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REVIEW

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A systematic review of nanocarriers used in medicine and beyond — definition and categorization framework

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Abstract

Nanocarriers are transport and encapsulation systems that primarily serve to protect and improve the dispersibility of predominantly hydrophobic active ingredients but also enable their targeted delivery and controlled release at the site of action. Nanocarriers are mainly made of either organic or inorganic materials, but various combinations of materials in complex structures are also under development. Most nanocarriers represent entities that are rationally designed to meet the functional requirements of a specific application. They can therefore be understood as Advanced Materials. Nanocarrier systems are already being used in medicine, cosmetics, agriculture, food, and household products. They are therefore used in a variety of products, ideally designed to be safe and sustainable, and may need to be registered before they can be placed on the market. Inspired by medical research, nanocarriers are also increasingly being used for precision farming (nano-agrochemicals) or products, such as air fresheners or lithium-ion batteries, and could thus be released into the environment in large quantities. To enable the identification of critical nanocarriers in subsequent investigations, a comprehensive literature review of the broad and heterogeneous research field of nanocarriers is provided, as well as an approach for categorization based on the origin and chemical composition of their constituent materials. A definition of nanocarriers based on size (1–1000 nm) and function is also proposed for their risk assessment.

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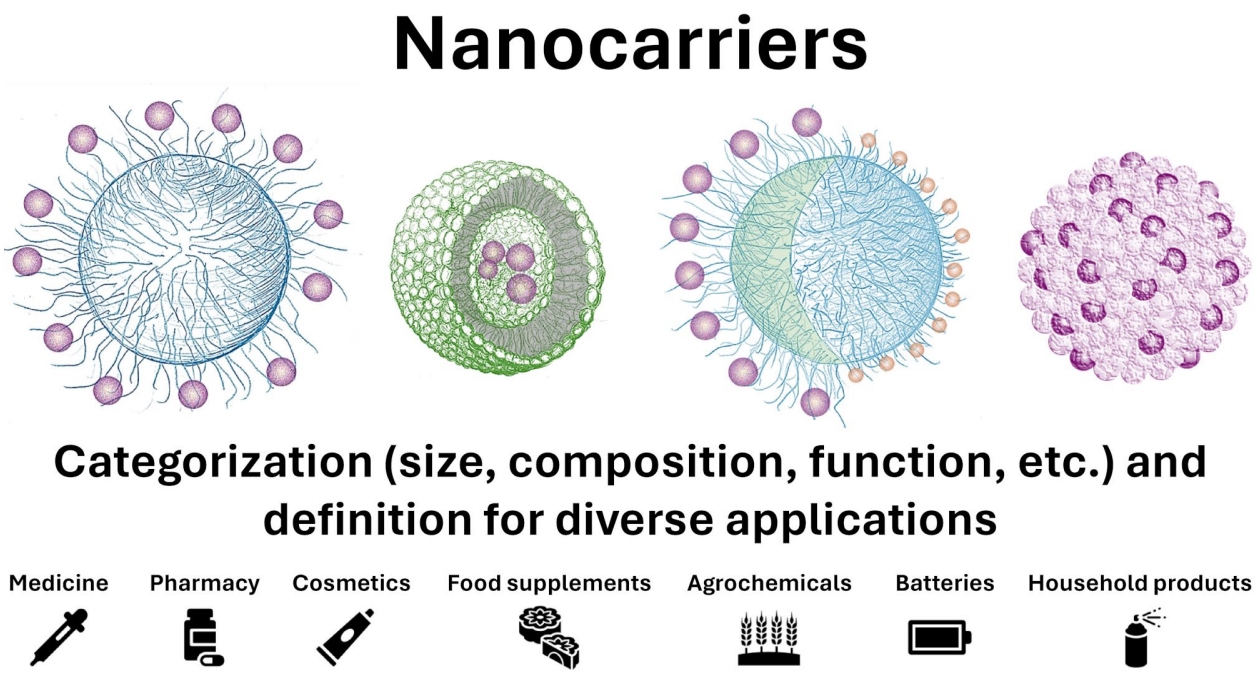
Graphical abstract



Keywords Nanocarrier, Advanced materials, Targeted delivery systems, Nanocarrier categorization, Nanoencapsulation

Introduction

Commonly, nanocarriers are understood to be transport and encapsulation systems of various origins and chemical compositions. Some have been researched for decades and are already in use, primarily in medicine and cosmetics, but also in agriculture, the food sector, and household products. A tabular overview of nanocarriers that are already approved for use in human and veterinary medicine and as pesticides in agriculture can be found in Chariou et al. [1]. The research field is dynamic and constantly evolving. More and more materials are being investigated for their suitability as nanocarriers, and more complex structures are being developed. However, the term "nanocarrier" appeared relatively late in the scientific literature, at the beginning of this century, whereby clinical studies using micellar, liposomal, proteinaceous, polymeric, or viral nanocarriers have been carried out since 1990 [1]. The use of nanocarriers is not limited to medicine, but their outstanding physicochemical properties can be useful for many other applications. For clinical use, nanocarrier-based systems for drug delivery, especially for cancer treatment, vaccines, diagnostics, and combined therapy and diagnostics ("theranostics"), are being intensively researched. In conventional systemic drug therapy, targeted delivery of the agent is not possible, and the entire body is exposed, resulting in potential adverse side effects. Many drugs are also poorly soluble or insoluble in water, limiting their clinical use [2]. To overcome these drawbacks, delivery systems have been developed to transport and protect the drug, enable targeted delivery to specific sites in the body, and increase bioavailability [3].

Various nanocarriers are used in cosmetic products to transport an active ingredient across the skin barrier, improve its dispersibility and stability, and reduce the amount needed [4].

Some vitamins, essential oils, phenolic compounds or carotenoids have beneficial properties for human health, but are poorly soluble in water, and sometimes sensitive to temperature and oxidation, which limits their use in the food industry [5]. By encapsulating such active ingredients in a nanocarrier, the bioavailability, solubility and dispersibility can be increased, and the taste of unpleasant ingredients can be masked. Nanocarriers loaded with antimicrobials can be used for "active packaging" to extend the shelf life of food products by controlled release of the active ingredient [6].

