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Nanocarriers for the Delivery of Medical, Veterinary, and Agricultural Active Ingredients

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Abstract

Nanocarrier-based delivery systems can be used to increase the safety and efficacy of active ingredients in medical, veterinary, or agricultural applications, particularly when such ingredients are unstable, sparingly soluble, or cause off-target effects. In this review, we highlight the diversity of nanocarrier materials and their key advantages compared to free active ingredients. We discuss current trends based on peer-reviewed research articles, patent applications, clinical trials, and the nanocarrier formulations already approved by regulatory bodies. Although most nanocarriers have been engineered to combat cancer, the number of formulations developed for other purposes is growing rapidly, especially those for the treatment of infectious diseases and parasites affecting humans, livestock, and companion animals. The regulation and prohibition of many pesticides have also fueled research to develop targeted pesticide delivery systems based on nanocarriers, which maximize efficacy while minimizing the environmental impact of agrochemicals.

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsnano.0c00173.
Tables summarizing gene therapy nanocarriers, viral nanocarriers, and polymer-protein conjugates undergoing clinical trials; and FDA/EMA approved polymer-protein conjugates and inorganic nanoparticles (PDF)

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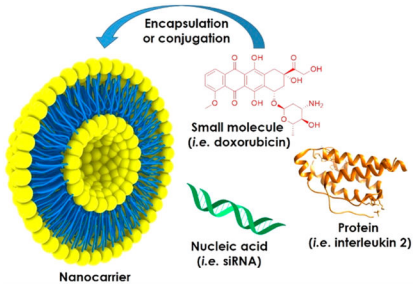
VOCABULARY

Active ingredient, a pharmaceutical or agriculture compound that confers activity against a specific abnormal condition; nanomaterial, a material with a least one dimension smaller than 1000 nm; nanocarrier, a nanomaterial used as a transport module for the delivery of an active ingredient; precision farming, site specific crop management relying on observing, measuring, and responding to field variability in crops in order to maximize yields while preserving resources; targeted drug delivery, engineered nanotechnologies promoting the accumulation of active ingredients to specific diseased sites to minimize dosage and administration frequency and off-target side effects.

Graphical Abstract



Keywords

nanocarrier; nanomedicine; veterinary medicine; drug delivery; gene delivery; clinical trials; cancer; precision farming; pest management; agrochemical delivery

Over the past 30 years, nanoparticle engineering has led to the development of delivery systems for active ingredients with medical, veterinary, and agricultural applications. The increasing cost of research and development combined with the growing number of competitive manufacturing entities, short patent cycles, and the tightening regulatory guidelines for active ingredients have made it difficult to bring additional formulations from the bench to the market.[1,2] Furthermore, the efficacy of many drugs is limited by their low solubility and/or stability as well as off-target effects following systemic delivery. For example, cancer therapy is often unsuccessful due to the toxicity of cancer drugs toward healthy cells and/or the development of resistant cells overexpressing efflux transporters and multidrug-resistance proteins.[3,4] The resulting low bioavailability of the active ingredient in the tumor requires the administration of larger doses to ensure the drug concentration stays within the therapeutic window, which in turn increases off-target toxicity. Nanocarriers can address this challenge by delivering active ingredients *via* the enhanced permeability and retention (EPR) effect, a well-established phenomenon based on the combination of leaky vasculature and poor lymphatic drainage at the tumor site.[5] The EPR effect is complex and often heterogeneous within the tumor microenvironment and only increases the tumor homing of nanoparticles by 2-fold compared to normal tissue;[6] nanoparticles can also be functionalized with targeting ligands, aptamers, antibodies, or antibody fragments to promote their binding to receptors overexpressed on tumor cells or in the surrounding extracellular matrix.[7,8] As reviewed elsewhere, two other translocation mechanisms of nanocarriers from the systemic circulation into the tumor microenvironment are being investigated, namely the interendothelial and transendothelial pathways.[9,10] The entrapment of active ingredients in nanocarriers also reduces the clearance rate *via* renal elimination and phagocytosis, which increases the active ingredient circulation time and therefore its therapeutic longevity.

The medical and veterinary applications of nanocarriers are analogous, but only experimental veterinary applications have been reported.[11] Most research in veterinary drug delivery has focused on diseases in animals that can be translated to humans. However, the importance of animal welfare *per se* is increasingly important to consumers, and

nanocarriers that improve the efficacy and safety of active ingredients are demanded in the context of companion animals such as cats, dogs, and horses as well as farm animals such cattle, sheep, swine, and poultry.[12] Pet owners consider companion animals as an extension of the family and are willing to pay their bills, including the high cost of cancer treatment, with the cost of veterinary care in the USA therefore rising from $7 billion in 2001 to $19 billion in 2019.[13] This increase most likely reflects a combination of inflation, high drug costs, better treatment options (with higher survival rates), and an increased willingness to care for pets. In contrast, the food industry works with low profit margins and would only treat animals suffering from temporary and low-risk diseases, such as infections.[14] Veterinary nanocarriers must therefore combine low costs with the release of active ingredients for sustained periods to minimize the frequency of animal handling and improve therapeutic efficacy. For example, animals are often subject to bacterial infections, and a nanomedicine approach could achieve the targeted delivery of drugs to pathogens, killing them on demand. This avoids the unnecessary use of antibiotics, which can encourage the emergence of resistant strains.

The controlled delivery of agrochemicals and nutrients to plants is conceptually similar to drug delivery in humans and animals. However, agricultural delivery takes place in an open field, with variable weather and geographic features and no specific transport pathway to the target, in contrast to the closed and regulated nature of the bloodstream. Nanocarriers can be administered *via* the foliage, where they are taken up passively through stomata and any wounds, or can be transported through the soil and taken up *via* the roots.[15] Among the agrochemicals that can be delivered using nanoparticles, pesticides are particularly suitable candidates because they are effective at very low doses (grams per acre) but are difficult to apply in such small amounts due to their non-uniform distribution in the field.[16] To compensate, the active ingredient can be diluted within a mixture of liquid or solid diluents. However, the active ingredient is often unstable, sparingly soluble, and binds with high affinity to soil particles, thus reducing its efficacy against target pests and increasing the amount required to achieve an effective dose.[17] In an analogous manner to the off-target effects caused by systemic drugs, the persistence of large quantities of pesticides in the environment is toxic to other species and contaminates the soil and groundwater, leading to health problems in domestic animals and humans, including cancer and infertility.[18,19] Governments have therefore started to prohibit many pesticides or strictly regulate their use. In one strategy, the active ingredient is enveloped in organic or inorganic coatings (microencapsulation) for protection against photolysis or biodegradation, allowing the controlled release of the ingredient.[20] But even microencapsulation is limited by the poor chemical and thermal stability of the capsules, and degradation promotes the acidification of soil, which can impair its fertility. As discussed in more detail below, these drawbacks can be addressed by the next generation of nanocarriers based on polymers, lipids and other materials.

The definition of a nanomaterial is not yet harmonized, but the International Organization for Standardization (ISO) defines nanoparticles as objects with dimensions of 1–100 nm, because the physicochemical properties of the material at this scale differ from the bulk material. Unfortunately, this ISO definition excludes most nanomaterials that are relevant in the medical, veterinary, and agricultural sectors. A less stringent definition would include

any materials with at least one dimension in the range of 1–100 nm, thus including nanowires and nanotubes.[21] In this review, we consider nanocarriers with at least one dimension smaller than 1000 nm and their use for the targeted delivery of active ingredients (drugs or pesticides) to achieve greater efficacy. The review focuses on the translation of nanocarriers from the bench to the market in the medical, veterinary, and agricultural industries in order to describe the current landscape and potential future directions for active ingredient delivery systems. Specifically, we discuss research articles (retrieved from PubMed and the Web of Science), patents (retrieved from Orbit Express using Questel software), clinical trials (listed in the clinicaltrials.gov database), and commercially available nanocarrier formulations approved by (1) the US Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) for medical use; (2) the American Veterinary Medical Association (AVMA) for use in animals, *i.e.*, products listed in the Approved Animal Drug Products (Green Book) and/or AVMA Animal Health Studies database; and (3) the US Environmental Protection Agency (EPA), *i.e.*, products listed in the National Pesticide Information Center database. Nanoparticles have also been used for diagnosis, drug discovery, gene delivery, immunotherapy, photothermal/photodynamic therapy, and biosensor applications, which are reviewed elsewhere.[22–27]

FROM IDEA TO COMMERCIAL PRODUCT

Trends in Active Ingredient Delivery.

The term “nanotechnology” was coined in 1974 by the Japanese scientist Norio Taniguchi,[28] but the worldwide proliferation of nanotechnology started in the 1990s and has thus far led to the publication of more than 60,000 research articles in the pharmaceutical and environmental sciences. More than 93% of these articles relate to medical research, whereas nanoparticles in agriculture and veterinary research emerged later in the 2010s and represent only ~4% and ~3% of the publications, respectively (Figure 1a). Even so, the growing political and consumer interest in global food security and environmental protection is likely to drive additional research in the use of nanocarriers in agriculture and veterinary research in the future. Nanoparticle-based innovations also account for more than 150,000 patents (Figure 1b). Since the Bayh–Dole (Patent and Trademark Law Amendments) Act was ratified in the United States in 1980, allowing small businesses, nonprofit institutions, and universities to own inventions created *via* research funded by the federal government, the majority of these patents have been filed by universities. The University of California is the largest patent holder in this field, with more than 1200. Interestingly, 16% of all nanotechnology patents (~24,000) are held by the pharmaceutical sector, highlighting the growing interest in nanoparticles for drug delivery, diagnosis, and imaging.

Nanocarriers for medical and veterinary applications are regulated by the FDA in the United States and the EMA in Europe. Since 1990, the FDA and EMA have approved 21 nanocarriers (Table 1), and more candidates are undergoing preclinical and clinical testing (Table 2). Most of these nanocarriers are administered orally or intravenously, and some transdermally. The materials used in these formulations include polymers, micelles, liposomes, proteins, and viruses. Most clinical trials (48%) involve micellar formulations, whereas viruses account for only 1% (Figure 1c). In contrast, most approved nanocarriers

are based on liposomes (47%), followed by viral (19%), micellar (14%), polymeric (10%), and proteinaceous (10%) formulations (Figure 1d). Most of these nanocarriers have demonstrated lower toxicity rather than improved efficacy compared to the active ingredient alone.[29] Accordingly, nanocarriers may not survive clinical trials because they do not achieve greater efficacy and because the reduction in toxicity might be achieved using an already-approved nanocarrier formulation.

