposomal formulation of the benzoporphyrin analog monoacid ring A photosensitizer (PS). In 2000, the FDA approved it for the treatment of choroidal neovascularization caused by wet macular degeneration associated with age. This proliferation of unwanted blood vessels in the back of the eye is one of the leading causes of blindness in adults. Visudyne is injected intravenously, followed by shining of a red laser through the pupil into the eye after 10 min. The PS absorbs light and is boosted into an excited state, where its energy is transferred to ambient oxygen, and singlet oxygen is produced. This reactive oxygen species harms the recently created leaky blood vessels, thus halting and reversing progressive vision loss. In addition to its use for age-related macular degeneration, a mixture of Visudyne photodynamic therapy and immunosuppression was recommended to help treat sub-foveal choroidal neovascularization that may occur as a side effect of inflammatory conditions. The side effects of Visudyne therapy are usually moderate and can include slight changes in vision; light flashes; dryness, redness, or swelling in the eyes; and headache (Table 1) [178,190].

3.1.10 Poractant Alfa (Curosurf)

Curosurf is a porcine minced pulmonary surfactant extract called Poractant Alfa, which was approved in 1995. Multivesicular vesicles are formed in the range of 100 nm to 5 μm in scale. It is formulated as a phospholipid and protein suspension of 80 g/L containing phosphatidylcholine lipids, phosphatidylglycerol, and SP-B and SP-C membrane proteins [191]. Curosurf is recommended and administered at a dosage of 200 mg/kg for the rescue treatment of respiratory distress syndrome (RDS) in premature infants. The use of nanoparticles for Poractant Alfa has been shown to increase delivery with lower volume and reduced toxicity. Acquired pneumonia, acquired septicemia, bronchopulmonary

dysplasia, intracranial hemorrhage, patent ductus arteriosus, pneumothorax, and pulmonary interstitial emphysema are side effects of Curosurf (Table 1) [192].

3.1.11 Perflutren (Definity)

Definity (perflutren lipid microsphere) injectable suspension is a contrast agent used to brighten and clarify the image of the heart during echocardiograms [193]. FDA approval was obtained for Definity as an ultrasound contrast agent in 2001 [194]. The perflutren lipid microspheres are composed of octa-fluoro propane encapsulated in an outer lipid shell consisting of DPPA, DPPC, and DPPE. The microsphere particle size ranges from 1.1 to 3.3 μm. However, it has several side effects, the most common being potential prolongation of QTc and headache (Table 1) [193].

3.1.12 Octocog alfa (Advate)

Advate is a drug used in patients of all ages with hemophilia A (an inherited bleeding disorder caused by a lack of factor VIII) to treat and prevent bleeding. It contains octocog alfa (human coagulation factor VIII) as the active material and was approved in 2004. Advate (antihemophilic factor (recombinant), plasma/albumin-free method) is a purified glycoprotein consisting of 2,332 amino acids. It is synthesized in a genetically engineered Chinese hamster ovary (CHO) cell line. CHO cells synthesize recombinant antihemophilic factor (rAHF) with the same biological effects as human AHF (hAHF). The recombinant protein has a mixture of heterogeneous heavy and light chains identical to those in hAHF. rAHF is secreted into cell culture medium by the CHO cells. It is then purified from the culture medium using a series of chromatography columns. The purification approach involves an immunoaffinity chromatography step, in which the rAHF is selectively removed from the medium, and a monoclonal antibody directed against Factor VIII is used. No additives of human or animal origin are used in the cell culture and purification processes. A dedicated viral inactivation solvent detergent treatment stage is included in the manufacturing process (Table 1) [195–198].

3.1.13 Mifamurtide (Mepact)

Mifamurtide is a drug used to treat osteosarcoma, a form of bone cancer that mainly affects children and young adults and is lethal in more than half of cases [199,200]. The medicine was approved in March 2009 in Europe. Mifamurtide is a phosphatidylethanolamine (MTP-PE) muramyl tripeptide, a synthetic muramyl dipeptide analog. The side chains of the molecule have a longer half-life than the specific product. The drug is encapsulated in liposomes to produce L-MTP-PE. The lipid bilayer of liposomes accumulates in the form of infusion or a micelle shape (Table 1) [201].

3.1.14 Propofol (Diprivan)

Diprivan (propofol) injectable emulsion is a sedative-hypnotic agent used with surgery or other surgical treatments to calm patients before and after general anesthesia. It is often administered to chronically ill patients who need a breathing tube attached to a ventilator. Propofol is partially soluble in water and is thus formed as an emulsion of white oil-in-water. Its pK_a is 11. For propofol, the octanol/water partition coefficient is 6,761:1 at a pH of 6–8.5. The formula also includes soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate (0.005 percent) in addition to the active ingredient propofol, with sodium hydroxide to modify the pH. Diprivan injectable emulsion, USP, has a pH of 7–8.5, and is isotonic. Propofol was discovered in 1977 and was approved for use in 1989 in the United States (Table 1) [202–205].

3.2 Polymer-based nanoparticles

3.2.1 Certolizumab pegol (Cimzia)

Certolizumab pegol was approved by the FDA in 2008 and is a PEGylated blocker of tumor necrosis factor-alpha (TNF-α). Cimzia is a PEGylated Fab fragment (part of a humanized IgG antibody without the Fc region) that specifically recognizes and binds to TNF-α, thus neutralizing its activity. Cimzia is used to treat arthritis in rheumatoid, psoriatic, and ankylosing spondylitis. These diseases are all related to autoimmunity, an unhealthy immune response of the patient to healthy cells. Strictly speaking, Crohn's disease is not an autoimmune disease, since it seems that the content of the gut lumen, and not self-antigens, triggers the response. TNF-α is a pluripotent pro-inflammatory cytokine and may be one of the main cytokines responsible for the autoimmune attack (Table 2) [178,206].

3.2.2 PEGfilgrastim (Neulasta)

Neulasta, a PEGylated form of filgrastim, was approved by the FDA in 2002. Neutropenia (low white blood cell

counts) is a common adverse effect found in patients with nonmyeloid cancer who receive chemotherapy. As a leukocyte growth factor, Neulasta is used for the treatment of febrile neutropenia and consequent infections arising due to a lack of neutrophils. Filgrastim (the parent molecule) is a recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) produced from *Escherichia coli*. Neulasta is synthesized by attachment of a monomethoxy-PEG aldehyde chain (20 kDa) to the *N*-terminal methionine residue of Filgrastim. The resulting imine is then reduced using sodium cyanoborohydride. PEGylation of filgrastim results in increased circulation time and higher solubility of the parent molecule. The half-life of the native molecule (filgrastim) is about 3.5–3.8 h, but Neulasta remains in circulation for up to 42 h (Table 2) [178,207].

3.2.3 Pegaspargase (Oncaspar)

Oncaspar, with the generic name pegaspargase, is a PEGylated-L-asparaginase approved by the FDA in 1994. Acute lymphoblastic leukemia and chronic myelogenous leukemia are treated with this agent. It can also be used as a replacement in patients with leukemia who display hypersensitivity to *E. coli*-derived L-asparaginase. Oncaspar is beneficial as it is only administered every 2 weeks, while the native compound, L-asparaginase, must be administered three times per week. The less frequent administration of Oncaspar is simply the result of a longer half-life due to PEGylation. Furthermore, Oncaspar demonstrates decreased hypersensitivity and considerable total cost savings for patients (Table 2) [178].

3.2.4 Peginterferon alfa-2a (Pegasys)

Pegasys, with the generic name peginterferon alfa-2a, was approved by the FDA in 2002. Pegasys is a recombinant human alfa-2a interferon conjugated to branched PEG for the treatment of hepatitis C and HBeAg-positive chronic hepatitis B. The increased half-life of Pegasys due to PEGylation makes it possible to administer a subcutaneous injection only every 12 weeks. Free interferon must be administered three times per week. Pegasys has been used with ribavirin, resulting in better hepatitis C therapy outcomes. In HBeAg-positive chronic hepatitis B patients, the combination of lamivudine and Pegasys also resulted in more remarkable survival (Table 2) [178,208].