The concept behind using nanocarrier systems in agriculture is similar to that in medicine. Nanocarriers are designed to enhance the properties of an agrochemical and provide targeted delivery of active ingredients to the desired site of action. This could improve the safety

and efficacy of primarily hydrophobic pesticides, fertilizers, or nutrients and, as a consequence, reduce the total quantities of agrochemicals needed. Controlled release could also help to improve soil fertility and mineral balance [1]. New nanocarrier systems based on sprayable RNA interference techniques show a trend that is also reflected in the plans to use gene drives instead of poisons to combat disease vectors and agricultural pests [7].

Nanocarriers are already also used in household products such as air and fabric fresheners to remove odours [8], and nanocarriers for lithium-ion batteries are being explored to improve battery cycling stability [9]. As research continues at a rapid pace, many more applications are expected to emerge in the future.

Regarding carrier design and particle structure, materials and substances used as nanocarriers are diverse, ranging from simple self-assembling lipid-based vesicles to highly complex DNA structures and particulate complexes. A large number of publications are available on the different types, functionalities, and applications of nanocarriers. Some reviews provide at least an overview of certain types of nanocarrier systems [1, 2, 4, 10–16].

The following attempts to structure the broad field of nanocarriers and provides a more comprehensive overview of nanocarriers that have already been applied or are currently under research and development. This work is an excerpt of a study conducted on behalf of the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection which aims to find suitable strategies for assessing the environmental behavior of nanocarriers. To enable a comprehensive literature search of nanocarriers as a basis for characterizing this area of Advanced Materials, a working definition of nanocarriers was formulated. We propose it as a general definition for nanocarriers as it has proven to be applicable in every context and can be used for any field of application.

Methods

To obtain an overview of the field of nanocarriers, a literature search was carried out using the Web of Science™ Core Collection (WOS) database. Since the term "nanocarrier" is not used in all relevant publications, additional keywords were selected in the context of application and carrier function. String terms consisted of combinations of the terms "nano", "carrier", "food", "food supplements", "medicine", "pharmacy", "agriculture", "cosmetics", "agrochemicals", "fertilizers", "herbicide", "insecticide", "pesticide", "plant", "diagnosis", "disease", "drug", "targeted delivery", "therapy", "controlled release", "delivery system", "delivery vehicle", "drug carrier", "encapsulation", "microencapsulation", "nanoencapsulation", "nanofluidic devices", "sustained release", "transdermal drug delivery" and "vesicular carrier". Author keywords were retrieved from the publications and consolidated by expert knowledge for possible nanocarriers. To complete the list of identified nanocarriers and to gather additional information on potential applications, a search for patent information using the database *SciFinder*^{n}, and a literature review between 1990 and 2023 according to the snowball principle were conducted. The search resulted in 132 different generic terms for nanocarriers (Table S1 of the Supplementary material). These terms formed the basis for deriving a working definition of nanocarrier systems that is applicable to all types of nanocarriers and fields of application (from their use in medicine to cosmetics, food, agrochemicals, etc.). In addition, we developed a categorization approach to systematically divide the type of nanocarriers into categories and subcategories based on their material composition. The methodological approach is described in more detail in Gressler et al. [17].

Results

To narrow down the field of research and to be able to categorize different types of nanocarriers, it was essential in a first step to propose a suitable definition for all areas of application. Although the prefix "nano" suggests it, nanocarriers are not limited to structures on the scale of 1–100 nm as proposed by the European Commission to define the term "nanomaterials" [18]. In the literature, especially in the medical field, carrier systems up to 1000 nm are referred to as "nanocarriers", and some of them, such as pollen shells, may even be several micrometers in size. Chariou and colleagues therefore proposed to apply the term "nanocarrier" to structures with at least one dimension smaller than 1000 nm [1].

For this study and with regard to all application areas, we have extended the size character (1–1000 nm) by the important attribute "functionality". In principle, any substance or material can act as a nanocarrier, provided it can incorporate, encapsulate or chemically bind another substance. Amphiphilic substances are particularly suitable, as they form vesicles in aqueous media, in the interior cavity of which active ingredients can be encapsulated. Alternatively, materials whose surface can be easily functionalized so that active ingredients can be bound to the surface. Together, nanocarriers and active ingredients form a system that performs a specific function. Different functions are possible depending on the application. The simplest is to protect sensitive active ingredients from external influences and premature degradation, and to improve the solubility of poorly water-soluble or highly hydrophobic substances. Novel nanocarrier systems can also perform other functions, such as passive or active transport of an active ingredient to the target site (targeted delivery), control of its release, and improving its safety and efficacy. Consequently, nanocarriers can be

understood as Advanced Materials, which can be defined as "materials that are rationally designed to fulfill the functional requirements of a certain application" [19, 20]. The function as a carrier or encapsulation system distinguishes nanocarriers from other nano objects, and also (nano)composites. The latter are also composed of different materials, but in a rigid structure that inhibits the dynamic changes necessary for cargo loading and release. The same applies if nanoparticles and other nano-objects are surface modified or functionalized with ligands, e.g., to increase their colloidal stability. These materials cannot be considered as nanocarriers either, as the purpose of such surface modifications or functionalization is to improve the performance of the object itself, rather than to transport or protect an active ingredient.

In summary, we therefore propose that nanocarriers be defined as any material, material combination, chemical substance, compound, or structure with at least one dimension smaller than 1000 nm, capable of encapsulating or binding an active ingredient, aiming, among other things, to protect, disperse, transport, or sustain the release of the active ingredient and thereby enhancing its efficacy and/or safety. It is not the carrier structure that brings about the intended effect of the active ingredient. Therefore, pure surface modifications of the active substance are not considered to be nanocarriers for this study. In addition, passive or active mobility is a central property of a nanocarrier in the sense of this definition. Immobile carrier structures such as sensor surfaces or structures used for affinity chromatography are therefore not considered nanocarriers.