The regulation of nanocarriers for agricultural applications is not yet harmonized because a clear definition of agricultural nanocarriers has not yet been agreed, which makes it difficult to determine how many products are already commercialized. Such products are overseen by the EPA in the United States and the European Commission in Europe. In 2011, the EPA approved a nanopesticide, but this nanosilver-based product was restricted to its use as an antimicrobial agent in clothing, not for agricultural applications. In contrast, an agricultural product consisting of tobacco mild green mosaic virus (TMGMV) was approved by the EPA in 2007 as a herbicide in the state of Florida for the treatment of tropical soda apple, an invasive weed.[30,31] No commercialized agricultural nanoformulations for pesticide or fertilizer delivery are yet branded as nanocarriers. This is most likely a marketing strategy to deal with the unclear regulation of agricultural nanocarriers while ensuring public acceptance. However, 42 microencapsulated products (including microscale and nanoscale carriers) have been approved by the EPA (Table 3). Although most of these formulations are used as herbicides or insecticides, a growing body of literature has demonstrated the usefulness of nanocarriers based on clay, chitosan, silica, or zeolites for the delivery of fertilizers, as discussed elsewhere.[32]

Ingredients Delivered by Nanocarriers.

The cargos delivered by nanocarriers include small molecules, peptides and proteins, nucleic acids, or combinations of the above. Small molecules are low-molecular-weight organic compounds with beneficial biological activities, such as cancer drugs, antibiotics, fertilizers, and pesticides. Relevant examples in clinical and veterinary medicine include the antimetabolites paclitaxel and vincristine, the DNA intercalator doxorubicin, and the antibiotic amphotericin B.[33–36] When delivered systemically, hydrophobic small molecules are rapidly metabolized and eliminated, narrowing their therapeutic window. Large doses are therefore required for therapeutic efficacy, which in the case of cancer drugs can lead to off-target effects such as cardiotoxicity and nephrotoxicity.[37,38] Similarly, only a small fraction of pesticides and fertilizers applied to fields ever reach their target, due to leaching, evaporation, photolysis, chemical hydrolysis, and biodegradation. To feed the growing world population, today’s yields must increase by 60–100%, and this must be achieved in part by more effective treatment methods to eliminate pests and by increasing the efficiency of fertilizers.[32]

Peptide and protein pharmaceuticals may act as receptor agonists, essentially fulfilling the functions of endogenous molecules, whereas others act as antagonists. Neuroprotective proteins such as nerve growth factor and brain-derived neurotrophic factor are examples of agonists. They may help to combat Alzheimer’s disease and Parkinson’s disease, although they remain at the preclinical development stage.[39] The blood–brain barrier (BBB) remains

a major hurdle to deliver these proteins to the central nervous system, and nanocarriers have been engineered to deliver proteinaceous active ingredients across the BBB.[40] Small peptides and proteins are often unstable *in vivo* due to the presence of proteases and may also be removed by renal filtration, reducing their bioavailability. Nanocarriers can also overcome this challenge. For example, the antimicrobial peptide $HPA3P^{His}$ was delivered using aptamer-targeted gold nanoparticles, which led to the complete inhibition of *Vibrio vulnificus* colonization in infected mice.[41] As well as stabilizing peptide and protein drugs with nanocarriers, multivalent display can be used as a strategy to enhance therapeutic efficacy, as demonstrated by the delivery of TNF-related apoptosis-inducing ligand (TRAIL) using liposomal and plant viral nanoparticle formulations.[42,43] Monoclonal antibodies (mAbs) are a large class of protein drugs that often act as antagonists. For example, Herceptin is a mAb approved by the FDA for the treatment of $HER2^+$ breast, gastric, and esophageal cancers by blocking HER2 receptor signaling.[44] Herceptin is one of 59 therapeutic mAbs that have been approved since 1992, when mAb formulations were introduced.[45] Four antibody–drug conjugates (ADCs) have also been approved, with another 22 currently undergoing clinical trials.[46] Antibody–nanoparticle conjugates can be targeted to specific cells using the properties of nanocarrier, the antibody, or both. Similarly, the target specificity of the antibody can be combined with the cargo-loading capacity of nanoparticles, which has proven effective in many research studies but has yet to be deployed successfully in the clinic.[47] Nanoparticle-mediated antibody delivery is particularly useful when the target is intracellular.[48] For example, a liposomal nanocarrier was designed to display CD44-specific antibodies on the surface in order to target $CD44^+$ cells and to carry a second IL6R-specific antibody as a cargo, which was taken up by the target cells to inhibit the intracellular IL6R-Stat3 signaling pathway in mice with triple-negative breast cancer. The treated mice showed a significant reduction in metastatic events.[49]

Like antibodies, peptides and proteins can also be used as targeting ligands to direct nanoparticles to disease sites. Such ligands displayed on nanoparticles promote cell binding, internalization, and endosomal escape, allowing the nanoparticles to accumulate and release their active ingredient within target cells while sparing healthy tissue from damage.[50] However, actively targeted nanocarriers developed for the treatment of cancer have yet to progress beyond clinical trials.[51] Targeted nanoparticles are more complex than their passive counterparts, which makes them more difficult to produce according to good manufacturing practice (GMP) and significantly increases the cost of therapy. Furthermore, it is unclear whether active targeting improves therapeutic efficacy. A meta-analysis of the literature over the past 10 years has shown that, on average, 0.9% of each dose of active nanocarriers reaches its target, compared to 0.6% for the passive nanocarriers.[52]

Finally, nucleic acids can be used as active agents in medical, veterinary, and agricultural applications, particularly DNA, microRNA (miRNA), and short interfering RNA (siRNA).[32] Gene therapy in humans and domestic animals involves the delivery of DNA to the nucleus in order to augment or repair malfunctioning genes, whereas gene transfer to crops can introduce additional functionalities, such as resistance to pests and diseases, or pesticide tolerance.[20,45] MicroRNA is noncoding RNA ~20 nucleotides in length that regulates endogenous genes, and the delivery of miRNA to the cytoplasm of target cells can be used to

suppress the expression of disease-causing genes.[53] The delivery of noncoding double-stranded dsRNA or siRNA derived from it promotes the assembly of a protein complex that binds complementary mRNA, leading to its cleavage and the targeted suppression of gene expression. The systemic delivery of miRNA and siRNA is generally ineffective because such molecules are rapidly degraded and cleared and often trigger an innate immune response, the exact nature of which is sequence dependent. Furthermore, miRNA and siRNA are hydrophilic and cannot penetrate the hydrophobic cell membrane to reach the cytoplasm. In the cytoplasm, they are rapidly degraded by nucleases, and multiple doses are therefore needed to suppress gene expression enough for a therapeutic effect. The drawbacks of conventional nucleic acid therapies can be addressed by encapsulating them in nanocarriers (Supporting Tables 1 and 2), and five such carriers have already reached the market (Table 1).

Genetic engineering has facilitated significant advances in human and veterinary medicine and has also helped to improve the yield of crops by enhancing pest and disease resistance and abiotic stress tolerance.[54] Most genetically engineered plants are produced by transformation using the soil bacterium *Agrobacterium tumefaciens*, which introduces DNA *via* a type IV secretion system, or by biolistic delivery systems, which introduce DNA by physically penetrating the cell wall using high-velocity metal particles.[55,56] Nanocarrier-based delivery systems would need to find an alternative strategy to pass through the cell wall, and current research is focusing on the size, charge, and surface properties of metallic, liposomal, silicon-based, and polymeric nanocarriers to enable cell wall penetration.[54]

The limitations of small molecules, peptides, proteins, and nucleic acids can be overcome by using nanocarriers to achieve three key goals: (1) enhance the aqueous solubility and therefore bioavailability of active ingredients; (2) increase the stability of active ingredients by inhibiting their degradation *in vivo* or in the environment, effectively increasing their half-life; and (3) promote the accumulation of the active ingredient at the target site. If all three goals are achieved, the dose of active ingredient required for efficacy is greatly reduced, thus limiting overall costs and avoiding off-target effects. These goals can be achieved using nanocarriers made from a wide range of materials (Table 2), which are discussed in more detail below.

Liposomal Nanocarriers.

Liposomes are spherical vesicles comprising one or more concentric lipid bilayers with an aqueous core.[57] These amphiphilic structures are well-suited to entrap both lipophilic and hydrophilic compounds, making them attractive nanocarriers for a diverse range of active ingredients. Hydrophobic ingredients can be inserted into the lipid bilayer or sequestered in the core, whereas hydrophilic ingredients can be encapsulated in the core. The lipid bilayer is usually composed of phospholipids and sterols such as cholesterol, the latter controlling membrane permeability and fluidity.