3.2.5 Pegvisomant (Somavert)

Somavert (pegvisomant [B2036-PEG]) is a PEGylated analog of human growth hormone (GH) for acromegaly treatment that was approved by the FDA in 2003. The pituitary gland secretes excessive quantities of growth hormone in patients with acromegaly, resulting in abnormal enlargement of the forehead, jaw, hands, and feet. Somavert is a GH receptor antagonist that blocks GH binding and interferes with GH signal transduction pathways, thereby reducing IGF-I serum concentration (one of the essential mediators of GH activity) by at least 50%. As expected, PEGylation of the active ingredient of Somavert (B2036) results in reduced clearance (estimated to be 28 mL/h for subcutaneous injection of 10–20 mg) and an increased half-life (approximately 6 days) (Table 2) [178,209].

3.2.6 Methoxy PEG glycol-epoetin β (Mircera)

Mircera or epoetin β (EPO) conjugated to methoxy-PEG is a drug formulation used to treat anemia. Both the European Commission and the FDA-approved Mircera in 2007. EPO is a genetically recombinant form of erythropoietin capable of stimulating erythropoiesis by functioning on the erythropoietin receptors of bone marrow progenitor cells. To create Mircera, the PEG moiety (~60 kD) is first linked with butanoic acid, and the NHS-modified structure is connected to the lysine moiety of the EPO structure *via* amide bonds. This formulation provides a controlled release system with a half-life of ~135 h. Naked EPO has a half-life of 7–20 h. The main benefit is the less frequent administration of Mircera. The administration of Mircera usually entails intravenous or subcutaneous injection of 0.6 µg/kg every 2 weeks (Table 2) [178,210].

3.2.7 Peginterferon alfa-2b (PEG-INTRON)

PEG interferon alfa-2b is a long-acting interferon; its structure contains an alpha interferon (INF) molecule conjugated to a mono PEG chain through succinimidyl carbonate. Compared to the regular interferon molecule, its longer half-life and slower elimination lead to less frequent administration. PEG interferon alfa-2b was approved by the FDA in 2001 and is commonly used as a monotherapy or in combination with other medicines, such as ribavirin, to treat chronic hepatitis C (Table 2) [178,211].

Table 2: Approved marketed drug-loaded polymer-based nanoparticles

No.	Drug loaded	Type of nanoparticle	Trade name (Company name)	Applications	Approval date	Ref.
1	Certolizumab pegol	PEGylated antibody fragment (Certolizumab)	Cimzia (UCB)	Chron's disease, rheumatoid arthritis, psoriasis, ankylosing spondylitis	2008 2009 2013	[307,308]
2	Glatiramer acetate	Random copolymer of L-glutamate, L-alanine, L-lysine and L-tyrosine	Copaxone (Teva)	Multiple sclerosis	1996	[307,308]
3	Leuprolide acetate	Leuprolide acetate and polymer [PLGH (poly (DL-lactide-coglycolide)]	Eligard (Tolmar)	Prostate cancer	2002	[307,308]
4	Methoxy PEG glycol-epoetin β	Chemically synthesized ESA (erythropoiesis-stimulating agent)	Mircera (Hoffman-LaRoche)	Anemia with chronic renal failure	2007	[307,308]
5	Pegfilgrastim	PEGylated GCSF protein	Neulasta (Amgen)	Leukopenia by chemotherapy	2002	[307,308]
6	Peginterferon alfa-2A	PEGylated IFN alpha-2a protein	Pegasys (Hoffman-La Roche)	Hepatitis B and C	2002	[307,308]
7	Peginterferon alfa-2B	PEGylated IFN alpha-2b protein	PegIntron (Schering)	Hepatitis C	2001	[307,308]
8	Pegvisomant	PEGylated HGH receptor antagonist	Somavert (Pharmacia)	Acromegaly	2003	[307,308]
9	Pegaspargase	Polymer–protein conjugate PEGylated L-asparaginase	Oncaspar (Sigma Tau)	Acute lymphocytic blood clot	1994	[307,308]
10	Pegloticase	Polymer–protein conjugate (PEGylated porcine-likeuricase)	Krystexxa (Horizon)	Chronic gout	2010	[307,308]
11	Peginterferon beta-1A	Polymer–protein conjugate (PEGylated IFNbeta-1a)	Plegridy (Biogen)	Multiple sclerosis	2014	[307,308]
12	PEGylated factor VIII	Polymer–protein conjugate (PEGylated factor VIII)	Adynovate (Baxalta)	Hemophilia	2015	[307,308]
13	Factor IX	Glycopegylated coagulation factor IX	Rebinyn (Novo Nordisk Inc.)	Hemophilia	FDA 2017	[178]
14	Triamconolone acetonide	PLGA hydrogel	Zilretta (Flexion Theraps Inc)	Osteoarthritis	2017	[178]
15	Trastuzumab	Maytansine derivative, DM1	Kadcyla	Breast cancer	2013	[312]
16	Paclitaxel	Protein NP	Abraxane (Abraxis Bioscience)	Breast cancer	2005	[194]
17	Denileukin diftitox	Protein NP	Ontak (Eisai Inc)	T-cell lymphoma	1999	[307,308]
18	Docetaxel	Micelle	Taxotere (Sanofi Aventis)	Antineoplastic	1996	[313]
19	Verapamil HCl	PLGA nanoparticles	Verelan PM (Schwarz Pharma)	Hypertension, angina, and rhythm disorders	1998	[15]
20	Ibritumomab tiuxetan	Suspension	Zevalin (Spectrum Pharms)	Lymphoma	2002	[307,308]

EUAs, emergency use authorization; NPs, nanoparticles.

3.2.8 Pegloticase (Krystexxa)

Krystexxa [212] is a treatment for patients with chronic refractory gout. In September 2010, FDA approval was obtained following investigations into its efficacy in reducing uric acid levels and reducing concentrations of uric acid crystals in joints and soft tissues. The EMA also approved this medication for the treatment of tophaceous gout disorder in January 2013. Tophi are nodular masses of uric acid crystals. Pegloticase is a recombinant porcine-like uricase that can metabolize uric acid to allantoin, similar to the nonpegylated Rasburicase. Pegloticase is composed of four uniform chains of approximately 300 amino acids; 9 of the 30 lysine residues in each chain are pegylated (PEG chains MW: 10 kDa). The improved solubility of pegloticase removes the risk of precipitate formation. Furthermore, the PEG molecules in pegloticase result in an increased drug half-life to about 10 days (in comparison with Rasburicase, which has a half-life of 8 h) and a reduction in its immunogenicity. Accordingly, pegloticase is a better choice than other treatments, especially for chronic therapy. The side effects of Krystexxa include infusion and allergic reactions, which should be noted before repeating the treatment. Other minor side effects include sore throat, vomiting, nausea, and chest pain (Table 2) [178,213].

3.2.9 Peginterferon beta-1a (Plegridy)

Plegridy contains the active material PEG-IFN-β-1a, a glycosylated recombinant PEG-conjugated IFN-β modified with a single, linear 20 kDa methoxy-PEG-O-2-methylpropionaldehyde molecule (mPEG). In 2014, the FDA-approved Plegridy to treat recurrent remitting multiple sclerosis in adult patients. Plegridy has been used to observe elevations in hepatic enzymes and liver damage. Patients must be checked for signs of hepatic impairment, and therapy must be stopped if icterus or other clinical symptoms of hepatic dysfunction occur (Table 2) [178,214].