Following this definition, a comprehensive literature search on nanocarriers was carried out and evaluated. The identified nanocarriers were categorized into four groups based on their origin and chemical composition (Fig. 1).

Most scientific publications are available for nanocarriers made of either organic or inorganic materials, but combinations of these materials into various hybrid systems are also possible, as well as the design of complex supraparticles of different composition, shape and size, which have been developed for potential use as nanocarriers. The least publications used for this review were identified for nanocarriers based on supraparticles, clusters of individual particles (organic, inorganic or hybrid) representing a distinct group of nanocarriers (Fig. 2).

Inorganic, organic, and hybrid nanocarriers, as well as supraparticles, are schematically illustrated in Fig. 3. Hydrophilic/-phobic or lipophilic/-phobic active ingredients can be covalently bound or electrostatically attached to the particle surface (A or C) consisting of, e.g., organic ligands with functional groups ($-NH_2$, $-COOH$, etc.) or charged polymer coatings, respectively. Alternatively, they can be encapsulated, for example, in nanoliposomes (B) or trapped in the pores of nanostructured materials such as supraparticles (D). Hybrid nanocarriers in the form of Janus particles even make it possible to carry two

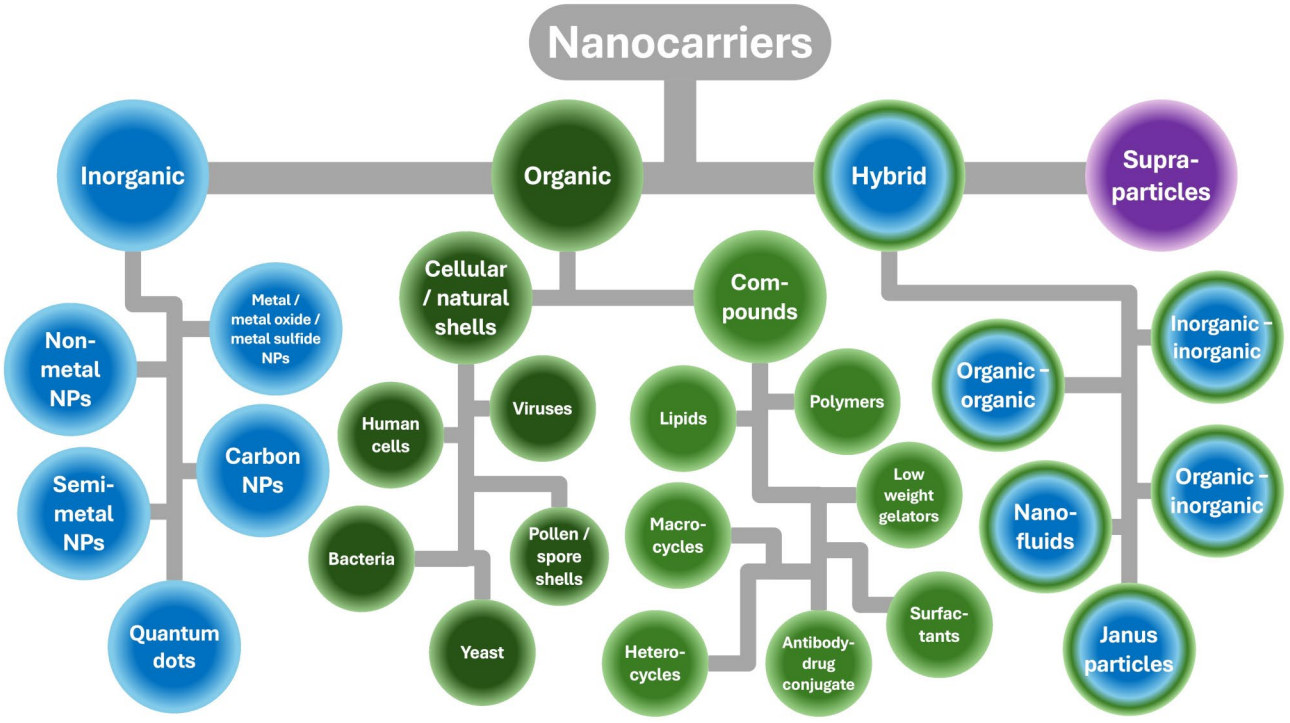


Fig. 1 Types of nanocarriers categorized by their origin and material composition based on Gressler et al. [17]