In the medical and veterinary fields, conventional liposomal nanocarriers can reduce the off-target effects of active ingredients by modifying their pharmacokinetic properties and biodistribution, promoting their accumulation at the target site and avoiding nontarget tissues.[58] Most liposomal nanocarriers deliver their cargo by fusing with the plasma

membrane of the target cell, causing the active ingredient to be deposited in the cytoplasm. For example, Myocet is a conventional liposomal carrier approved by the EMA for the delivery of doxorubicin to metastatic breast cancer cells.[59] Commercially available liposomal nanocarriers range from 30 to 1000 nm in diameter, which makes them the largest nanocarriers used in the clinic (Table 1). The physicochemical properties of liposomes are determined by the lipid composition, sterol concentration, surface charge, and nanoparticle size.[60] Increasing the concentration of unsaturated phospholipids (*e.g.*, phosphatidylcholine) ensures that the lipid bilayer is permeable, whereas saturated phospholipids (*e.g.*, dipalmitoylphosphatidylcholine) make the barrier impermeable. By controlling the lipid composition and length of the fatty acid chains, liposomal nanocarriers can be engineered to respond to temperature and/or pH, allowing the controlled release of the active ingredient under physiological conditions that are specific to the disease site. The cellular uptake of liposomes can be also tuned by the lipid composition, which influences the overall surface charge.[61,62] Neutral liposomes tend to remain in circulation longer and do not readily interact with cells, promoting the release of active ingredients in the extracellular space. This strategy is used by DaunoXome (for the delivery of daunorubicin to Kaposi's sarcoma), Marqibo (for the delivery of vincristine to lymphoblastic leukemia), and Onivyde (for the delivery of irinotecan to pancreatic cancer cells).[63–65] Whereas positively charged liposomes readily interact with the negative charge on the cell surface *via* electrostatic forces, neutral liposomes are prone to faster clearance. However, conventional liposomes of all types are rapidly eliminated from the bloodstream due to opsonization and uptake by Kupffer cells in the liver and spleen, which limits their bioavailability.[66] This has been addressed by conjugating hydrophilic polymers to the liposome surface, such as polyethylene glycol (PEG) in the case of Doxil.[67] Depending on the liposome formulation, PEGylation has been shown to increase the half-life of the active ingredient from 2 to 24 h in rodents and up to 45 h in humans, resulting in a 4–16-fold higher concentration at the target site.[68] However, PEGylation can inhibit the interaction between liposomes and the cell surface, preventing fusion and uptake. Furthermore, passive targeting is limited by the heterogeneity of the EPR effect both within the tumor environment and when comparing different types of cancer. Ligand-targeted liposomes have therefore been engineered to promote site-specific binding. Low-molecular-weight molecules such as folate, as well as peptides and monoclonal antibodies or their fragments, have been incorporated onto the surface of liposomes to achieve targeted delivery.[69,70] Liposomes also have the versatility to deliver multiple active ingredients simultaneously at a suitable molar ratio to maximize their synergistic interactions. The liposomal nanocarrier Vyxeos is thus far the only approved formulation that delivers more than one active ingredient, namely cytarabine and daunorubicin (5:1 molar ratio).[70]

Liposome nanocarriers reached the market in 1995, and since then 10 further products have been approved by the FDA/EMA for clinical use, mostly for combination cancer therapy (Table 1). Exceptionally, AmBisome (carrying amphotericin B) is indicated for fungal infections,[71] Curosurf (carrying poractant α) is indicated for respiratory distress syndrome, and Visudyne (carrying verteporfin) is indicated for macular degeneration.[72] The most recent addition is Onpattro, an siRNA delivery formulation approved in 2018 by the FDA.[73] Onpattro encapsulates a transthyretin-directed siRNA for the treatment of amyloidosis.

Additional liposomal nanocarriers are undergoing clinical trials against a wide range of diseases, including ocular and topical applications (Table 2). Although many of the recent formulations are cancer therapies, the landscape of current trials highlights the potential of nanomedicine across the field. For example, liposomal alprostadil is a potent vasodilator that increases peripheral blood flow, inhibits platelet aggregation, and induces bronchodilation (NCT02889822); liposomal cyclosporine A is also being investigated as an inhaled delivery formulation for the treatment of bronchiolitis obliterans syndrome.[74] Another example targeting cardiovascular disease consists of sodium alendronate encapsulated in liposomes of distearoylphosphatidylglycerol, 1,2-distearoyl-*sn*-glycero-3-phosphocholine, and cholesterol. Phase II testing is underway for the treatment of *de novo* stenotic lesions in native coronary arteries in patients undergoing percutaneous coronary intervention with implantation of a bare metal stent (NCT00739466). Furthermore, a topical gel nanoliposome formulation of vitamin B12 (adenosylcobalamin) is undergoing clinical trials to treat moderate atopic dermatitis (HL-009; NCT01568489), and liposomal latanoprostis being tested as a means to lower intraocular pressure in patients with open-angle glaucoma and ocular hypertension.[75] Liposomal meglumine antimoniate and liposomal paromomycin are being investigated for the treatment of anthroponotic cutaneous leishmaniasis caused by *Leishmania tropica* in both humans and dogs.[76]

Additional liposomal nanocarriers are also undergoing veterinary trials (Table 4).[77,78] In 2006, a phase I trial of doxorubicin encapsulated into temperature-sensitive liposomes was carried out in companion dogs suffering from spontaneous tumors.[79] Injection of the nanocarrier followed by the induction of tumor hyperthermia caused 100% of the drug cargo to be released within 20 s at 41.3 °C. Of the 21 dogs enrolled in the study, 18 showed a decrease in tumor volume, including 12 with a decrease of more than 50%. Liposomal doxorubicin in combination with palliative radiotherapy improved the clinical outcome of cats with soft tissue sarcomas.[80] Clodronate encapsulated in liposomes was able to eliminate malignant histocytosis in dogs.[81] Liposome-encapsulated amphotericin B demonstrated high efficacy in dogs infected with the blastomyces fungus, while reducing the adverse effects often associated with amphotericin B.[82]

Liposomes have also been used to facilitate the absorption of hydrophobic active ingredients *via* the cuticles of plants and insects.[20,83] However, because they are so expensive to produce, agricultural applications are likely to be restricted for the foreseeable future. For example, Doxil costs $1313 for 5 mg (despite being on the market for two decades and the fact that doxorubicin costs only $8.5 for 5 mg), whereas newer formulations are even more expensive, such as Marquibo ($15,747 per 5 mg kit) and Onpattro ($9500 per vial, typical annual cost $345,000). Even so, a few studies have investigated the liposomal delivery of pesticides such as entofenprox.[84] An alternative and less expensive solution may be the use of liposomes comprising plant-derived lipids (or alternative nanocarrier systems). This was proposed for the delivery of Fe and Mg to tomato plants, and 33% of the encapsulated metal was able to penetrate leaves and enter plant cells compared to 1% of the free active ingredient.[85]

Polymeric Nanocarriers.

Polymeric biomaterials are easy to produce at low cost and have therefore been developed and tested as inert shells to promote the accumulation and controlled release of active ingredients at a given target site. Natural polymers have been derived from chitosan, sodium alginate, collagen, heparin, and silk, whereas many different synthetic polymers have been tested, including, polyacrylate (PAL), PEG, polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), polyesters, and polyurethanes. Natural and synthetic polymers can be biocompatible and biodegradable, and their physicochemical properties (*e.g.*, size, morphology, porosity, surface charge, surface chemistry, and hydrophilicity) are inherently flexible and can be tuned to control mechanical and physiological behavior.[86]

For clinical and veterinary applications, the nanocarrier shell must comprise linear or branched polymers with a molecular weight in the range 0.4–40 kDa to increase the circulation time of the active ingredient while ultimately ensuring renal elimination.[87] PLGA is particularly promising as a nanocarrier material because the PLA-to-PGA ratio can be adjusted to control the rate of degradation, and thus the release rate of the active ingredient. Using this concept, Eligard was approved by the FDA in 2002 to deliver leuprolide acetate to prostate cancer cells (Table 1).[88] PLGA nanocarriers are also being tested in the veterinary field for the delivery of Temozolomide to canine brain tumors (Table 4). The only other polymeric nanocarrier approved by the FDA is Welchol, an allylamine polymer that encapsulates colesevelam hydrochloride to lower the levels of sugar and low-density lipoproteins (LDL) circulating in adults suffering from type 2 diabetes and high cholesterol.[89] Although the development pipeline for polymeric drug-delivery systems is moving rapidly, there is a puzzling lack of approvals. A possible explanation is that most polymeric drug delivery systems do not improve efficacy but rather enhance safety and thus do not achieve significant improvements over liposomal formulations or the free drug at a lower dose.

Dendrimers are a special class of highly branched polymeric nanocarriers with organized tree-like structures and a low polydispersity, ranging in size from 5 to 500 kDa.[90–92] They comprise a central core that radiates a series of repeated branching units (generations), terminating with chemical groups available for functionalization. The active ingredient can be encapsulated in the core micelle *via* hydrophobic/electrostatic interactions or conjugated to the surface. The greater the number of branches, the more reactive terminal groups can be coupled with the active ingredient. Branches exposed on the surface can also be functionalized to increase tissue specificity.[93] Most of the dendrimers used as nanocarriers are synthesized from hydrophilic polyamidoamine (PAMAM) or polypropylene imine units, which are not recognized by the immune system. Poly-L-lysine dendrimers are positively charged and are therefore ideal for the delivery of nucleic acids. Other dendrimers are being developed from PEG, polyglycerol, polyglycerol-*co*-succinic acid, poly-2,2-bis(hydroxymethyl)propionic acid, melamine, and triazine.[93] Only two dendrimer-based nanocarriers are currently undergoing clinical trials (Table 2). One (OP-101) consists of *N*-acetyl cysteine covalently coupled to a metabolically stable inactive hydroxyl dendrimer and has been administered to healthy volunteers to determine its safety, tolerability, and

pharmacokinetics. The other (imdendrim) is a poly-L-lysine dendrimer that encapsulates nitro-imidazole-methyl-1,2,3-triazol-methyl-di-[2-pycolyl]amine bound to a rhenium isotope (^{188}Re) and is currently under investigation for the treatment of liver cancer.

Many other polymeric nanocarriers are undergoing clinical trials (Table 2). CriPec is a polymeric nanocarrier, 30–100 nm in diameter and of uncertain composition (Crystal Therapeutics does not disclose the details), which encapsulates docetaxel and is shielded by PEG. It is being tested for the treatment of solid tumors and platinum-resistant ovarian cancer. PEOX is a branched polymer shell composed of polyethyloxazoline, encapsulating paclitaxel for the treatment of solid tumors. PEOX circumvents the need to solubilize paclitaxel with Kolliphor EL (formerly Cremophor EL), a toxic solvent that requires the coadministration of antihistamines to prevent an immune response.[34] IMX-110 is a polymeric nanoshell encapsulating curcumin and doxorubicin for the treatment of solid tumors. Following its release in the tumor environment, curcumin targets and inhibits the activation of the transcription factors STAT3 and NF-κB, which prevents apoptotic tumor resistance and enhances the efficacy of doxorubicin.[94] Another example is eRapa, the protein kinase inhibitor rapamycin encapsulated in poly(methyl methacrylate), which is undergoing clinical testing for the treatment of prostate cancer.[95] A nanocarrier for the delivery of cisplatin to canine brain tumors has been developed using hyaluronic acid, a linear polymer of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine residues. Hyaluronic acid is a component of the extracellular matrix and is degraded by hyaluronidase, an enzyme overexpressed in the glioma microenvironment.[96] Therefore, the nanocarrier accumulates in the tumor environment, where its degradation causes the local release of cisplatin to minimize systemic toxicity.