3.2.10 PEGylated factor VIII (Adynovate)

Adynovate is a recombinant pegylated antihemophilic factor used to treat hemophilia A in patients with repeated bleeding events. Adynovate functions by temporarily raising blood clotting factor VIII levels in the blood. In the human body, Adynovate has an extended circulation time, which means it requires a decreased injection frequency. The structure consists of coagulation factor VIII conjugated

to PEG. Clinical studies have demonstrated the safety and effectiveness of this drug against hemophilia. Common side effects include diarrhea, nausea, headache, vomiting, rash, and other common allergic reactions (Table 2) [178,215].

3.2.11 Glatiramer acetate (Copaxone)

Copaxone or glatiramer acetate (GA; known as COP-1) is a synthetic polymer consisting of L-alanine, L-glutamic acid, L-tyrosine, and L-lysine in a ratio of 0.141:0.338:0.427:0.095, respectively. The FDA has approved its use for the treatment of multiple sclerosis (MS). Although the mechanism of action of this random copolymer is not fully known, it may suppress inflammatory responses by blocking MHC II and modifying the T-cell population phenotype, according to some studies. Its therapeutic advantage (particularly in autoimmune disorders) can be inferred from its marketing approval in many countries, including the United States, Canada, and some European countries. However, clinical studies have shown that GA has various side effects in a number of organs, including the heart, eyes, skin, and gastrointestinal and immune systems (Table 2) [178,216,217].

3.2.12 Leuprolide acetate (Eligard)

Eligard is a formulation of leuprolide acetate (Atrigel) as a polymeric injectable nanosuspension agent that received FDA approval in 2002 as a palliative agent for prostate cancer treatment. Leuprolide acetate (known as Lupron) is a gonadotropin-releasing hormone (GnRH) synthetic peptide-type analog capable of interacting with the GnRH receptor and altering gonadotropin secretion. The decline in gonadotropin release decreases other hormones, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The outcomes are hypogonadism and decreased levels of estradiol and testosterone. Artigel is a DDS based on a mixture of polymers (usually polylactic and polyglycolide). Eligard is an example of a nanopharmaceutical that acts as a sophisticated system for Lupron delivery. It is an injectable liquid formulation that solidifies in the body and slowly releases the drug over 1 month as it degrades. Irritation and erythema are the most common adverse effects of Eligrad after subcutaneous injection (Table 2) [178,218].

3.2.13 Triamcinolone acetonide (Zilretta)

Triamcinolone acetonide that has been embedded in a PLGA hydrogel is known as Zilretta and was approved

by it's the FDA in 2017 for the treatment of knee osteoarthritis. This formulation is administered by intra-articular injection to alleviate knee osteoarthritis pain, but its overall beneficial effects are still being studied. Despite the benefits seen in clinical trials, Zilretta demonstrated no significant advantage over the immediate release of triamcinolone in a clinical trial. In clinical trials, 32 mg of Zilretta was administered to 424 patients, 143 of whom were aged 65 years or older, and the adverse effects did not vary between old and young patients (Table 2) [178,219].

3.2.14 Factor IX (Rebinyn)

Rebinyn is an injectable drug used to replace clotting factor IX, which is absent in patients with hemophilia B. It was approved by the FDA in 2017. In all age groups, hemophilia B is an inherited bleeding disorder that usually prevents blood from clotting. In patients with hemophilia B, Rebinyn is used to treat and control bleeding. It was developed in CHO cells using recombinant DNA technology. No additives of human or animal origin are used in cell culture, purification, conjugation, or preparation of Rebinyn. The rFIX protein is isolated by a sequence of chromatographic steps to selectively extract rFIX from the cell culture media, including an affinity chromatography step using a monoclonal antibody (produced in CHO cells). Two dedicated viral clearance steps are used in the development process, namely, a detergent treatment stage for inactivation and a 20 nm filtration step for virus elimination. During the purification process, conjugation of the PEG group is carried out by an enzymatic reaction, followed by the final purification of Rebinyn (Table 2) [220,221].

3.2.15 Paclitaxel (Abraxane)

Abraxane is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nm, also known as nanoparticle albumin-bound paclitaxel. Paclitaxel exists in a noncrystalline, amorphous form in these particles. ABRAXANE is provided as a 20 mL injection in 0.9% sodium chloride (USP). It is a white to yellow, clean, lyophilized powder that is reconstituted before use. It is used to treat breast cancer, lung cancer, and pancreatic cancer, among others. By avoiding the natural breakup of microtubules during cell division, paclitaxel destroys cancer cells. Paclitaxel is bonded to albumin as a transport vehicle in this formulation. It is manufactured under the trade name Abraxane, which is

designated as an orphan drug for first-line treatment, combined with gemcitabine, for metastatic adenocarcinoma of the pancreas. This treatment was approved in the United States in 2005 and the European Union in 2008 for breast cancer cases that did not respond to other chemotherapy or had relapsed (Table 2) [178,222].

3.2.16 Denileukin diftitox (Ontak)

Denileukin diftitox, known as Ontak, was approved by the FDA in 1999 to treat T-cell lymphoma. It consists of an IL-2-conjugated recombinant diphtheria toxin protein and has been developed to bind to the IL-2 receptor. In leukemia and lymphoma therapy, Ontak is used because it selectively transmits diphtheria toxin to target cells expressing interleukin-2 receptors. Some studies have shown that Ontak may be used to treat fungal mycosis, the most common type of cutaneous T-cell lymphoma. The side effects include hypersensitivity reactions during infusion with low blood pressure, back pain, headache, shortness of breath, nausea and vomiting, blood test anomalies and liver issues, fatigue, rash, and poor appetite. In 2006, severe problems with loss of vision emerged, and the FDA added a black box warning to the drug labeling, including a description of ophthalmologic adverse events. In 2014, the marketing of Ontak was discontinued in the United States (Table 2) [178,223].

3.2.17 Docetaxel (Taxotere)

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semi-synthesis, starting with a precursor derived from renewable needle biomass of yew plants. Docetaxel ($C_{43}H_{53}NO_{14}$) is a white to near-white powder with a molecular weight of 861.9 kDa. In water, it is strongly lipophilic and insoluble. Taxotere is recommended to treat patients with locally advanced or metastatic breast cancer when previous chemotherapy has failed (Table 2) [224,225].

3.2.18 Ibritumomab tiuxetan (Zevalin)

Zevalin (ibritumomab tiuxetan) is an immunoconjugate between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan arising from the stable thiourea covalent link. This linker-chelator offers an Indium-111 or Yttrium-90.0 site for high affinity, conformationally limited chelation. Ibritumomab tiuxetan has an average

molecular mass of 148 kDa. Ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen, is the antibody moiety of zevalin. Ibritumomab tiuxetan is a transparent, colorless, sterile, preservative-free, pyrogen-free solution containing fine particles. It is provided in single-use vials containing 3.2 mg of ibritumomab in 2 mL of 0.9% sodium chloride. Zevalin (ibritumomab tiuxetan) is a protein used in conjunction with other drugs to treat non-Hodgkin lymphoma that attacks white blood cells (Table 2) [226,227].

3.3 Crystalline nanoparticles

3.3.1 Aprepitant (Emend)

Emend is the nanocrystalline form of the antiemetic drug aprepitant, approved by the FDA in 2003. It is used to prevent nausea and vomiting during chemotherapy, especially in courses containing high-dose cis-platin. Cis-platin is known to be highly emetogenic, which means it induces vomiting and nausea in patients. Aprepitant is a human substance-P-ligand antagonist with a high affinity for neurokinin-1 (NK1) receptors in the postrema region, known as the brain's vomiting area. The benefit of aprepitant over other NK1 antagonists is that it has minimal or no preference for receptors of serotonin (5-HT3), corticosteroids, or dopamine. Thus, there is no interference from the activity of other pharmaceutical agents targeting those receptors. Furthermore, aprepitant absorption occurs in the upper gastrointestinal (GI) tract. It is insoluble in water. By applying a technology called Elan Drug Delivery Nanocrystals, these problems can be solved. Oral Emend possesses better water solubility, greater absorption in the upper GI, and better bioavailability. In 2008, the FDA approved the IV injectable form of Emend. The active ingredient of this formula is fosaprepitant dimeglumine, a prodrug of aprepitant. Fosaprepitant is water soluble and can be converted to aprepitant within 30 min of iv administration (Table 3) [178,228].