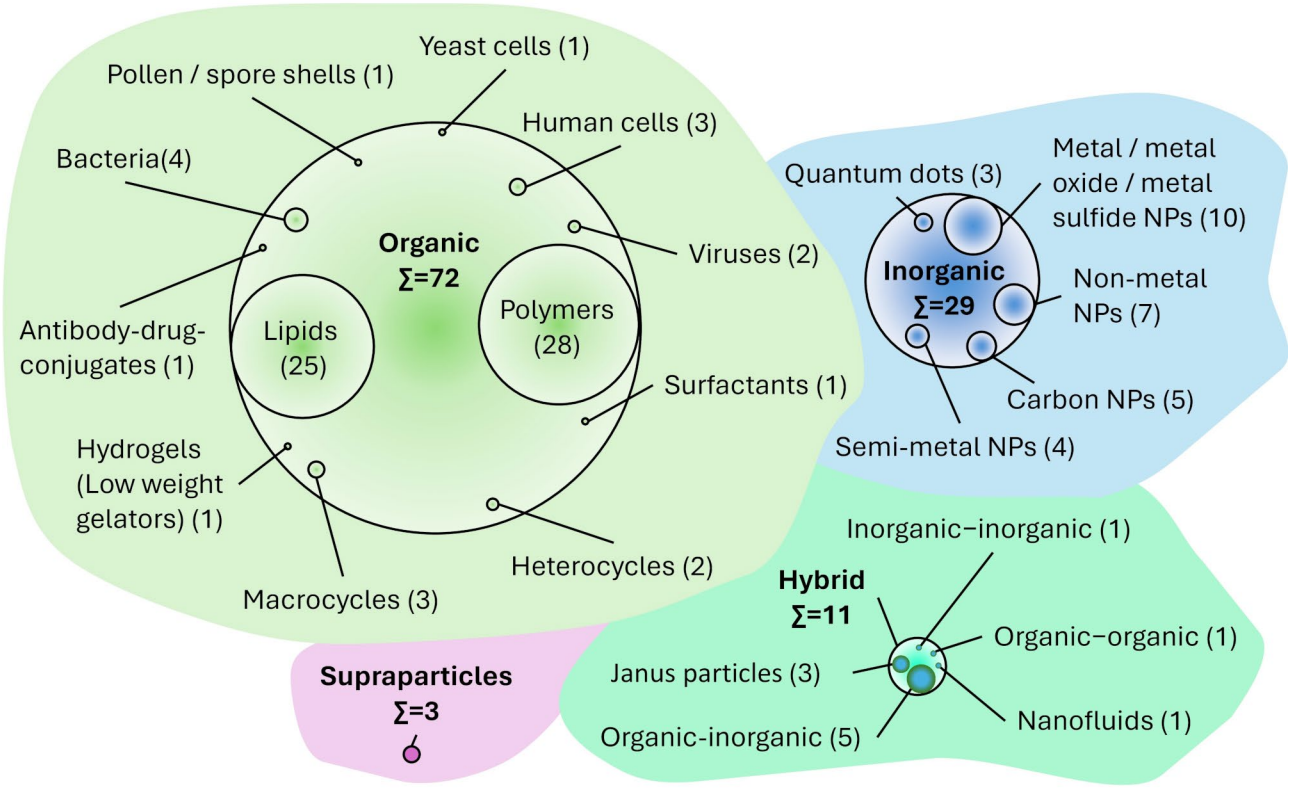


Fig. 2 Number of publications considered for each nanocarrier category. A total (Σ) of 115 studies were analyzed in detail for this review

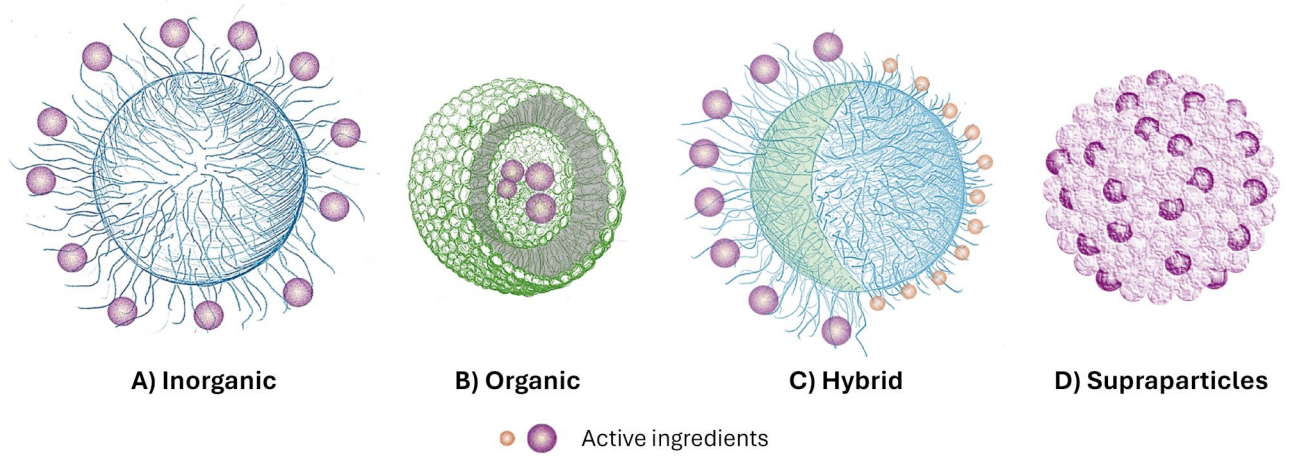


Fig. 3 Schematic illustration of examples of (**A**) inorganic, (**B**) organic, (**C**) hybrid nanocarriers, and (**D**) supraparticles. Active ingredients (purple dots) can be covalently bound or electrostatically attached to the particle surface (**A** or **C**), encapsulated in vesicles (**B**) or trapped in the pores of nanostructured materials (**D**)

different active ingredients on separate parts of the carrier (C).

The different types of nanocarriers, their material and chemical composition, properties, and applications are briefly described in the following chapters. Table 1 provides an overview of the identified types of nanocarriers, related terms, their composition, and main characteristics.

Organic

A wide variety of organic materials, ranging from human cells, viruses, bacteria, pollen and spore shells and yeast cells to various polymers, lipids and other compounds, are suitable materials for organic nanocarriers. Depending on the material used, they exhibit favorable properties such as good biocompatibility, potential biodegradability, high loading capacity, amphiphilicity, and low toxicity,