One formulation that did not progress beyond clinical trials is BIND-014, a PLA-PEG copolymer displaying a ligand targeting the extracellular domain of the prostate specific membrane antigen. Early studies in rats indicated that BIND-014 could delay tumor growth by preferentially delivering docetaxel to prostate cancer xenografts, limiting the accumulation of this drug in the liver and bone marrow.[97] BIND-014 was applied in several clinical trials for the treatment of prostate cancer, nonsmall-cell lung cancer, cervical cancer, and head and neck cancer.[98] Unfortunately, the trials did not demonstrate sufficient efficacy, with an objective response of only 10% in the head and neck cancer cohort. Pfizer acquired BIND Therapeutics for $40 million in 2016, but no further clinical trials have been reported.

Various synthetic and natural biodegradable polymers have also been synthesized for the delivery of agrochemicals. The formulations have been prepared using emulsion or double emulsion strategies as well as layer-by-layer deposition, nanoprecipitation, and solvent evaporation.[20,99] Such formulations include nanospheres (where the active ingredient is uniformly distributed throughout the polymer matrix) and nanocapsules (where the active ingredient is encapsulated in the liquid inner core). These nanocarriers have been prepared from PEG, PCL, PAL, chitosan, or sodium alginate[20] and have been used to deliver diverse pesticides, including ametryn,[100] atrazine,[100] acephate,[101] emanectin benzoate,[102] garlic essential oil,[103] imidacloprid,[104,105] lansiumamide B,[106] methomyl,[107] paraquat,[108] and simazine.[100] However, these formulations are currently at an early developmental stage and are still being tested *in vitro* as well as in field trials.

Polymers have also been used to prepare other forms of active ingredient delivery system, such as hydrogels,[20,109,110] polymer–drug conjugates,[111] and seed coatings.[112] Hydrogels are cross-linked hydrophilic polymers with a high water retention capacity. A reservoir of the active ingredient may be present at the core of the hydrogel, or it may be uniformly dispersed. The controlled release of the active ingredient is achieved by regulating the physical properties of the hydrogel matrix, such as its porosity and swelling capacity. Environmental stimuli such as temperature, pH, ionic strength, and enzyme activity are often use to control the rate of polymer degradation to achieve the slow and sustained release of the active ingredient. Examples include the FDA-approved intracanalicular implant Dextenza, a dexamethasone-loaded PEG hydrogel for the treatment of ocular pain following ophthalmic surgery[113] as well as hydrogel compositions containing dextran, PAL, propylene glycol, hyaluronic acid, or carboxymethyl cellulose.[114]

Although not technically a nanocarrier application, active ingredients are often conjugated to PEG in a process known as PEGylation, which increases the hydrophilicity and hydrodynamic radius of small-molecule drugs and proteins, thus improving their solubility, masking them from the immune system, slowing their renal clearance, and increasing their circulation half-life while retaining their bioactivity.[115] Adagen, a PEGylated adenosine deaminase reached the clinic in 1990 to treat severe combined immunodeficiency disease. Since then, 16 more PEGylated drugs have been approved by the FDA/EMA, and the majority are indicated for cancer, hepatitis C, or hemophilia (Supporting Tables 3 and 5).[111,116] To our knowledge, only one PEGylated drug has been approved for veterinary applications. This is Imrestor, a PEGylated granulocyte colony-stimulating factor, which was approved in 2016 to increase the number of circulating neutrophils in cows and thus prevent breast tissue inflammation (Table 2).[117] Although PEGylated drugs have been successfully translated to the clinic, a growing body of literature has highlighted the increased presence of PEG-specific antibodies in the general population due to the extensive use of PEG in cosmetic and pharmaceutical products, correlating with the declining therapeutic efficacy of PEGylated active ingredients.[118] This issue is being addressed by the development of alternative polymer-drug conjugates (Supporting Table 5).

In the agricultural industry, polymeric seed coatings are used to control pests and diseases that would otherwise inhibit germination and growth.[112,119] Coating seeds increases their viability, reduces the risk of the active ingredient leaching into the environment, and minimizes off-target toxicity to other organisms compared to free pesticides. More than 180 coating formulations have been reported, including chitosan, polyvinyl acetate (latex), poly(vinyl alcohol), PEG, ethyl cellulose, and methyl cellulose.[112] On the market, the majority of seed coating technologies have been developed by Bayer Crop Science, BASF, Corteva, Monsanto, Syngenta, Incotec/Croda, and Germains.

Micellar Nanocarriers.

Micelles are composed of amphiphilic surfactant molecules that spontaneously aggregate into spherical vesicles in an aqueous environment. This phenomenon is only possible if the quantity of the surfactant molecules is greater than the critical micelle concentration. The core of the micelle is hydrophobic and can sequester hydrophobic active ingredients. The

size of the micelle and therefore the amount of active ingredient that can be loaded in its core is dependent on the molecular size, geometry, and polarity of the surfactant.[45] The small size of polymeric micelles (20–80 nm) reduces their recognition by scavenging phagocytic and interendothelial cells located in the liver and spleen, respectively, and therefore increases the bioavailability of the active ingredient.[120,121] Most micelles are made of block copolymers with alternating hydrophilic and hydrophobic segments, and the ratio of drug molecules to the block copolymers determines their properties. Micelles are often composed of PEG, PLA, PCL, polypropylene oxide, poly-L-lysine, or combinations of the above. Estrasorb was approved by the FDA in 2003 as a topical lotion and consists of micelles designed for the transdermal delivery of 17β-estradiol to the blood for the treatment of menopausal-related vasomotor symptoms.[122] This administration route evades first-pass metabolism, achieving stable levels of 17β-estradiol in the serum for 14 days. Furthermore, paclitaxel and docetaxel are commercially available formulated as micellar nanocarriers, thus avoiding the use of Kolliphor EL as a solvent.[123,124]

Various micellar nanocarriers are currently undergoing clinical trials (Table 2). For example, NK012 is a micellar polyglutamate-PEG formulation covalently bound to the antineoplastic topoisomerase inhibitor SN-38 *via* an ester bond. SN-38 is slowly released from NK012 by the hydrolysis of the ester bond under physiological conditions, which increases the SN-38 half-life to 210 h. NK012 is undergoing clinical trials for the treatment of solid tumors, triple-negative breast cancer, colorectal cancer, and small-cell lung cancer.[125] Similarly, the NK105 micelle is being investigated for the delivery of paclitaxel to breast cancer, gastric cancer, and nonsmall-cell lung cancer. NK105 polymers consist of PEG as the hydrophilic segment and modified polyaspartate as the hydrophobic segment.[126] NK105 demonstrated efficacy in patients with advanced gastric cancer that failed to respond to chemotherapy. Genexol-PM is a micellar nanocarrier consisting of mPEG-block-D,L-PLA for the delivery of paclitaxel for the treatment of nonsmall-cell lung cancer, hepatocellular carcinoma, urothelial cancer, ovarian cancer, and pancreatic cancer.[127] Genexol-PM was shown to behave similarly to the FDA/EMA-approved nanocarrier Abraxane and has been approved for the treatment of metastatic breast cancer and advanced nonsmall-cell lung cancer in South Korea. NC-6004 is being investigated for the delivery of cisplatin to head and neck cancer as well as nonsmall-cell lung cancer. NC-6004 demonstrated a significant reduction in cisplatin-induced neurotoxicity and nephrotoxicity (again, the nanocarrier enhances safety not efficacy). Micelles are also being investigated for the treatment of cystic fibrosis, metabolic syndrome, psoriasis, and rheumatoid arthritis.[128]

In veterinary medicine, a randomized trial was initiated in 2013 to investigate the safety and efficacy of micellar paclitaxel (Paccal Vet-CA1) for the treatment of dogs with grade II or III mast cell tumors (Table 4).[129] The micelle consisted of a surfactant derivative of retinoic acid (XR-17). Dogs treated with micellar paclitaxel showed a 3-fold higher treatment response compared to a control group receiving the standard-of-care drug lomustine. However, the FDA conditional approval of Paccal Vet-CA1 was withdrawn in 2017 by the manufacturer Oasmia Pharmaceutical AB to allow them time to study lower doses in order to reduce adverse effects such as neutropenia, hepatopathy, anorexia, and diarrhea. In a different application, a micellar vitamin E has been tested as an antioxidant in race horses undergoing prolonged aerobic exercise to prevent exercise-induced oxidative lesions and

maintained the general oxidative status to a healthy level for horses undergoing intensive training.[130]

Micelles have also been developed as promising nanocarriers for the encapsulation of pesticides, helping to prevent adsorption to soil particles. Examples include the micellar encapsulation of azadirachtin,[131] carbendazim,[132] carbofuran,[133] imidacloprid,[134,135] rotenone,[136] thiamethoxam,[137] and thiram.[138] These formulations are still undergoing development and have been tested *in vitro* and in the field.

Inorganic Nanocarriers.

Inorganic nanocarriers include natural and synthetic materials based on silica, clay, and metals such as silver, gold, titanium, iron, copper, and zinc. These nanocarriers are physiologically compatible, resistant to microbial degradation, and environmentally friendly, which makes them suitable for medical, veterinary, and agricultural applications. Even so, their use as nanocarriers has been somewhat overshadowed by their success in other medical applications. In particular, metallic nanoparticles have been developed as theranostic and photothermal reagents and for the treatment of iron deficiency.[24,139,140] In 1974, the FDA approved iron dextran (INFeD) for the treatment of iron deficiency. Eight more formulations have since been approved by the FDA or EMA (Supporting Table 5). We do not consider these formulations as nano*carriers* because the treatment modalities rely entirely on the nanoparticle itself without a cargo of active ingredients. However, metallic nanocarriers have recently been proposed in which the active ingredient is attached to the surface by physical absorption, electrostatic interactions, or conjugation.[141] In particular, gold nanoparticles allow the conjugation of many biological ligands, including DNA and siRNA.[142] Thus far, only one clinical trial has been carried out using metallic nanocarriers, namely spherical nucleic acid gold nanoparticles (NU-0129) for the delivery of siRNA to patients with glioblastoma or gliosarcoma (Supporting Table 1). More advanced metallic nanocarriers are under development, including particles that can respond to external triggers, such as light, magnetic fields, and hyperthermia to release their cargo in a controlled manner. For example, gold and silver nanoparticles have been conjugated to various cancer drugs.[143–146]

Mesoporous silica nanocarriers (MSNs) have been investigated extensively because they are stable particles with a high payload capacity due their porous structure, they have a tunable pore diameter (2–50 nm), and surface modifications can impart additional functionalities such as targeted delivery.[147] MSNs have already been tested in the laboratory to deliver cancer drugs such as doxorubicin and camptothecin, antibiotics such as erythromycin and vancomycin, and anti-inflammatories such as ibuprofen and naproxen, with high loading rates of up to 600 mg of cargo per gram of silica.[147] This loading capacity of up to 60% far exceeds that of liposomal and polymeric nanocarriers. For example, the liposomal formulation Doxil and the polymeric formulation Eligard achieve loading capacities of 31% and 27%, respectively. However, some silica nanoparticle formulations have been shown to cause hemolysis due to strong interactions between silanol groups on the carrier and phospholipids in the erythrocyte plasma membrane.[148] Another concern is their persistence *in vivo* due to the absence of renal clearance. These issues could be addressed by modifying the surface chemistry or applying coatings.