3.3.2 Sirolimus (Rapamune)

Rapamune, with the generic name sirolimus (rapamycin), was the first nanocrystalline-type drug that was approved by the FDA in 2000. It is used to prevent the rejection of kidney transplants. Sirolimus is a macrocyclic triene antibiotic derived from *Streptomyces hygroscopicus*, and it works as an immunosuppressant. The release profile of poorly soluble drugs increases dramatically using the Elan Drug Delivery Nanocrystals technology involving bead/pearl milling, enabling better bioavailability. Although extended release for Rapamune is not entirely critical, nanoformulation leads to more convenient storage and enables oral administration. Rapamune blocks T-lymphocyte proliferation induced by stimuli operating *via* either Ca^{2+}-dependent or Ca^{2+}-independent pathways, resulting in a weakened cellular immune system to accept the transplanted organ. In 2015, the FDA approved the use of Rapamune to treat lymphangioleiomyomatosis, a rare progressive lung disease (Table 3) [178,229].

3.3.3 Methylphenidate (Ritalin)

Ritalin, also known as methylphenidate, was approved by the FDA in 1955 to treat hyperactivity disorders in children. The medication is primarily used to treat attention deficit hyperactivity disorder (ADHD). Since the 1990s, the drug has been increasingly administered for more prevalent ADHD diagnoses. In 2007, in England, general practitioners administered this drug to around 420,000 individuals, and by 2012, the amount had increased to 657,000, reflecting a 56% increase. According to research, in disorders such as ADHD, norepinephrine and dopamine release are imbalanced, and the brain's dopamine and norepinephrine receptor control is dysregulated. Ritalin inhibits dopamine reuptake, thus increasing the concentration of dopamine in the synaptic cleft [178,230–233].

Consequently, there is an increase in cognitive and executive functions in the brain. In addition, it can increase the overall alertness of the central nervous system, resulting in short-term benefits as a cost-effective therapy. Similar to most drugs, ritalin also displays side effects; these include irritability, anxiety, disturbance in motor function, and poor appetite (Table 3) [178,234].

3.3.4 Fenofibrate (TriCor)

TriCor was approved in 2004 to reduce triglyceride and cholesterol levels to prevent atherosclerosis development by reducing plaques on the inner wall of arteries, leading to strokes and heart attacks. Fenofibrate is metabolized in the intestine by the oral administration of fenofibric acid. Fenofibric acid can activate peroxisome proliferator-activated receptor alpha (PPAR-alpha). Apolipoprotein C-III (an inhibitor of lipoprotein lipase activity) decreases the lipolysis of triglyceride-rich molecules and increases when lipoprotein lipase is enabled. This process finally reduces

Table 3: Approved marketed drug-loaded crystalline nanoparticles

No.	Drug loaded	Type of nanoparticle	Trade name (company name)	Applications	Approval date	Ref.
1	Aprepitant	Nanocrystal	Emend (Merck)	Vomiting agent	2003	[307,308]
2	Fenofibrate	Nanocrystal	Tricor (Abbvie)	Hyperlipidemia	2004	[307,308]
3	Sirolimus	Nanocrystal	Rapamune (PF Prism CV)	Immunosuppressant	2000	[307,308]
4	Megestrol acetate	Nanocrystal	MegaceES (Endo Pharms Inc)	Anorexia	2005	[307,308]
5	Dexmethylphenidate HCl	Nanocrystal	Focalin XR /(Novartis)	Mental stimulant	2005	[307,308]
6	Metyhlphenidate HCl	Nanocrystal	Ritalin LA (Novartis)	Mental stimulant	1955	[307,308]
7	Tizanidine HCl	Nanocrystal	Zanaflex (Covis)	Muscle relaxant	2002	[307,308]
8	Paliperidone Palmitate	Nanocrystal	Invega Sustenna (Janssen)	Schizoaffective disorder	2009 2014	[314]
9	Dantrolene sodium	Nanocrystal	Ryanodex (Eagle Pharmaceutical)	Malignant benign hypothermia	2014	[315]
10	Olanzapine	Nanocrystal	Zyprexa (Lilly Pharma)	Schizophrenia	1996	[307,308]
11	Nabilone	Nanocrystal	Cesamet (Bausch)	Anti-emetic	1985	[15]
12	Naproxen sodium	Nanocrystal	Naprelan (Almatica)	Anti-inflammation	1996	[15]
13	Theophylline	Nanocrystal	Elixophyllin Nostrum Labs Inc	Bronchial dilation	1979	[15]
14	Brinzolamide	Nanocrystal	Azopt (Novartis)	Glaucoma	1998	[15]
15	Griseofulvin	Nanocrystal	Gris-Peg (Novartis)	Fungal infection	1982	[15]

EUAs, emergency use authorization; NPs, nanoparticles.

circulating total cholesterol and triglycerides, as well as triglyceride-rich low-density lipoprotein, very low-density lipoprotein, and apolipoprotein B. It also increases apo A-I and apo A-II of high-density lipoprotein and apolipoproteins. Using Elan drug delivery nanocrystal technology, water-insoluble fenofibrate can be made more water soluble in TriCor. Without this technology, fenofibrate must be taken with food, and it passes unchanged through the varying pH conditions of the GI tract because it lacks ionizable groups. Fenofibrate should be taken with food due to the presence of surfactants and lipids in food that can emulsify it. The higher water solubility of TriCor allows this drug to be taken with or without food (Table 3) [178,235].

3.3.5 Megestrol acetate (Megace ES)

Megace ES oral suspension includes megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol acetate is a white, crystalline solid chemically referred to as 17-hydroxy-6-methyl pregna-4,6-diene-3,20-dione acetate. Its solubility in water at 37°C is 2 μg/mL, and its solubility in plasma is 24 μg/mL. It has a molecular weight of 384.52. Megace ES oral suspension is indicated in individuals with a history of acquired immunodeficiency syndrome (AIDS) to prevent anorexia, cachexia, or unexpected substantial weight loss. Several

investigators have documented the appetite-stimulating effects of megestrol acetate and its potential use in cachexia. Currently, the exact mechanism by which megestrol acetate treats anorexia and cachexia symptoms remains unclear (Table 3) [236,237].

3.3.6 Dexmethylphenidate HCl (Focalin XR)

Focalin XR is a dexmethylphenidate extended-release formulation with a bimodal release profile. The patented SODAS (spheroidal oral drug absorption system) technology is used in Focalin XR. Each focal XR bead-filled capsule contains half the dose as immediate-release beads and half as entero-coated delayed-release beads, giving an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate. Dexmethylphenidate hydrochloride is a white to off-white powder, which is acidic in solution. It is freely soluble in methanol and water, soluble in alcohol, and slightly soluble in acetone and chloroform. In patients aged 6 years and older, focal XR is recommended for the treatment of ADHD (Table 3) [233,238].

3.3.7 Tizanidine HCl (Zanaflex)

Zanaflex (tizanidine hydrochloride) is a central alpha-2-adrenergic agonist. Tizanidine HCl is a fine crystalline

powder that is white to off-white and odorless, although it sometimes has a faint characteristic odor. In water and methanol, tizanidine is slightly soluble, and its solubility in water decreases as the pH increases. The molecular formula of izanidine is C9H8ClN5S–HCl, with a molecular weight of 290.2. Zanaflex has been suggested for the treatment of spasticity. Due to its limited duration of therapeutic benefit, Zanaflex therapy should be reserved for particular everyday tasks and periods when relief of spasticity is necessary. Tizanidine is a key agonist of the alpha-2-adrenergic receptor, which probably decreases spasticity by increasing motor neuron presynaptic inhibition. Tizanidine's effects on polysynaptic pathways are strong. The cumulative influence of these actions is assumed to decrease spinal motor neuron facilitation (Table 3) [239–241].