Table 1 Types, composition, and characteristics of nanocarriers

Nanocarrier type	Related terms	Examples of composition and main components	Examples of nanocarrier-relevant properties and functions	Ref.
Organic				
Human cells	-	Naturally derived human cells (erythrocytes, neutrophils, macrophages, T cells, stem cells)	Biodegradable, biocompatible; regenerative, anti-inflammatory, immunomodulatory properties; sustained and targeted delivery of agents	[21–23]
Viruses	VLPs, virosomes	Naturally derived virus envelopes; membrane lipids, spike glycoproteins	Biocompatible, easy functionalization, morphological uniformity; drug encapsulation in the viral capsid	[24, 25]
Bacteria	Bacterial spores, bacteria ghosts, minicells	Attenuated or genetically modified bacteria, spores, envelopes of bacteria, achromosomal bacteria	Tumoricidal; expression of therapeutic genes, stimuli-responsive, motile; ability to carry and express multiple therapeutic agents	[25–28]
Yeast cells	-	Naturally derived yeast cells	Encapsulation of hydrophobic and hydrophilic agents; low cost; food ingredient	[29]
Pollen and spore shells	-	Naturally derived microcapsules; cellulose, sporopollenin	Size uniformity; resistant to alkaline solutions, acids, and high temperatures; simple production	[30]
Polymer-based	Aerogel, hydrogel, polymer-drug conjugate, protein-polymer conjugate, polyplex, dendrimer, hyperbranched polymer, micelle, polymersome, micro(nano) capsule, micro(nano)sphere, bead, microbead, protein nanocage, DNA origami, micro(nano) sponge	Biopolymers: proteins, polysaccharides, natural polyesters, amidines, nucleic acids; Synthetic polymers: e.g., PLA, PEG, PCl, PSA, DMAEMA; Semi-synthetic polymers	Design of biocompatible, water-soluble and biodegradable structures possible; agents can be encapsulated, integrated in the matrix, chemically conjugated, or bound to the surface of the polymer; stimuli-responsive; delivery of a wide variety of agents	[1, 10, 13, 16, 31–52]
Lipid-based	Liposome, nanosome, niosome, transfersome, ethosome, ultrasome, AOCS, bilosome, spongosome, phytosome, lipofectamine, vesosome, dendrosome, pharmacosome, lipoplex, LNP, SLN, emulsome, NLC, cubosome, hexosome, ISAsomes, nanobubbles, LDC, micro(nano)emulsion, SMEDDS, EV (exosomes, endosomes), organogel	(Phospho)lipids and combinations with, e.g., surfactants, cholesterol, ethanol, enzymes, perfluorocarbons, bile salts, botanical derivatives; complexes with drugs and nucleic acids; cell-derived extracellular vesicles; oils	Easy synthesis, high loading capacity; biocompatible, many modifications and functionalizations possible; most frequent class of nanocarriers; delivery of hydrophobic and hydrophilic agents	[10, 16, 53–73]
Surfactants	Micelle	Amphiphilic surfactants, e.g., Polysorbate 80	Vesicular structure; encapsulation of hydrophobic agents	[74]
Macrocycles	-	Cyclodextrins, cucurbiturils, calix[n]arenes, pillar[n]arenes	Ring-shaped structure, amphiphilic nature, formation of inclusion complexes with agents; many modifications possible; stimuli-responsive, biocompatible	[75, 76]
Heterocycles	-	Spiropyrans, porphyrins	Photochromic molecular switches; biocompatible, stimuli-responsive, fluorescence and photoacoustic properties, low water solubility	[77, 78]
Hydrogels based on low weight gelators	-	Gelators such as gemini imidazolium, sugar functionalized naphthalimide, bis-imidazolium	Transport of agents across skin barrier; pH-responsive	[76]
Antibody drug-conjugate	-	Monoclonal antibody conjugated to a drug	Combination of chemotherapy and immunotherapy; reduction of systemic exposure of drug	[79]

Table 1 (continued)

Nanocarrier type	Related terms	Examples of composition and main components	Examples of nanocarrier-relevant properties and functions	Ref.
Inorganic				
Metal NPs Metal oxide NPs Metal sulfide NPs	MDDS, IONPs, gold nanoflowers	Iron oxides, metal alloys, rare earth minerals, transition materials, Au, Ag, Pd, Pt, Cu, ZnO, TiO_2, MeS, HfO, W, Gd	Magnetic drug delivery possible; enhanced tuneable optical properties; functionalization with targeting ligands, various surface modifications; biocompatible, photothermal and radiofrequency therapy possible; combinations of radiosensitizer and drug	[10, 13, 80–87]
Semi-metallic NPs	MSNs, BPMOs,	SiO_2 NPs, MSNs, BPMOs, SiO_2 aerogels	(Bio)degradable, high loading capacity, easy surface modification; stimuli-responsive; functionalization with targeting ligands	[13, 88, 89]
Non-metallic NPs	BioClay, HNTs, LDHs	CaP, montmorillonite, kaolinite, halloysite, LDHs, Se, HAP	Biocompatible, good loading capacity, high specific surface area, enhancement of drug dissolution; controlled release of agents; systems of LDHs and dsRNA (Bioclay) for sprayable crop protection products; high mechanical strength, pH and temperature resistance of ceramic materials	[13, 90–94]
Carbon-based nanomaterials	CNTs, graphene, MCNs, nanodiamonds, fullerenes, carbon dots	Carbon	Large surface area, thermal conductivity, optical transparency, high strength; some show toxicity, formation of biocorona, functionalization improves dispersibility, biocompatibility and reduce toxicity; targeted delivery possible; stimuli-responsive; MCNs regarded nontoxic and environmentally friendly	[95–98]
Semiconductor QDs	-	CdSe, CdSe/ZnS, CdTe, CdTe/CdS, ZnO QDs; with organic ligands such as PEG or TOPO	High specific surface area and functional groups for drug attachment, pass easily through cell membranes; fluorescent properties for imaging applications; bioconjugations possible; surface modifications necessary for biocompatibility and solubility; stimuli-responsive	[13, 99–101]
Hybrid systems	Nanofluids, Janus nanoparticles	Various combinations of organic and inorganic materials	Combine advantageous properties of organic and inorganic systems; anisotropic nature of JNPs allows loading of two different drugs; suitable for "theranostics"	[102–108]
Supraparticles	-	Nanodiamonds modified with alkylamine; silica combined with cellulose nanofibrils	Particulate systems of one, two or more types of building blocks; combination into complex supraparticle entities leads to new properties and functionalities	[109–111]