In an agricultural context, silica is already highly abundant in soil, and such particles could therefore be engineered for the controlled release of active ingredients without the carrier itself causing environmental harm. For example, MSNs have been used to deliver the insecticide chlorfenapyr over a period of 20 weeks, which doubled the insecticidal activity in field tests.[149] The fungicide metalaxyl was also loaded into MSNs, allowing its slow release in soil and water for a period of 30 days.[150] Similarly, nanocarriers based on naturally occurring aluminum silicates have been formed into phyllosilicate sheets for the intercalation of antibiotics and herbicides, allowing sustained delivery.[151,152] Also in the context of delivery of antiviral nucleic acid therapeutics, sustained delivery of the therapeutic is desired. For example, application of small interfering RNAs onto leaves provided protection against plant viral infection for ~6 days; the therapeutic window was greatly enhanced achieving antiviral activity for ~20 days by making use of layered double hydroxide clay nanosheets.[153] Several metallic nanoparticles have demonstrated antimicrobial properties, and the EPA has already approved silver nanoparticles for use as an antimicrobial agent in clothing, but not yet for the delivery of active ingredients.[142] Finally, carbon nanotubes are also being investigated for medical and agricultural uses because their shape and surface chemistry confer advantageous properties, although their toxicity remains a translational barrier. We recommend the following reviews for further information found in refs 154–156.

Proteinaceous Nanocarriers.

Over the course of evolution, nature has yielded a variety of biomaterials with great structural complexity that remains difficult to emulate. The analysis of such complexity requires the appropriate molecular methods, and for this reason, the development of proteinaceous nanocarriers has lagged behind that of the simpler liposomal, polymeric, and micellar structures.[157,158] The production of proteinaceous nanocarriers has also required the development of tools for the expression of recombinant proteins and strategies for creation or diversity, such as directed evolution, genome editing, and synthetic biology. These tools have allowed the production of hierarchically organized proteinaceous structures, including albumin nanoparticles, heat shock protein cages, vault proteins, and ferritins.[159] These comprise repeated protein subunits forming highly organized nanostructures that are identical in size and chemical composition. Although synthetic nanoparticles can also be assembled into complex structures, the sophistication and monodispersity that can be achieved with proteins has yet to be replicated. Proteinaceous nanoparticles have been used as biocatalysts for the synthesis of materials, but are also useful for the delivery of active ingredients in medicine and agriculture.[158]

Early on, proteinaceous nanocarriers were developed to mimic the properties of plasma proteins, thus increasing circulation times and reducing systemic side effects. In 2005, the FDA approved the proteinaceous nanoshell Abraxane, consisting of albumin-bound paclitaxel for the treatment of breast cancer. The conjugation of paclitaxel to albumin stabilized the drug even in the absence of Kolliphor EL and enhanced the uptake of the active ingredient compared to the Kolliphor EL formulation.[34] Given the safety and efficacy of drugs conjugated to albumin, two other albumin nanocarriers are undergoing clinical trials (Table 2). One is an albumin conjugate of the protein kinase inhibitor rapamycin (ABI-009)

indicated for colorectal cancer, bladder cancer, glioblastoma, sarcoma, and myeloma.[160] The other is an albumin conjugate of docetaxel (ABI-008) indicated for the treatment of prostate cancer. Albumin has a long circulation half-life due to its interaction with the recycling Fc receptor. It is beneficial for the delivery of small molecules that are unstable or have low solubility in blood as well as proteins and peptides that are rapidly cleared from the circulation. Small molecules can be chemically fused to albumin and administered as conjugate, and strategies to target small-molecule drug cargoes to albumin *in vivo* have also been developed.[161]

Heat shock protein cages, vault proteins, and ferritins have also been investigated for the delivery of active ingredients, although no clinical trials have been reported thus far. Heat shock proteins are chaperones that promote the folding of newly synthesized proteins and the refolding of denatured ones, which means they are naturally stable and possess channels and cavities for the sequestration of cargo.[159] There are five families of heat shock proteins: Hsp100, Hsp90, Hsp70, and Hsp60 (which are named for the molecular mass of the proteins in kDa) and the small heat shock protein (sHsp) family, ranging in size from 12 to 43 kDa. Heat shock proteins assemble into large complexes that vary in size and shape (including rings and spheres), and they can be engineered to carry and deliver active ingredients such as doxorubicin.[162,163] Vault nanoparticles are barrel-like ribonucleoproteins found in many eukaryotes. They are 41 × 73 nm in size and resemble the vault of a gothic cathedral. Their precise biological function remains unknown, although they are thought to play a role in nuclear transport, immunity, and defense against toxins.[164,165] Several proteins have been encapsulated in vault nanocarriers, including the lymphoid chemokines CCL19 and CCL21, the New York esophageal squamous cell carcinoma 1 (NY-ESO-1) antigen, the precursor of adenovirus protein VI (pVI), the major outer membrane protein of *Chlamydia trachomatis*, and the egg storage protein ovalbumin.[165] Vault Pharma is one company specializing in the development of these structures. Finally, ferritin is an iron-storage protein with 24 subunits that self-assemble into a spherical cage structure 12 nm in diameter with a molecular mass of 450 kDa.[166] Each ferritin complex can sequester up to 4500 Fe^{2+} ions and convert them to Fe^{3+} to prevent oxidative stress in the cytosol, nucleus, and mitochondria. Ferritin has been investigated as an imaging reagent and vaccine platform as well as a nanocarrier.[166] It has already been used to deliver cisplatin,[167] doxorubicin,[168] and curcumin,[169] and the contrast agents gadolinium[170] and Mn(II).[171]

There are few examples of proteinaceous nanocarriers used in agriculture, but nanocarriers based on maize storage proteins (zeins) are being tested for the delivery of pesticides that protect soybean crops from defoliator parasites.[172]

The number of proteinaceous nanocarriers reaching the market will continue to grow as we learn more from nature and expand our bioengineering tools and processing capabilities, including the use of genome editing and directed evolution.[173] Furthermore, rather than harnessing protein complexes from nature, advances in *de novo* protein design will allow us to select customized proteins with shapes that may be difficult to obtain *via* the directed evolution of natural proteins.[174] Modular building concepts have been established to achieve the defined folding and programmed assembly of proteins into complex architectures.[175,176] Accordingly, some synthetically designed protein-based nanoparticles have entered

translational development. For example, the start-up company Tychon Bioscience is developing prosthetic antigen receptors that modulate protein dimerization to produce self-assembling nanoscale ring structures for applications in cancer immunotherapy.

Virus-based Nanocarriers.

Viruses have evolved to deliver their genetic payload to host cells and can therefore be regarded as nature's nanocarrier systems. The structure of a virus capsid is genetically programmed so replication yields millions of identical particles, a level of monodispersity that cannot yet be achieved with synthetic nanoparticles. Viruses are proteinaceous structures and are therefore similar to the protein cages discussed above in terms of biocompatibility. The capsids are highly symmetrical structures that come in various shapes and sizes, and they are amenable to both chemical and genetic modification to impart additional functionalities, including the encapsulation or conjugation of active ingredients[177]

Given the natural function of viruses, it is unsurprising that one of the early applications of virus-based nanocarriers was the delivery of nucleic acids. Mammalian viruses such as Adeno-associated virus (AAV) are established as gene delivery vectors.[178] The AAV-based gene therapy vector (Glybera) was approved by the EMA in 2012 for the treatment of lipoprotein lipase deficiency, but was not approved by the FDA, and UniQure subsequently announced its withdrawal from the European market in 2017 following the treatment of only 31 patients.[179] The FDA has since approved two AAV-based vectors, namely Luxturna in 2017 for the treatment of patients with RPE65 mutation-associated retinal dystrophy, and Zolgensma in 2019 for the treatment of young infants with spinal muscular atrophy. One of the major drawbacks of AAV therapies is their high cost. Luxturna treatment is estimated to cost $850,000, whereas Zolgensma was priced at $2.125 million by Novartis as a one-time cure. In addition to AAV nanocarriers (ssDNA, 4-kb inserts), other mammalian viruses have been developed for gene delivery including adenoviruses (dsDNA, 7.5-kb inserts), herpesviruses (dsDNA, >30 kb inserts), and lentiviruses (ssRNA, 8 kb inserts) and are undergoing clinical trials (Supporting Table 2), whereas retroviruses (ssRNA, 8 kb inserts) and alphaviruses (ssRNA, 6–8 kb inserts) remain at the preclinical development stage.[178,180,181]

As an alternative to mammalian viruses, several plant viruses and bacteriophages have also been repurposed as nanocarriers or vaccines because they are noninfectious to humans and can be manufactured on a large scale as viral nanoparticles (VNPs, which retain the virus genome) or virus-like particles (VLPs, which are empty shells devoid of nucleic acid). For example, based on the immunostimulatory nature of VNPs/VLPs, several have been developed as *in situ* cancer vaccines, including Cowpea mosaic virus (CPMV),[182,183] bacteriophage M13,[184] Potato virus X (PVX),[185] Tobacco mosaic virus (TMV),[186] and Papaya mosaic virus.[187] The CPMV system has already demonstrated efficacy in canine trials.[188–190] The development of plant viruses or bacteriophages as vaccine candidates for infectious diseases, autoimmune disorders, and cancer has been extensively reviewed.[191–193] One of the key applications of VNP/VLP vaccine candidates is the display of heterologous epitopes.[194–196] This protects the epitope from degradation, ensures delivery to antigen-presenting cells, provides an inbuilt adjuvant, and also generates cross-stimulatory virus-

based antigens to boost humoral and cellular immunity.[15–17] Several VNPs/VLPs presenting heterologous epitopes have been tested in human clinical trials[197] and veterinary tests.[198]