3.3.8 Paliperidone palmitate (Invega Sustenna)

Invega Sustenna is an atypical antipsychotic containing paliperidone palmitate. Paliperidone is a psychotropic agent belonging to the benzisoxazole family. In Invega Sustenna, a racemic mixture of (+)-and (−)-paliperidone palmitate is used. Paliperidone palmitate is only partially soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate. Invega Sustenna is a white or off-white sterile aqueous extended-release suspension prescribed for the treatment of schizophrenia (Table 3) [242–246].

3.3.9 Dantrolene sodium (Ryanodex)

Ryanodex (dantrolene sodium) [247] is a skeletal muscle relaxant used to treat malignant hyperthermia and prevent malignant hyperthermia in high-risk patients, in combination with effective supportive interventions [248–252]. Advanced nanosuspension technology is paired with a lyophilized formulation that makes it possible to reconstitute and deliver Ryanodex in substantially less time than other dantrolene sodium formulations. Ryanodex (dantrolene sodium) is a sterile lyophilized powder. The unique nanosuspension technology enables fast reconstitution within 10 s with less sterile water than high-volume low-concentration dantrolene sodium formulations because it does not need to be dissolved before administration. Dantrolene has been shown to induce relaxation in isolated nerve muscle preparations by manipulating the contractile reaction of the muscle at a position outside the myoneural junction. One of the potential pathways involves the breakdown of skeletal muscle tissue by inhibiting the release of Ca^{2+} from the sarcoplasmic reticulum. Evidence points to an underlying abnormality in skeletal muscle tissue in anesthetic-induced malignant hyperthermia syndrome. In affected humans, "triggering agents," such as general anesthetics and depolarizing neuromuscular blocking agents, have been postulated to induce a transition within the cell that increases myoplasmic calcium. Malignant hyperthermia can be initiated by elevated myoplasmic calcium syndrome, which can also progress to an elevation in the amount of intracellular calcium. The addition of dantrolene can restore a normal level of ionized calcium in the myoplasm of the "triggered" malignant hyperthermal muscle cells. Inhibition by dantrolene of the release of calcium from the sarcoplasmic reticulum restores the myoplasmic balance of calcium, thereby increasing the percentage of bound calcium. Thus, it is possible to counteract or attenuate hormonal, metabolic, and biochemical changes associated with malignant hyperthermia (Table 3) [252,253].

3.3.10 Olanzapine (Zyprexa)

Olanzapine, sold under the trade name Zyprexa, is an atypical antipsychotic that is primarily used to treat schizophrenia and bipolar disorder. It can be used for both new-onset schizophrenia and long-term maintenance. Weight gain, movement disturbances, dizziness, exhaustion, constipation, and dry mouth are typical side effects. Olanzapine was patented in 1971 and approved in the United States in 1996 for clinical use (Table 3) [254–256].

3.3.11 Nabilone (Cesamet)

Cesamet (nabilone) [257,258] is a synthetic orally delivered cannabinoid. Nabilone is a white to off-white polymorphic crystalline powder. The solubility of nabilone is less than 0.5 mg/L in aqueous media, with pH values varying from 1.2 to 7.0. Cesamet capsules are administered in patients who have not successfully responded to traditional antiemetic medications for the treatment of nausea and vomiting resulting from cancer chemotherapy. This limitation is appropriate because a large proportion of patients administered Cesamet undergo alarming psychotomimetic responses that have not been seen with other antiemetic agents. Sleepiness, vertigo, dry throat, euphoria

(feeling "high"), ataxia, headache, and attention issues are the most frequently encountered side effects (Table 3).

3.3.12 Naproxen sodium (Naprelan)

Naprelan (naproxen sodium) controlled-release tablets are nonsteroidal anti-inflammatory drugs. Naproxen sodium is an odorless crystalline powder that is white to creamy in texture. This compound is soluble in methanol and water. The following inactive components are also used in Naprelan: copolymer ammoniomethacrylate type A, copolymer ammoniomethacrylate type B, citric acid, crospovidone, magnesium stearate, copolymer methacrylate type A, microcrystalline cellulose, povidone, and talc. The covering of the tablet includes hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide. NSAIDs have been used to treat medical problems such as multiple types of arthritis, menstrual cramps, and other types of short-term discomfort, including pain, redness, swelling, and heat (inflammation) (Table 3) [259,260].

3.3.13 Theophylline (Elixophyllin)

Elixophyllin [261–264] (theophylline anhydrous liquid) is a methylxanthine indicated for treating symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, such as emphysema and chronic bronchitis. Theophylline is structurally classified as methylxanthine. It is a white, odorless, crystalline powder with a bitter taste (Table 3).

3.4 Nonpolymeric nanoparticles

3.4.1 Ferumoxytol (Feraheme)

Ferumoxytol, known as Feraheme, approved by the FDA in 2009, is an intravenous drug formulation with a neutral pH for the treatment of anemia. It is recommended for adult patients with evidence of iron overload. Clinical trials have shown that 510 mg intravenous ferumoxytol injection is well tolerated. According to the AMAG label for Feraheme, hypersensitivity reactions and hypotension were encountered in 0.2 and 1.9% of patients, respectively. Some of the severe side effects of Feraheme seen in clinical trials include nausea, diarrhea, hypotension, constipation, dizziness, and peripheral edema (Table 4) [178].

3.4.2 Iron sucrose (Venofer)

Venofer (iron sucrose) was the first colloidal particle-based nano-sized medication. It was developed as a substitute for oral iron supplements to treat iron deficiency [265]. Venofer (iron sucrose injection, USP), an iron replacement component, is a brown, sterile, aqueous complex of polynuclear iron(III)-hydroxide in sucrose. It has a molecular weight between 34,000 and 60,000 Da. Venofer injection is an iron substitute medication used in patients with kidney disease to treat iron deficiency anemia. Venofer is typically provided with another drug to stimulate red blood cell formation (Table 4) [266–268].

3.4.3 Sodium ferric gluconate (Ferrlecit)

Ferrlecit is an iron replacement medication used to treat iron deficiency anemia in adults and children aged 6 years and older with severe kidney disease who are undergoing hemodialysis and receiving supplementary epoetin treatment. Ferrlecit is a sodium ferric gluconate complex in sucrose. It is a macromolecular complex with an apparent molecular weight of 289–440 kDa. At alkaline pH, the macromolecular complex is negatively charged and is found in solution with sodium cations. The substance has a deep red color, caused by the ferric oxide bonds. The chemical name of Ferrlecit is D-gluconic acid, iron (3+) sodium salt (Table 4) [269–271].

3.4.4 Iron dextran (INFeD)

INFeD (Iron Dextran Injection USP) is a dark brown, slightly viscous sterile liquid complex of ferric hydroxide and dextran for intravenous or intramuscular use. Intravenous or intramuscular injections of INFeD are recommended for the treatment of patients with confirmed iron deficiency who are unsatisfactory or unable to undergo oral administration (Table 4) [272–275].