Abbreviations: Virus-like particles (VLPs), polylactic acid (PLA), polyethlene glycol (PEG), polycaprolactone (PCL), polysebacic acid anhydride (PSA), 2-(dimethylamino)ethyl methacrylate) (DMAEMA), asymmetric oxygen carrier system (AOCS), lipid nanoparticle (LNP), solid lipid nanoparticle (SLN), nanostructured lipid carrier (NLC), internally self-assembled somes (ISAsomes), lipid-drug conjugate (LDC), self-microemulsifying drug delivery system (SMEDDS), extracellular vesicle (EV), nanoparticles (NPs), magnetic drug delivery system (MDDS), iron oxide nanoparticles (IONPs), mesoporous silica nanoparticles (MSNs), biodegradable periodic mesoporous organosilica nanoparticles (BPMOs), halloysite nanotubes (HNTs), layered double hydroxides (LDHs), hydroxyapatite (HAP), carbon nanotubes (CNTs), mesoporous carbon nanomaterials (MCNs), Janus nanoparticles (JNPs), quantum dots (QDs), trioctylphosphine oxide (TOPO)

and many of them are easy to manufacture [112]. Lipidic nanocarriers, in particular, have been used in medicine and cosmetics for decades, and organic nanocarriers based on polymers, surfactants or cyclodextrins are already used for various applications [1, 113]. A variety of other materials remain still in an early developmental stage.

Human cells

Human cells such as erythrocytes, neutrophils, macrophages, T-cells and stem cells have attracted much interest in medical research due to their biodegradability, low immunogenicity and cytotoxicity, and several clinical trials are currently underway [21]. In particular, erythrocytes have been studied for drug delivery since 1973 [22]. They have a high loading capacity, a reversibly deformable membrane and a long half-life, making them suitable for encapsulating a wide range of drugs and contrast media and for controlled drug release [21]. Stem cells are also the focus of drug delivery research because they can be easily isolated, grown in culture and targeted to a specific site of action [23]. They also exhibit regenerative and immunomodulatory properties. However, there are still some obstacles to overcome for their use as nanocarriers, such as the possibility of immune reactions and tumor formation, poor retention after transplantation, and low drug loading efficiency [21].

Viruses

The capsids of a wide range of different viruses, such as Cowpea chlorotic mottle virus, Cowpea mosaic virus, Red clover necrotic mosaic virus, Tobacco mosaic virus, Beet yellow mosaic virus, Brome mosaic virus, Human polyomavirus, Hibiscus chlorotic ringspot virus, Alphaviruses, and Bacteriophage MS2 and M13 have been investigated for their use as nanocarriers [24]. These so-called Virus-Like Particles (VLPs) range in size from about 10 nm to over a micron, showing good biocompatibility and ease of manufacture. The encapsulation of drugs, gold or magnetic nanoparticles, for example, follows the same principles of self-assembly and disassembly as the packaging of viral RNA or DNA into the viral capsid. The surface of VLPs can also be modified, for example with polymers such as polyethylene glycol (PEG), to reduce their immunogenicity and increase their half-life [24]. Targeting ligands such as folic acid or antibodies can also be attached to their surface. However, a thorough investigation of the toxicity and biodistribution of VLPs in vivo is essential before their application in medicine. Concerning agricultural applications, the group of N.F. Steinmetz has shown that spherical nanoparticles obtained by heat treatment from the Tobacco mild green mosaic virus (TMGMV) can be used to deliver agrochemicals [114]. The same nanoparticles derived from plant viruses are also being considered as a drug delivery system [115].

Virosomes are particles consisting of membrane lipids and spike glycoproteins from viruses, including, for example, the Sendai virus, Semliki Forest virus, vesicular stomatitis virus, and Sindbis virus. They have been developed as carriers for nucleic acids, genes, or drugs [25]. Virosomes fuse with the endosome or plasma membrane and deliver the cargo into the cytoplasm of host cells. Different routes of application for drug delivery are possible, such as topical, oral, and transdermal [25].

Bacteria

Some species of bacteria, attenuated or genetically modified, are currently under research for cancer therapy due to their intrinsic tumoricidal properties and for drug delivery [26]. They have favorable drug delivery properties, such as high motility and the capability to carry and express various therapeutic proteins. They can also be eliminated by antibiotics [26]. Anaerobic bacteria such as species belonging to the genus *Clostridium* as well as *Salmonella typhi*, *Bifidobacterium*, *Salmonella choleraesuis*, *Vibrio cholerae*, *Listeria monocytogenes*, and *Escherichia coli* can proliferate and accumulate in the oxygen-poor environment of tumor tissue, leading to the destruction of the tumor, while being harmless to oxygen-rich healthy tissue [27]. Combination with chemotherapeutic agents can enhance the tumoricidal effect [26]. Responsiveness to stimuli such as temperature, light, and pH can also be observed in bacteria and can be exploited for targeted delivery [25]. Drug delivery systems based on bacteria are currently in clinical trials, but there are still obstacles to overcome, such as toxicity and the potential for mutation [27].

Hollow and empty vesicles constituted by the membrane of genetically modified Gram-negative bacteria such as *Escherichia coli* are called "Bacteria ghosts" [25]. They are unable to replicate but have structural, immunogenic, and bioadhesive properties that are favorable for drug delivery. Active ingredients such as DNA, antigens or proteins can be encapsulated within these structures [25].

"Bacteria minicells" are usually the result of aberrant cell division in bacteria and consist of membranes, ribosomes, RNA, and proteins. They are achromosomal, unable to proliferate, and are being investigated for the delivery of drugs, vaccines, and RNA in medicine [28]. *Escherichia coli* bacteria, for example, are capable of first producing dsRNA, and then the "minicells" in which the dsRNA is encapsulated [28].

Yeast cells

Yeast cells are surrounded by a phospholipid membrane, making them suitable for encapsulating hydrophobic as

well as hydrophilic substances. They are frequently used in the food industry for fermentation [29]. In particular, yeast of the species *Saccharomyces cerevisiae* or baker's yeast is being investigated for potential application in drug delivery. Yeast cell encapsulation is a relatively cheap and simple method, requiring only the yeast cells (live, wet, or dried, plasmolyzed or non-plasmolyzed), the active ingredient, and water. For example, yeast cells can be used in the food industry to encapsulate flavors or other hydrophobic substances to protect and control their release [29].