The use of VNPs and VLPs as nanocarriers for active ingredients can be achieved by passive infusion through pores in the capsid, encapsulation during assembly, as well as chemical conjugation and/or genetic fusion of active ingredients to the outer or inner surfaces. For example, doxorubicin has been conjugated to TMV,[199] infused into Cucumber mosaic virus (CMV)[200] and Red clover necrotic mosaic virus (RCNMV),[201] and passively complexed with PVX.[202] Virus-based nanocarriers have also been used to deliver bortezomib,[203] cisplatin,[204,205] 5-fluorouracil,[206] hygromycin,[207] mitoxantrone,[208,209] phenanthriplatin,[210] and paclitaxel.[211] Examples of protein delivery include TRAIL,[42] TPA,[212] and Herceptin.[213,214] Filamentous phages have been developed to deliver antibiotics such as chloramphenicol and neomycin to prevent the growth of *Escherichia coli*, *Streptococcus pyogenes*, and *Staphylococcus aureus*.[215,216] Finally, siRNA has been delivered using bacteriophage MS2[217] and Cowpea chlorotic mosaic virus (CCMV),[218] and mRNA for the *in situ* expression of green fluorescent protein (GFP) has been successfully encapsulated into CCMV and TMV, followed by the release of the mRNA cargo into the cytosol of mammalian cells and its subsequent translation.[219,220]

Plant VNPs have also been proposed as pesticide carriers because they are already part of the natural soil ecosystem and are harmless to humans and domestic animals.[221,222] Compared to synthetic nanocarriers, plant viruses are highly mobile in soil and can deliver pesticides to the roots, where many pests are concentrated. TMGMV was approved by the EPA in 2007 as a bioherbicide for the treatment of the invasive tropical soda apple weed in the state of Florida.[30] Since then, RCNMV has been proposed for the delivery of abamectin to crops.[221] The higher stability and superior soil mobility of abamectin encapsulated in RCNMV increased the efficacy of the nematicide in tomato seedlings infested with root knot nematodes (*Meloidogyne hapla*) compared to the free chemical. Similarly, TMGMV loaded with the anthelmintic drug crystal violet was highly toxic toward the nematode *Caenorhabditis elegans in vitro*.[222] Rational design and size and shape engineering in plant virus-based carriers may enable multilevel targeting of different soil zones.[223]

CONCLUSIONS

Nanocarriers have revolutionized the medical, veterinary, and agricultural sectors through their ability to deliver active ingredients in a targeted and controlled manner to appropriate sites, such as cancer cells or plant roots, thereby maximizing efficacy while minimizing off-target effects. Based on the current landscape of research articles, patents, clinical trials, and approved nanocarriers, we have revealed a growth trend which predicts that more formulations will be commercially available over time, allowing the targeted delivery of small molecules, peptides, and proteins as well as nucleic acids to combat pests, pathogens, and diseases in animals and plants. We observed a shift away from the development of nanocarriers for small-molecule reagents and toward the delivery of peptides, proteins, and nucleic acids. Advances in bioengineering have also encouraged the development of bioinspired nanocarriers that are friendly to the environment.

Several challenges must be addressed to streamline the translation of nanocarriers from the bench to the market. In medicine, nanocarriers could greatly benefit from the incorporation of targeting ligands, aptamers, antibodies, or antibody fragments to promote their binding to receptors overexpressed on target cells or in the surrounding extracellular matrix. Additional targeted nanocarriers must undergo clinical trials before we can conclude that active targeting achieves greater therapeutic efficacy. In parallel, the development of veterinary nanocarriers has intensified with the growing public interest in animal welfare and food safety and security. Companion animals with cancer have benefited the most from nanocarriers, whereas livestock require low-cost and prolonged treatments, such as the delivery of antibiotics. The future of veterinary nanocarriers will depend on our ability to manufacture products at a relatively low cost. Finally, precision agriculture is required to meet the growing demand for food. Nanocarriers provide the opportunity to increase crop yields in an environmentally friendly manner by delivering fertilizers and pesticides directly to plants while minimizing leaching. However, the translation of nanocarriers for agricultural applications is restricted by the lack of well-structured regulations for commercial approval. More research is therefore required to determine the fate and toxicity of nanocarriers applied in the field.

METHODS

All patent searches were carried out with Orbit Express using Questel software. Initially, the key word “nanoparticle” was used with a time frame starting from 1990 to the present. The total number of patent families for this search was grouped and plotted according to the year of publication and the application field based on World Intellectual Property Organization (WIPO) patent classifications. Approved clinical drugs were extracted and compiled from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) databases. Nanocarriers undergoing clinical trials were mined from the ClinicalTrials.gov database, excluding any trials whose clinical status was unknown. Approved veterinary nanocarriers were mined from the Approved Animal Drug Products (Green Book) on the FDA website, whereas nanocarriers undergoing veterinary trials were compiled from the American Veterinary Medical Association (AVMA) Animal Health Studies database. Federally approved nanoencapsulated pesticides are listed on the National Pesticide Information Center (NPIC) database (NPRO). Peer-reviewed publications were searched using PubMed and the Web of Science database using keywords: nanoparticle, medicine, agriculture, and veterinary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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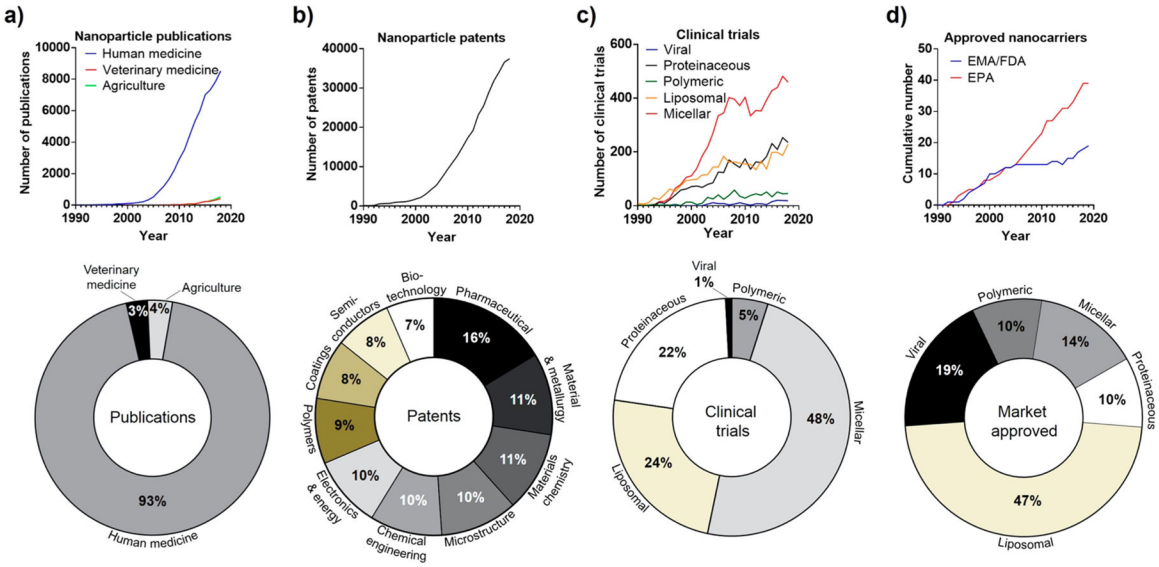

Figure 1.

Timeline and corresponding distribution of: (a) peer-reviewed publications involving nanoparticles in the medical, veterinary, and agricultural fields; (b) patent applications involving nanoparticles; (c) clinical trials using nanocarriers based on different materials; and (d) market approved nanocarrier formulations. See Methods section for more information on the data compilation and analysis.

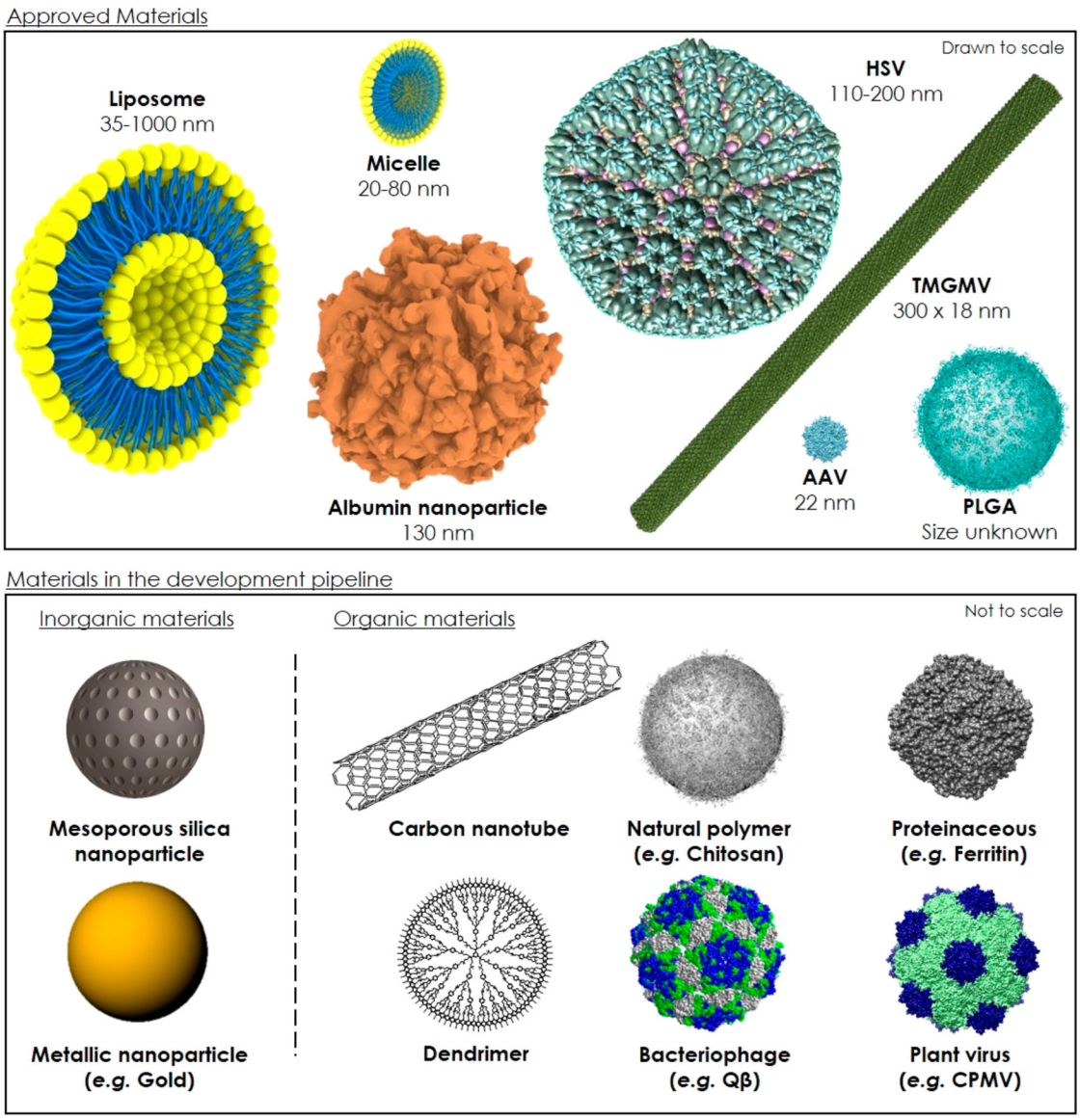

Figure 2.