3.4.5 Ferric carboxymaltose (Injectafer)

Iron is required for red blood cell formation. When the body does not receive enough iron, it cannot produce enough red blood cells. This disease is known as iron deficiency anemia. Injectafer (ferric carboxymaltose injection) is used to treat anemia caused by iron deficiency. Several medical problems including excessive menstrual

Table 4: Approved marketed drugs loaded non polymeric nanoparticles

No.	Drug loaded	Type of nanoparticle	Trade name/(company name)	Applications	Approval date	Ref.
1	Ferumoxytol	Inorganic/metallic NPs	Feraheme™/(Amag)	Chronic renal failure with iron deficiency	2009	[307,308]
2	Iron sucrose	Inorganic/metallic NPs	Venofer (Am Regent)	Chronic renal failure with iron deficiency	2000	[307,308]
3	Sodium ferric gluconate	Inorganic/metallic NPs	Ferrlecit (Sanofi Avertis)	Chronic renal failure with iron deficiency	1999	[307,308]
4	Iron dextran (low MW)	Inorganic/metallic NPs	INFeD (Allergan)	Chronic renal failure with iron deficiency	1974	[307,308]
5	Ferric carboxymaltose	Inorganic/metallic NPs	Injectafer/(Am Regent)	Iron deficiency anemia in chronic kidney disease	2013	[316]
6	Lanreotide acetate	Nanotube	Somatuline depot/(Ipsen Pharma)	Acromegaly	2007	[313]

EUAs, emergency use authorization; NPs, nanoparticles.

bleeding, breastfeeding, miscarriage, inflammatory bowel disease, other malabsorption diseases, bariatric surgery, or chronic kidney disease may be responsible for iron deficiency anemia. Injectafer is a dark brown, clean, aqueous, isotonic colloidal solution. Each 1 mL contains 50 mg of iron in water for injection as ferric carboxymaltose. Injectafer is available in 15 mL single-use vials. Sodium hydroxide or hydrochloric acid may be added to change the pH to 5.0–7.0 (Table 4) [276,277].

3.5 COVID-19 vaccines

3.5.1 Pfizer-BioNTech

By reporting that their coronavirus vaccine was over 90% successful, New York-based Pfizer and the German firm BioNTech made history on November 9, 2021. On December 11, just over a month later, the FDA gave it the first emergency use permit ever issued to a coronavirus vaccine by the United States. BioNTech's researchers initiated the work on the vaccine in January 2020, based on a genetic molecule called messenger RNA (mRNA). The vaccine includes genetic instructions to develop a coronavirus protein, known as a spike. The vaccine allows cells to produce spike proteins, which are then released into the circulation and provoke an immune response. In March, to scale up the study, BioNTech partnered with Pfizer, initiating a clinical trial in May [170,278]. They gave the vaccine the generic name tozinameran and the brand name Comirnaty. Tozinameran is loaded in liposomal nanoparticles (LNPs) or PEGylated liposomes (PEGLips). PEGLips are artificial phospholipid vesicles that are effective in stabilizing pharmaceutical products and enhancing their pharmacological properties [279]. In the case of COVID-19 vaccine, this liposome formulation enables mRNA to be stabilized due to its lability [280,281]. Lipid nanoparticle (LNP)-formulated mRNA vaccine technology enables antigen-presenting cells to be given correct genetic information along with an adjuvant [282]. Preclinical models have shown the prophylactic efficacy of this technology against several viral targets [283–285]. In clinical trials, LNP and liposome-formulated RNA vaccines to prevent infectious diseases or treat cancer have been safe and well tolerated [286]. The mRNA is transiently expressed and is not incorporated into the genome. It is well established, free from animal-derived materials, and synthesized from DNA templates by an efficient, cell-free *in vitro* transcription process [283,286–288]. The rapid and highly versatile processes of mRNA production and LNP formulation allow several vaccine doses to be

developed quickly [284,285,289], making it ideal for the rapid development of vaccines and the delivery of pandemic vaccines (Tables 5–7) [286].

3.5.2 Moderna vaccine

The FDA issued emergency use permission on December 18, a week after the vaccine produced by Pfizer and BioNTech, for a vaccine developed by Moderna, a Boston-based firm. The Moderna vaccine was the second COVID-19 vaccine approved by the FDA. Moderna produces the vaccine from mRNA, similar to the Pfizer and BioNTech vaccines. The organization has been testing mRNA vaccines for various diseases in recent years, but they have yet to put one on the market. They started developing a vaccine for coronavirus in January 2020 [279,286]. Moderna packages this vaccine in LNPs or PEGLips. Packaging these vaccines in liposomes aids in preserving the mRNA and conferring its lability (Tables 5–7) [280].

3.5.3 Oxford-AstraZeneca

To create and validate the coronavirus vaccine known as ChAdOx1 nCoV-19 or AZD1222, the University of Oxford collaborated with the British-Swedish Corporation AstraZeneca. Clinical trials showed that when two doses were administered 12 weeks apart the vaccine was 82.4% effective. Despite confusion regarding the outcome of some trials in December 2020, Britain approved the vaccine for emergency use. In January 2021, India approved a variant of the Covishield vaccine. Like the Pfizer-BioNTech vaccine, the Oxford-AstraZeneca vaccine is based on the genetic instructions for the construction of the virus spike protein. However, the Oxford vaccine uses double-stranded DNA, unlike the Pfizer-BioNTech and Moderna vaccines, which store the instructions in single-stranded RNA. The researchers attached an adenovirus to the gene encoding the coronavirus spike protein. Adenoviruses are natural viruses that generally cause flu-like symptoms or colds. A modified version of a chimpanzee adenovirus, known as ChAdOx1, was used by the Oxford-AstraZeneca team. It can enter cells but cannot replicate. The Oxford-AstraZeneca vaccine for Covid-19 is more rigorous than the Pfizer and Moderna mRNA vaccines. Although DNA is not as fragile as mRNA, the protective protein coating of the adenovirus helps coat and protect the genetic material. As a result, the Oxford vaccine does not have to be stored frozen. The vaccine is expected to last for at least 6 months when refrigerated at 2–8°C (Tables 5–7) [290–294].

Table 5: COVID-19 vaccines loaded nanoparticles [317]

Vaccine	Technology	Dosing	Efficacy	Storage
Pfizer-BioNTech	mRNA	2 doses, 3 weeks apart	95% symptomatic illness, 90% severe COVID-19	−70°C, 5 days at 2–8°C
Moderna	mRNA	2 doses, 4 weeks apart	94.1% symptomatic illness, 100% severe COVID-19	−20°C for 6 months 30 days at 2–8°C
Oxford-AstraZeneca	Viral vector	3 doses, 4 weeks apart	62% symptomatic illness, 100% severe COVID-19	Refrigerated at 2–8°C
Johnson & Johnson	Viral vector	Single dose	66% symptomatic illness, 85% severe COVID-19	2 years at −20°C, 3 months at 2–8°C
Novavax	Protein	2 doses, 3 weeks apart	89.3% symptomatic illness, 49% symptomatic illness in South Africa phase 2b	Refrigerated at 2–8°C
Sinopharm	Inactivated virus	2 doses, 3 weeks apart	79% symptomatic illness, 100% severe COVID-19	Refrigerated at 2–8°C

Table 6: Characteristics of the Pfizer/BioNTech, Oxford University/AstraZeneca and Moderna vaccines [290–294]