Pollen and spore shells

The shells of pollen or spores are a new class of naturally derived carriers being explored for drug delivery. They are studied for medical purposes or for the delivery of nutraceuticals in the food industry because of several interesting properties such as size uniformity (1–2 µm), resistance to alkalis, acids, and high temperatures [30]. The porous shells are composed of an inner layer of mainly cellulose and an outer layer of the protein sporopollenin. They can be easily loaded with a cargo in solution by simple mixing. Encapsulating an active ingredient in empty pollen or spore shells can enhance bioavailability, allow controlled release and protect the cargo from oxidation [30].

Polymers

A wide variety of natural or synthetic polymers are under investigation or already in use for the delivery of drugs, vaccines, nucleic acids, small molecules, proteins, agrochemicals, and cosmetic ingredients. The structures can be manifold, ranging from spherical particles, dendrimers, gels, porous sponges and complexes to sophisticated, computer-generated three-dimensional structures. Polymers enable the design of water-soluble, biocompatible, stable and some even biodegradable nanocarriers [10]. However, they may also have some drawbacks to overcome, such as toxicity, which is why only a few polymeric nanocarriers are currently approved for medical use. There are several ways to create a polymeric nanocarrier system. The active ingredient can either be encapsulated, conjugated to the polymer, bound to its surface or integrated into the polymer matrix [10].

A variety of natural polymers has proven suitable for polymeric nanocarriers, including proteins such as albumin, fibroin, ferritin, vault protein, gliadin, elastin or soy protein, and polysaccharides, such as heparin, chitosan, carboxymethylchitosan, chitin, alginate, carageenan, xanthan, cellulose, carboxymethylcellulose, starch, gum arabic, hyaluronic acid, dextran, zein, gelatin, lignin, pectin, collagen, gellan or fucoidan. For example, the active ingredient can be entrapped or encapsulated (in oil droplets) in lignin for use as an antimicrobial, drug or gene vector [116]. Natural polyesters such as polyhydroxyalkanoate (PHA), amidines, such as guanidin, glycosides, such as glycyrrhizic acid or nucleic acids (DNA, RNA) have also been investigated.

There is also a wide range of synthetic polymers with suitable properties such as polylactic acid (PLA), poly(lactide-co-glycolide) acid (PLGA), PEG, polycaprolactone (PCL), polysebacic acid anhydride (PSA), polymethacrylates, poly(2-(dimethylamino)ethyl methacrylate (PDMAEMA), 2-(dimethylamino)ethyl methacrylate (DMAEMA), poly(alkyl cyanoacrylate) (PACA), polyethyleneimine (PEI), polyamidoamine (PAMAM), polyethylene oxide, polypropylene oxide, poloxamers (block copolymer of ethylene oxide and propylene oxide), polyethyleneimines, tocopheryl polyethylene glycol succinate (TPGS), poly(epsilon(ε)-caprolactone), polyurethanes, silicone (polyorganosiloxanes). Research is also being carried out on semi-synthetic polymers, such as methyl acrylamide-modified gelatine. Patents have already been authorized where polyelectrolytes, such as poly(acrylic acid), poly(methacrylic acid), poly (styrene sulfonate), chitosan, poly (dimethyldiallylammonium chloride), poly (allylamine hydrochloride), or copolymers or graft polymers and combinations thereof, are used for nanocarriers of herbicides, insecticides, fertilizers etc. [117].

The following is an attempt to give a brief overview of the diversity of polymeric nanocarriers, starting with aerogels made of biopolymers. Aerogels are highly porous and consist of 99.98% air by volume but exhibit outstanding strength [31]. They have several other beneficial properties, such as a wide range of functional groups, making them interesting for drug delivery purposes. Aerogels even enable the controlled release of active ingredients by adjusting their pore size or by selecting a suitable pH value or temperature that triggers a release [31].

Another form of gel of interest for use as a nanocarrier is the so-called hydrogel, which has a high capacity to absorb and retain water. Hydrogels can have different properties depending on the polymer used and are already applied in medicine, particularly for transdermal drug delivery. By using appropriate functional groups, they can be made to respond to different stimuli such as pH, temperature or light [32]. A variety of natural or synthetic polymers can be used for cross-linked hydrogels, also known as nanogels [13].

Pharmaceutical agents can be incorporated into a polymer backbone to reduce their toxicity and increase their stability and bioavailability. With such a polymer-drug conjugate, drugs can be released in a controlled and sustained manner, and even targeted delivery is possible using targeting moieties such as folic acid, antibodies or peptides [33]. Either linear polymers such as polyaspartimide, poly(malic acid), poly(vinyl pyrrolidone), PEG,

and poly(vinyl alcohol) polymer (PVP) or branched polymers such as poly(amidoamine) and poly(ethyleneimine) polymers can be used to synthesize polymer-drug conjugates [33]. Proteins are used as therapeutic agents in medicine, but their instability, rapid clearance from the body, and immunogenicity often limit their use [34]. Attaching a polymer such as PEG to the protein can help to overcome these problems. Such protein-polymer conjugates also allow for controlled release by choosing a stimuli-responsive polymer, such as poly(N-isopropylacrylamide) (PNIPAM) [34].

Gene therapy is becoming increasingly important in medical research and the treatment of genetic diseases. Viral vectors are commonly used for gene transfer, but they harbor immunological risks. A promising alternative is polyplexes, which consist of a polymer conjugated with DNA [13]. Cationic polymers such as polyethyleneimine (PEI), poly-L-lysine (PLL), PAMAM and poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) have been investigated for the synthesis of polyplexes. Polyplexes are biocompatible, and targeted delivery of DNA to cancer cells is possible with appropriate ligands targeting specific membrane proteins of these cells [13].