Size and structure of nanocarriers (approved and in development). Adeno-associated virus (AAV, PDB ID: 1LP3), Herpes simplex virus (HSV, PDB ID: 5ZAP), Tobacco mild green mosaic virus TMGMV (PDB ID: 1VTM), ferritin (PDB: 6BP7), bacteriophage Qβ (PDB ID: 5KIP), and Cowpea mosaic virus (CPMV, PDB ID: 1NY7) were reconstructed using the UCSF Chimera software. The albumin, micelle, liposome, PLGA, chitosan polymer, mesoporous silica, and gold nanocarriers were rendered using Rhinoceros 3D v5.0. The carbon nanotube and dendrimer were drawn using ChemDraw software.

Table 1.

FDA and EMA Approved Medical Nanocarriers

Liposomal nanocarriers				
Drug name (company)	**Active ingredient**	**Nanoparticle size**	**Specific treatment**	**Year of approval**
Ambisome (Gilead Sciences)	amphotericin B	80–120 nm	fungal infection	1997 [US]
Curosurf (Dey Laboratories)	poractant α	50–1000 nm	respiratory distress syndrome	1998 [US]
DaunoXome (Galen)	daunorubicin	35–65 nm	Kaposi's sarcoma	1996 [US] Discontinued in 2016
Doxil (Janssen)	doxorubicin	50–100 nm	Kaposi's sarcoma	1995 [US] - 1996 [EU]
			breast cancer	1996 [EU]
			ovarian cancer	2005 [US] - 1996 [EU]
			myeloma	2008 [US] - 1996 [EU]
Marqibo (Onco TCS)	vincristine	100 nm	acute lymphoblastic leukemia	2012 [US]
Myocet (Teva UK)	doxorubicin	150–250 nm	metastatic breast cancer	2000 [EU]
Onpattro (*Ainylam* Pharmaceuticals)	transthyretin-directed small interfering RNA	80 nm	hereditary transthyretin-mediated amyloidosis	2018 [US] - 2018 [EU]
Onivyde (Merrimack)	irinotecan	90–130 nm	pancreatic cancer	2015 [US] - 2016 [EU]
Visudyne (Novartis)	verteporfin	150–300 nm	macular degeneration	2000 [US] - 2000 [EU]
Vyxeos (Jazz Pharmaceuticals)	daunorubicin and cytarabine	100–200 nm	acute myeloid leukemia	2017 [US] - 2018 [EU]
Polymeric nanocarriers				
Drug name (company)	**Active ingredient**	**Nanoparticle size**	**Specific treatment**	**Year of approval**
Eligard (Tolmar)	leuprolide acetate in PLGA	N.A.	prostate cancer	2002 [US]
Welchol (Daiichi-Sankyo)	colesevelam hydrochloride in allylamine polymer	N.A.	type 2 diabetes	2000 [US]
Micellar nanocarriers				
Drug name (company)	**Active ingredient**	**Nanoparticle size**	**Specific treatment**	**Year of approval**

Estrasorb (Novavax)	17β-estradiol	20–80 nm	menopausal therapy	2003 [US]
Taxol (Bristol Myers Squibb)	paclitaxel	20–80 nm	ovarian cancer	1992 [US]
			breast cancer	1994 [US]
			Kaposi's sarcoma	1997 [US]
			non-small-cell lung cancer	1998 [US]
Taxotere (Sanofi-Aventis)	docetaxel	20–80 nm	breast cancer	1996 [US] - 1995 [EU]
			non-small-cell lung cancer	1999 [US] - 1995 [EU]
			prostate cancer	2004 [US] - 1995 [EU]
			gastric cancer	2006 [US] - 1995 [EU]
			head and neck cancer	2006 [US] - 1995 [EU]
Proteinaceous nanocarriers				
Drug name (company)	**Active ingredient**	**Nanoparticle size**	**Specific treatment**	**Year of approval**
Abraxane (Celgene)	albumin-bound paclitaxel	130 nm	breast cancer	2005 [US] - 2008 [EU]
			non-small-cell lung cancer	2012 [US] - 2005 [EU]
			pancreatic cancer	2013 [US] - 2008 [EU]
Ontak (Eisai)	diphtheria toxin fragments + human interleukin-2	58 kDa	cutaneous T-cell lymphoma	1999 [US] Discontinued in 2014
Viral nanocarriers				
Drug name (company)	**Active ingredient**	**Nanoparticle size**	**Specific treatment**	**Year of approval**
Glybera (UniQure)	AAV1 vector containing lipoprotein lipase gene	22 nm	lipoprotein lipase deficiency	2012 [EU] Discontinued in 2017
Imlygic (Amgen)	Herpes simplex type I	110–200 nm	melanoma	2015 [US] - 2015 [EU]
Luxtuma (Spark Therapeutics)	AAV2 vector containing RPE65 cDNA	22 nm	RPE65 mutation associated retinal dystrophy	2017 [US] - 2018 [EU]
Zolgensma (Novartis)	AAV9 vector containing SMN1 gene	22 nm	spinal muscular atrophy	2019 [US]

Table 2.

Medical Nanocarriers in Clinical Trials

Liposomal nanocarriers						
Active ingredient	**Nanoparticle**	**Specific treatment**	**Start**	**Phase**	**Status**	**ClinicalTrials.gov ID**
alprostadil	liposome	cardiovascular diseases	2010	I	completed [2010]	NCT02889822
(irinotecan HCl:floxuridine)	CPX-1	colorectal neoplasms	2006	II	completed [2008]	NCT00361842
gemcitabine	FF-10832	solid tumors	2018	I	recruiting	NCT03440450
alendronate	liposome	coronary artery stenosis	2008	II	completed [2015]	NCT00739466
annamycin	liposome	acute lymphocytic myelogenous leukemia	2007	I	terminated [2009]	NCT00430443
		myeloid leukemia	2018	I/II	recruiting	NCT03315039
			2018	I/II	recruiting	NCT03388749
cyclosporine A	liposome	bronchiolitis obliterans	2019	III	recruiting	NCT03657342
			2019	III	recruiting	NCT03656926
			2012	I/II	completed [2015]	NCT01650545
adenosylcobalamin	HL-009	mild to moderate atopic dermatitis	2012	II	completed [2013]	NCT01568489
latanoprost	liposome	ocular hypertension	2013	I/II	completed [2013]	NCT01987323
meglumine antimoniate and paromomycin	liposome	cutaneous leishmaniasis	2011	I	completed [2012]	NCT01050777
BoNT-A (botulinum toxin A)	liposome	interstitial cystitis	2014	IV	completed [2017]	NCT02247557
		overactive bladder	2010	II	completed [2013]	NCT01167257
docetaxel	LE-DT	pancreatic cancer	2010	II	completed [2011]	NCT01186731
		prostate cancer	2010	II	withdrawn [2011]	NCT01188408
mitoxantrone hydrochloride	liposome	metastatic breast cancer	2015	II	recruiting	NCT02596373
		neoplasms	2011	I	completed [2013]	NCT02043756
		Relapsed-refractory diffuse large B cell lymphoma and peripheral T/NK cell lymphoma	2015	II	recruiting	NCT02597387
		T cell lymphoma	2015	II	terminated [2019]	NCT02597153
		T cell and NK/T cell lymphoma	2018	II	recruiting	NCT03776279
rhenium	liposome	glioblastoma/astrocytoma	2015	I/II	recruiting	NCT01906385
SN-38	liposome	colorectal cancer	2006	II	completed [2010]	NCT00311610

		lung cancer	2016	II	withdrawn [2016]	NCT00104754
		neoplasms	2002	I	completed [2010]	NCT00046540
Polymeric nanocarriers						
Active ingredient	**Nanoparticle**	**Specific treatment**	**Start**	**Phase**	**Status**	**ClinicalTrials.gov ID**
chlorhexidine gluconate	chitosan nanoparticles	intra canal antiseptic	2018	N.A	active	NCT03588351
docetaxel	CriPec	solid tumor	2015	I	completed [2018]	NCT02442531
		platinum resistant ovarian cancer	2018	II	recruiting	NCT03742713
rapamycin	eRapa	prostate cancer	2018	I	recruiting	NCT03618355
cetuximab	ethylcellulose polymer coated with somatostatin analogue	colon cancer	2018	I	recruiting	NCT03774680
N-acetylcysteine	hydroxyl dendrimer (OP-101)	inflammation	2018	I	completed [2018]	NCT03500627
curcumin + doxorubicin	IMX-110	solid tumors	2017	I/II	recruiting	NCT03382340
paclitaxel	polyethylozaxoline (PEOX)	solid tumors	2018	I	recruiting	NCT03537690
^{188}Re	poly-l-lysine dendrimer (ImDendrim)	liver cancer	2017	N.A	recruiting	NCT03255343
docetaxel	PSMA-targeted PLA (BIND-014)	prostate cancer	2013	II	completed [2016]	NCT01812746
		non-small-cell lung cancer	2013	II	completed [2016]	NCT01792479
		metastatic cancer	2011	I	completed [2016]	NCT01300533
		cervical cancer squamous cell carcinoma of the head and neck	2015	II	terminated [2016]	NCT02479178
Micellar nanocarriers						
Active ingredient	**Nanoparticle**	**Specific treatment**	**Start**	**Phase**	**Status**	**ClinicalTrials.gov ID**
paclitaxel	micelle (NK105)	breast cancer	2012	III	completed [2017]	NCT01644890
	NK105 + cisplatin	non-small-cell lung cancer	2016	III	active	NCT02667743
	Genexol PM	non-small-cell lung cancer	2009	III	completed [2017]	NCT01023347
		hepatocellular carcinoma	2017	II	recruiting	NCT03008512
		hepatocellular carcinoma	2017	II	recruiting	NCT03008512
		urothelial cancer	2011	II	completed [2011]	NCT01426126
	Genexol PM + carboplatin	ovarian cancer	2011	II	completed [2017]	NCT01276548
	Genexol PM + gemcitabine	pancreatic cancer	2016	II	recruiting	NCT02739633
	Genexol PM + gemcitabine	pancreatic cancer	2009	I	completed [2017]	NCT00882973