Characteristics	Pfizer/BioNTech	Oxford University/AstraZeneca	Moderna
Therapeutic indication	For effective immunization to suppress SARS-CoV-2 virus-induced COVID-19 in persons 16 years of age and older.	For effective immunization for the prevention of COVID-19 in persons 18 years of age and older.	For effective immunization to prevent SARS-CoV-2 virus-induced COVID-19 in persons 18 years of age and older.
Type of vaccine	Messenger RNA (mRNA).	Adenovirus vector.	Messenger RNA (mRNA) multidose.
Number of doses	A multidose vial.	One dose.	
Pharmaceutical form	Concentrate for solution for injection.	Solution for injection.	Dispersion for injection.
Color	White to off-white frozen solution.	Colorless to slightly brown, clear to slightly opaque, and particle free.	White to off-white frozen dispersion (pH: 7.0–8.0).
Dosage schedule	Two doses (0.3 mL each) with an interval of between 3 and 12 weeks.	Two doses (0.5 mL each) with an interval of between 4 and 12 weeks.	Two doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose.
Route of administration	Intramuscular	Intramuscular	Intramuscular
Contraindication	Hypersensitivity	Hypersensitivity	Hypersensitivity
Special warnings and precautions	Hypersensitivity and anaphylaxis	Hypersensitivity	Anaphylaxis: events of anaphylaxis have been reported
	Traceability: to enhance the traceability of biological medicinal products, the name, and the batch number of the administered product should be clearly recorded.	Acute severe febrile illness	Traceability: to enhance the traceability of biological medicinal products, the name, and the batch number of the administered product should be clearly recorded.
	Acute severe febrile illness	Traceability: to enhance the traceability of biological medicinal products, the name, and the batch number of the administered product should be clearly recorded.	Anxiety-related reactions
	Anticoagulant therapy and bleeding disorders: the vaccine should not be given to people receiving anticoagulant treatment or those with a bleeding condition that contraindicates intramuscular injection unless the possible benefit clearly outweighs the hazard of administration. Immunocompromised individuals.	Anticoagulant therapy and bleeding disorders: the vaccine should not be given to people receiving anticoagulant treatment or those with a bleeding condition that contraindicates intramuscular injection unless the possible benefit clearly outweighs the hazard of administration Immunocompromised individuals.	Immunocompromised individuals

Coagulation disorders: should be given with caution in individuals with bleeding disorders.
Acute severe febrile illness |
| Interactions with other medicinal products | Interaction studies have not been performed. | Interaction studies have not been performed. | Interaction studies have not been performed. |
| Shelf life and special precautions for storage | Store for 6 months in a freezer at −80°C to −60°C shelf life. Stored at −90°C to −60°C in a thermal container.

Stored to protect from light in the original package. | Unopened multidose vial: in the refrigerator for 6 months (2°C to 8°C). Don't freeze. To protect against light, hold vials in the outer carton.

After first use: use as soon as practically possible and within 6 h. The vaccine may be preserved during the in-use time between 2°C and 25°C. | Store shelf life of 7 months at −25°C to −15°C. Do not store or move on or below −40°C dry ice. Should be protected from light.

The vaccine cannot be refrozen after thawing and should be kept refrigerated at 2°C to 8°C, protected from light for up to 30 days, unless used (needle punctured). |

(Continued)

Table 6: *Continued*

Characteristics	Pfizer/BioNTech	Oxford University/AstraZeneca	Moderna
	When taken from the fridge, the undiluted vaccine may be kept at 2°C to 8°C for up to 5 days and at temperatures up to 25°C for up to 2 h until usage. Minimize exposure to room light during storage and prevent exposure to direct sunlight and ultraviolet light.		The chemical and physical stability of an unopened vial was illustrated for 12 h at 8 °C to 25°C following release from refrigerated environments. Don't refreeze. Punctured vial: after first puncture, chemical and physical in-use stability was demonstrated for 6 h at 2°C to 25°C. From a microbiological standpoint, the products can be automatically used.
	Thawed vials can be handled in room light conditions.		When not used instantly, in-use storage times and situations are the responsibility of the user.
	Stock the vaccine at 2°C to 25°C after dilution and use as soon as technically possible and within 6 h. The vials must be labeled with the dilution time when diluted then discarded during 6 h of dilution. Once thawed, the vaccine cannot be refrozen.		
Nature and contents of container	Five doses of concentrate solution for injection in a 2 mL clear vial. Pack size of 195 vials.	In 10-dose vials, 5 mL of solution, or in 8-dose vials, 4 mL of solution. The box size is 10 vials. Not all pack sizes are permitted to be sold.	A limit of 10 doses of 0.5 mL each are found in each vial. The box size is 10 vials.
Suitability in pediatrics	In children younger than 16 years, safety and effectiveness have not yet been identified.	In children younger than 18 years, safety and effectiveness have not yet been identified.	In children younger than 18 years, safety and effectiveness have not yet been identified.
Suitability in pregnancy	There is insufficient evidence of the vaccine in pregnant women. Administration must be considered only once the possible benefits outweigh any possible risks.	The experience for pregnant women is limited. Pregnancy administration can only be taken into consideration where the possible advantages outweigh the possible risks.	The experience for pregnant women is limited. Animal studies do not suggest that breastfeeding, embryo/fetal growth, parturition or postnatal development have direct or indirect adverse consequences.
	The Joint Committee on Vaccination and Immunization (JCVI) has recognized that the possible benefits of vaccination are particularly important for some pregnant women. This includes those at very high risk of getting the infection or those with health problems that place them at high risk of severe COVID-19 complications.		Pregnancy administration can only be taken into consideration where the possible advantages outweigh the possible risks.
Suitable in breastfeeding	Unknown	Unknown	Unknown
Effects on fertility	Animal experiments do not show any direct or indirect harmful fertility outcomes.	Animal experiments do not show any direct or indirect harmful fertility outcomes.	Animal experiments do not show any direct or indirect harmful fertility outcomes.

(Continued)

Table 6: *Continued*

Characteristics	Pfizer/BioNTech	Oxford University/AstraZeneca	Moderna
Alcohol content	In the production process, ethanol is used and then extracted down to trace amounts. Consequently, it is not used in the final product formulation.	A very small quantity (0.002 mg of alcohol (ethanol) per 0.5 mL dose) of alcohol. That's not enough to cause any noticeable effects.	Awaiting confirmation
Interchangeability	To complete the vaccination sequence, individuals who have received one dose of COVID-19 mRNA Vaccine BNT162b2 should receive a second dose of COVID-19 mRNA Vaccine BNT162b2.	Individuals receiving the first dose of the AstraZeneca COVID-19 vaccine should get a second dose of the AstraZeneca COVID-19 vaccine to complete the vaccination sequence.	To complete the vaccination sequence, individuals who have received one dose of COVID-19 Vaccine Moderna should receive a second dose of COVID-19 Vaccine Moderna.

3.5.4 Sinopharm

An inactivated coronavirus vaccine, known as BBIBP-CorV, was developed by the Beijing Institute of Biological Products by the end of 2020. A state-owned corporation, Sinopharm performed clinical trials and found that BBIBP-CorV had a 79% efficacy score. The vaccine was approved by China and rapidly distributed to other countries. When researchers began producing greater quantities of coronavirus, they preserved them in droplets with a chemical called beta-propiolactone. The compound disables coronavirus particles by binding to their DNA. The inactivated coronaviruses can no longer replicate. However, their proteins, including spikes, remain intact. BBIBP-CorV functions by training the immune system to produce antibodies against SARS-CoV-2. The antibodies bind to viral proteins, such as the spike proteins that stud their surface (Table 5) [295–299].

3.5.5 Novavax

Recombinant nanoparticle technology was used to generate antigens engineered from the genetic sequence of COVID-19 spike proteins. In combination with the proprietary Matrix-M™ adjuvant, NVX-CoV2373 has been demonstrated in preclinical studies to bind efficiently with human receptors targeted by the virus, a critical aspect for effective vaccine protection (Table 5) [300].

3.5.6 Johnson & Johnson

A coronavirus vaccine known as JNJ-78436735 or Ad26.COV2 has been studied by Johnson & Johnson. Scientific trials have shown that the effectiveness of a single dose of the vaccine was as high as 72%. In partnership with the Beth Israel Deaconess Medical Center, Janssen Pharmaceutical (a Belgian-based division of Johnson & Johnson) manufactures the vaccine. The researchers placed the gene for the coronavirus spike protein into an adenovirus. Other vaccines for coronaviruses are also based on adenoviruses, such as the Oxford-AstraZeneca vaccine. A modified adenovirus, which can enter cells but cannot replicate or induce illness, was used by the Johnson & Johnson team. The vaccine from Johnson & Johnson comes out of decades of adenovirus-based vaccine research. The first was an Ebola vaccine approved for general use in July and was also developed by Johnson & Johnson. The organization is now performing trials on vaccines based on adenoviruses for other illnesses, including HIV and Zika (Table 5) [301].