antioxidant-rich multivitamin supplement (AquADEKs)	Micelle	cystic fibrosis	2009		completed [2012]	NCT01018303
cisplatin	micelle (NC-6004) + pembrolizumab	head and neck cancer	2018	II	not recruiting	NCT03771820
	micelle (NC-6004) + 5-FU + cetuximab	head and neck cancer	2017	I	active	NCT03109158
	micelle (NC-6004) + gemcitabine	non-small-cell lung cancer	2014	I	recruiting	NCT02240238
curcumin	micelle	metabolic syndrome	2018	N.A	recruiting	NCT03534024
paclitaxel	micelle	psoriasis	2000	II	completed [2008]	NCT00006276
	Paxceed	rheumatoid arthritis	2003	II	completed [2008]	NCT00055133
SN-38	poly(l-glutamic acid)-PEG (NK012)	solid tumors	2007	I	completed [2013]	NCT00542958
		triple-negative breast cancer	2009	II	completed [2015]	NCT00951054
		small-cell lung cancer	2009	II	completed [2013]	NCT00951613
	poly(l-glutamic acid)-PEG (NK012) + 5-FU	colorectal cancer	2010	I	completed [2014]	NCT01238939
	poly(l-glutamic acid)-PEG (NK012) + carboplatin	triple-negative breast cancer	2010	I	completed [2014]	NCT01238952
Proteinaceous nanocarriers						
Active ingredient	**Nanoparticle**	**Specific treatment**	**Start**	**Phase**	**Status**	**ClinicalTrials.gov ID**
dodecanol alkyl ester of bendamustine (RXDX-107)	albumin nanoparticle	solid tumors	2015	I	terminated [2018]	NCT02548390
rapamycin	albumin nanoparticles (ABI-009)	*mTOR*-mutated cancer	2016	I	active	NCT02646319
		epilepsy intractable	2018	I	recruiting	NCT03646240
		glioblastoma	2018	II	recruiting	NCT03463265
		neuroendocrine tumors	2018	II	recruiting	NCT03670030
		malignant PEComa	2015	II	active	NCT02494570
		leigh syndrome	2018	II	not recruiting	NCT03747328
		bladder cancer	2013	I	recruiting	NCT02009332
	ABI-009 + folfox + bevacizumab	colorectal cancer	2018	I	recruiting	NCT03439462
	ABI-009 + nivolumab	advanced sarcoma	2017	I	recruiting	NCT03190174
	ABI-009 + pazopanib	soft tissue sarcoma	2018	I	not recruiting	NCT03660930
	ABI-009 + pazopanib	soft tissue sarcomas	2018	I	active	NCT03660930
	ABI-009 + pomalidomide + dexamethasone	myeloma	2018	I	not recruiting	NCT03657420
	ABI-009 + temozolomide + irinotecan	recurrent or refractory solid tumors	2016	I	recruiting	NCT02975882

Table 3.

EPA Approved Pesticide Nanocarriers

Product name (Company)	Active ingredient	Specific treatment	Year of approval	Registration no.
Poridon (Neogen Corporation)	permethrin + piperonyl butoxide	insecticide, miticide	1985	72726–1
Sump Buddy WT antimicrobial (Dow Chemical)	2,2-dibromo-3-nitrilopropionamide	algaecide, bacteriostatic, fungicide, microbicide	1989	464–624
Ezject (EZ-Ject)	glyphosate-isopropylammonium	herbicide	1989	83220–1
Whitmire PT 275 Dur-O-Cap (BASF)	chlorpyrifos	insecticide, miticide	1993	499–367
NoMate TPW MEC (Scentry Biologicals)	(E)-4-tridecen-l-yl acetate	biochemical pesticide	1994	26638–28
ReJeX-IT AG-36 (Avian Enterprises)	methyl antranilate	repellent	1994	91897–3
Command (FMC)	clomazone	herbicide	1995	279–3150
Sump Buddy MWF (Dow Chemical)	2,2-dibromo-3-nitrilopropionamide	microbicide	1996	464–632
Optashield CS (BASF)	cyfluthrin	insecticide	1998	499–477
For-Mite (Mann Lake)	formic acid	miticide	1999	61671–3
Strategy (Loveland Products)	clomazone + ethalfluralin	herbicide	2001	34704–836
CheckMate DBM-F (Suttera)	(Z)-11-hexadecenal	biochemical pesticide	2002	56336–35
Evercide Esfenvalerate CS (McLaughlin Gormley King Company)	esfenvalerate	insecticide	2005	1021–1815
Ricemax (Riceco)	clomazone + propanil	herbicide	2006	71085–25
Apiguard (Vita Bee Health)	thymol	insecticide, miticide	2006	79671–1
Casoron CS (Macdermid Agricultural Solutions)	dichlobenil	herbicide	2007	400–541
LX417 lambda-Cyhalothrin (BASF)	lambda-cyhalothrin	insecticide	2007	499–535
MGK F-2926(P) (McLaughlin Gormley King Company)	cyphenothrin	insecticide, miticide	2008	1021–1873
TC 251B (BASF)	permethrin	insecticide	2008	499–528
CSI Chlorpyrifos (Control Solutions)	chlorpyrifos	insecticide	2009	53883–264
Declare (FMC Corporation)	gamma-cyhalothrin	insecticide	2009	279–3571
Instinct (Dow Agrosciences)	nitrapyrin	fertilizer	2009	62719–583
Mon 63410 Herbicide (Monsanto)	acetochlor	herbicide	2010	524–591
Warrior II (Syngenta)	lambda-cyhalothrin	insecticide, miticide	2010	100–1112
MGK Formula 2964 (McLaughlin Gormley King Company)	esfenvalerate + piperonyl butoxide + prallethrin	insecticide	2011	1021–2574
GAT Permethrin 25 CS (FMC)	permethrin	insecticide	2011	279–9573

Product name (Company)	Active ingredient	Specific treatment	Year of approval	Registration no.
CSI Permethrin 25 CS (Control Solutions)	permethrin	insecticide	2011	53883–282
Trinexapac-ethyl 1 ME (Syngenta)	trinexapac-ethyl	fungicide, plant growth regulator	2011	100–1401
Permatek 100 Encaps (Lonza)	bifentrin	insecticide	2013	72616–8
Chlorpyrifos 42 CS (FMC)	chlorpyrifos	insecticide	2013	279–9574
Deer-Ban (TR Labs)	coyote urine	repellent	2013	91132–1
Aqua-Tec (Silversan)	silver	algicide	2013	91025–1
Lambdastar Urban Cap (Farmhannong America)	lambda-cyhalothrin	insecticide	2014	71532–33
Force CS Insecticide (Syngenta)	tefluthrin	insecticide	2014	100–1253
Trupick 0.7 (Decco US Post-harvest)	1-methylcyclopropene	pesticide	2016	2792–79
Clomazone 360 CS (Sipcam Agro USA)	clomazone	herbicide	2016	60063–58
EH-1594 Herbicide (PBI/Gordon Corporation)	2,4-D, 2-ethylhexyl ester + dicamba + mecoprop-P + sulfentrazone	herbicide	2017	2217–1018
AiM-A Abamectin (Smartvet USA)	abamectin	insecticide	2017	88050–3
Oxon Clomazone 360 CS (Oxon Italia)	clomazone	herbicide	2017	35915–25
Fendona CS II (BASF)	alpha-cypermethrin	insecticide	2018	7969–425
Fenvastar Ecocap (Farmhannong America)	esfenvalerate	insecticide	2018	71532-28-91026
RightLine Pyraprop Mec (Rightline)	pyraclostrobin	fungicide	2018	93051–2

Table 4.

Nanocarriers for Veterinary Applications

Approved veterinary nanocarriers				
Drug name (company)	**Active ingredient**	**Nanoparticle**	**Specific treatment**	**Year of approval**
Imrestor (Elanco US)	PEGylated granulocyte colony stimulating factor (pegbovigrastim)	30 kDa protein + PEG	inflammation in the breast tissue of cows	2016 [US]
Paccal Vet-Cal (Oasmia Pharmaceutical)	paclitaxel	retinoic acid (XR-17) micelle	canine mast cell tumors	2017 discontinued
Veterinary nanocarriers undergoing clinical trials				
Active ingredient	**Nanoparticle**	**Specific treatment**	**Start**	**Animal health studies ID/ref. number**
amphotericin B	liposome	dogs injected with blastomyces fungus	1996	ref. 114
cisplatin	hyaluronate nanoparticles	canine brain tumors	2013	AAHSD000024
			2017	AAHSD004339
clodronate	liposome	canine histocytosis	2010	ref. 113
DNA	cationic liposome-DNA complexes + losartan	canine metastatic osteosarcoma	2016	AAHSD004241
doxorubicin	liposome	canine spontaneous tumors	2006	ref. 111
	liposome + radiotherapy	canine soft tissue sarcoma	2010	ref. 112
interleukin-12	GEN-1	canine brain tumors	2016	AAHSD000445
paclitaxel	CTI 52010	canine solid tumors	2010	AAHSD000021
SOD1 gene silencing	adeno-associated virus	canine degenerative myelopathy	2016	AAHSD004063
temozolomide	PLGA	canine brain tumors	2015	AAHSD000385
vitamin E	micelle	equine oxidative stress during prolonged aerobic exercise	2013	ref. 74