4 Discussion

Currently, 58 nanoparticle therapies and imaging agents have been approved for clinical use, whether in the United States by the FDA or in the European Union by the European Medicines Agency (EMA). The different categories of FDA-approved nanomedicines are shown in Figure 2. Many clinically approved nanoparticle formulations are used for the treatment of different cancers at various stages. All drugs use liposomal nanoparticle systems except Abraxane. The first approved cancer nanomedicine (FDA 1995) was Doxil, polyethylene glycol (PEG)-functionalized liposomal doxorubicin. Shortly thereafter, the FDA approved other liposomal formulations, including liposomal daunorubicin (DaunoXome), liposomal vincristine (Marqibo), and liposomal irinotecan (Onivyde), while the EMA approved non-PEGylated liposomal doxorubicin

Table 7: Excipient information of the Pfizer/BioNTech and Oxford University/AstraZeneca vaccines [290–294]

Vaccine	Antibiotic free	Preservative free	Sodium free	Gluten free	Nut free	Soy free	Egg free	Vegetarian and vegan suitability	Halal certification
Pfizer/BioNTech	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Oxford University/AstraZeneca	Awaiting confirmation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Awaiting confirmation
Moderna	Awaiting confirmation	Yes	Yes	Awaiting confirmation	Awaiting confirmation	Awaiting confirmation	Awaiting confirmation	Awaiting confirmation	Awaiting confirmation

(Myocet) and liposomal mifamurtide (MEPACT). Abraxane is an albumin-bound paclitaxel nanoparticle. With the exception of Doxil and Onivyde, most of these formulations are not PEGylated, which may be surprising considering the well-known advantages that even small amounts of PEG have been shown to confer on nanoparticle delivery systems. In addition, with no active or chemical-based targeting moieties, all of these formulations passively target the diseases. Other benefits, such as minimized toxicity resulting from their selective accumulation at tumor sites and minimal off-target side effects through the enhanced permeation and retention (EPR) effect, are likely to be responsible for the success and improved efficacy of these approved particles over their free drug equivalents [229,302–306] (Figure 2).

Another clinical field where nanoparticles have made a large impact is iron-replacement therapeutics for the treatment of anemia. In these applications, nanoparticles (iron-oxide colloids) can be used to increase iron concentrations in the body. The need to address toxicity concerns associated with the injection of free iron has led to these nanoparticle approaches. Many of these toxicity problems have been overcome using sugar-coated colloidal iron. It should be mentioned that nanoparticles indicated for iron replacement undergo significantly different approval procedures, by both the FDA and EMA, as they are nonbiological complex medications. It is a common belief that additional factors, stemming from their colloidal and nanoparticle nature, need to be considered during their approval (e.g., manufacturing conditions) [303]. The main advantages
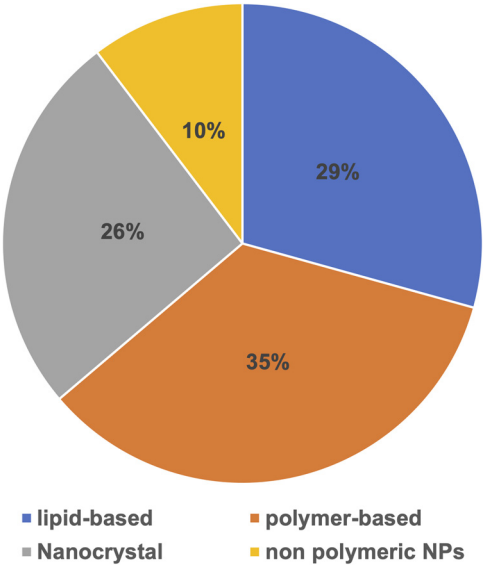

Figure 2: The percentage distribution of approved nanoparticle medications in the global market.

of nanoparticles are as follows: (1) enhanced bioavailability by improving water solubility, (2) increased resistance time in the body (increasing half-life for clearance/ increasing specificity for its cognate receptors), and (3) drug targeting to a specific region in the body (its site of action).

A variety of other clinical situations also require the use of nanoparticles or liposomes. Diprivan, a general anesthetic, was the first liposome delivery system approved by the FDA in 1989. Two vaccines packaged in liposomal systems have received authorization for emergency use: the Pfizer/BioNTech and Moderna COVID-19 vaccines. Both are formed in liposomal nanoparticles (LNPs) or PEGLips. PEGlips are artificial phospholipid vesicles that are effective in stabilizing pharmaceutical products and enhancing their pharmacological properties. In the case of these COVID-19 vaccines, this liposome formulation enables mRNA to be stabilized due to its lability [290–294]. Liposomes or lipid-based nanoformulations have also been clinically approved for fungal and parasitic infections. For example, liposomes have been formulated for the highly toxic antifungal drug amphotericin B (AmBisome), which is used to treat systemic fungal infections. As the pharmacokinetics and tissue distribution are improved through liposomal encapsulation, toxicity is significantly decreased. In addition, liposomal formulation solves a major problem related to the free drug formulation of amphotericin B, i.e., its insolubility in pH 7 saline. There are other lipid-complexed formulations of amphotericin B, such as Abelcet, approved by the FDA. Visudyne is a liposomal formulation of verteporfin that is triggered by light. Liposomal encapsulation enhances absorption by proliferating cells, which improves specific targeting and absorption in neovascular areas. The endothelium is damaged upon light stimulation, and local blood vessels are blocked to prevent and treat neovascularization [303].

Bobo *et al.* [229] published an article in 2016 that counted the number of approved nanoparticles used in the clinic; in 2016, 51 nanomedicines were being used. In this review, we have updated the list, as some of the drugs have been discontinued. Discontinued nanomedicines include Feridex, GastroMARK, Dexferrum, Avinza, Estrasorb, DepoDur, Renagel, Macugen, and Adagen. Currently used drugs include Definity, Diprivan, Vyxeos, Pfizer-BioNTech, Moderna, Zilretta, Kadcyla, Taxotere, Verelan, Zevalin, Zyprexa, Cesamet, Naprelan, Elixophyllin, Azopt, Gris-Peg, INjectafer, and Somatuline depot. Polymeric nanoparticles are the most commonly approved nanomedicine, but there is a noticeable increase in the approval of lipid nanoparticles, and they are expected to be the most commonly used in the future.

5 Conclusion

Several nanoparticle drugs that are used in the clinic to treat or diagnose disease have been authorized by the FDA or EMA. Researchers are pushing these same technologies even further by seeking approval for additional indications. Beyond these efforts, there are a significant number of clinical trials researching new nanoparticle systems that are, in several ways, more developed than those that have already been authorized. Moreover, the nanoparticle systems undergo continued progress in clinical trials for future use, such as active targeting methods to enhance biodistribution or even the use of stimuli-responsive mechanisms to enhance drug release in specific parts of the body. NPs have greater stability that help to extend shelf life, large carrier capacity that can be used to integrate several drug molecules in the particle medium, capability of incorporating both hydrophilic and hydrophobic compounds, and feasibility of multiple routes of administration. Nanoparticles can be developed to allow sustained drug release. Nanoparticles have properties that enhance solubility, allowing for greater drug bioavailability and reduced dose frequency, as well as resolving the problem of poor adherence. Direct delivery of the drug to the site of action can minimize systemic toxicity while also increasing drug concentration at the target site. This development in the clinic over the past 20 years (since the approval of Doxil) has been made possible by comprehensive efforts in preclinical, industrial, and clinical trials. In addition, the overall outlook of nanoparticle drug delivery systems is encouraging, as liposomal nanoparticles are also being used in both the Pfizer/BioNTech and Moderna vaccines to treat COVID-19.

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