Dendrimers are another example of polymeric nanocarriers. These are arborescent structures with a central core and radially oriented branches ending in chemical groups that can be functionalized [1, 10]. Dendrimers are suitable for delivering a wide variety of active ingredients, which can be either incorporated into the dendrimer or attached to the surface but are being investigated mainly for delivering nucleic acids, and small molecules [10]. A cationic polymeric dendrimer called “Star Polycation” (SPc) has been developed to deliver dsRNA in sprayable form to plants for agricultural pest control [36, 37]. Complexation of dsRNA and SPc promotes the uptake of the agent by plant cells [38]. Hyperbranched polymers (HBPs) resemble dendrimers with their highly and randomly branched structure [39]. They have several beneficial properties for drug delivery, such as good solubility and a high number of terminal functional groups. Active ingredients of different sizes can be incorporated into the internal cavities of HBPs [39].

Amphiphilic block copolymers contain both hydrophobic and hydrophilic segments and can form spontaneously spherical structures in aqueous solutions by self-assembly termed micelles [1]. These polymeric micelles can encapsulate hydrophobic active ingredients and serve as nanocarriers in medicine or agriculture. They are currently being tested in clinical trials [1]. Micelles made from only one type of block copolymer have some disadvantages, but it is possible to combine two or more different amphiphilic polymers into so-called “mixed micelles” to improve their properties, such as stability and drug loading capacity [40]. Polyion complex (PIC) micelles exhibit a core-shell structure where a polyion complex forms the core and a neutral copolymer forms the hydrophilic shell and stabilizes the structure [41]. Apart from synthetic charged block copolymers, other hydrophilic macromolecules such as peptides, proteins, nucleic acids, or oligonucleotides can be used for their synthesis [41].

Polymersomes are vesicular structures similar to liposomes with a bilayer membrane enclosing an aqueous cavity. They are formed by self-assembly of amphiphilic copolymers [42]. Their size ranges from tens of nm to μm, and they are particularly interesting for applications in cancer therapy, diagnostics, and vaccines. Polymersomes are suitable for the encapsulation of both hydrophilic and hydrophobic active ingredients as well as amphiphilic substances. They show better stability than other vesicular nanocarriers due to their thick and tough membrane [42].

Micro- or nanoencapsulation is a process in which a solid, liquid, suspension or gas is surrounded by another material, such as a polymer, using various chemical or physical methods [43]. The result is what is known as a microcapsule or nanocapsule, depending on the size, from about 50 nm to 2 mm. There are also other terms used interchangeably in the literature for this type of spherical structure, such as microbeads or microspheres. These vesicles are suitable for the delivery and controlled release of active ingredients or pharmaceutical agents in medicine, the food industry or cosmetics [43]. Various natural or synthetic polymers can be used for synthesis, for example, microspheres called “Elsepher” made from algae extract, or “Unispheres” made from cellulose are used in cosmetic products [16]. Pyraclostrobin, a fungicide, can be encapsulated in lignin-based polyurethane nanocapsules for agriculture use, which exhibit long-term stability and enzyme-responsive release [116].

Protein-based nanocages are formed by the self-assembly of natural or synthetic proteins into a cage-like structure and have interesting properties for medical applications, such as good biocompatibility and flexibility of design. Drugs or diagnostics can be loaded into the interior of these structures. Surface modifications improve biocompatibility and allow targeted delivery [44].

Polymeric nanocarriers can even be made from nucleic acids (DNA, RNA), which are polymers composed of monomers called nucleotides [118]. They are interesting candidates for drug delivery and gene therapy in medicine because of their programmability and predictability [47]. Computer software enables the design of complex DNA nanostructures with different shapes and names, such as “analogous China map” structure, dolphin-like structure, DNA tweezers, DNA box, DNA polyhedron, etc [48]. The so-called DNA origami technique makes

it possible to design sophisticated structures that allow precise control of the cargo. Such structures can be used, for example, for super-resolution optical imaging [48]. By binding a long strand of DNA to shorter "staple" strands, DNA origami "nanorobots" can be created that could be used to deliver gold or fluorescently labelled antibody fragments, for example [49]. They can even be designed to respond to stimuli. Functional units such as aptamers or small interfering RNAs (siRNAs) can be attached to RNA nanostructures, making them interesting for gene therapy [50].

Polymeric nanosponges are highly porous structures of interest for drug delivery because of their high entrapment efficiency and narrow size distribution [51]. They can be made from polymers such as ethyl cellulose, protect a hydrophobic drug from degradation, and improve its solubility [51]. Microsponges with a size of 5–300 µm consist of microspheres that can be synthesized from methacrylic acid/ethyl acrylate copolymer and can encapsulate a wide range of cosmetic ingredients such as UV filters or fragrances as well as pharmaceuticals [52]. For precision and sustainable agriculture, nanoporous chitosan is a promising nanocarrier to entrap fertilizers, plant protection agents, etc., that can be applied by foliar spraying [119, 120].

Silicone polymers such as dimethicone are widely used in the cosmetic industry for transdermal controlled delivery of cosmetic ingredients due to their high permeability. Active ingredients can also be entrapped within the matrix of cross-linked solid silicone elastomers, which have only recently attracted interest for use in cosmetic products [16].

Lipids

Nanocarriers based on various natural or synthetic lipids are the most common class of approved carriers in medicine and are also widely applied in cosmetic products. These typically spherical structures are formed by self-assembly and exhibit beneficial properties for drug delivery, such as ease of synthesis, the ability to carry high amounts of active ingredients, and the controllability of their physicochemical properties [10].

Liposomes, amphiphilic spherical vesicles with at least one membrane bilayer, consist mainly of phospholipids and are the most common type of lipid-based nanocarriers [53]. Their size ranges from 30 nm to several microns, whereas nano-sized liposomes are called nanosomes, and they are suitable for the delivery of both hydrophilic and hydrophobic compounds [53, 54]. The first liposomal drug was approved in 1995, and since then, several others have entered clinical use. Apart from medicine, liposomes are already being used in cosmetic products and are also of interest to the food industry. Liposomes functionalized and stabilized with PEG have a longer half-life in the bloodstream and are termed "stealth liposomes" [55]. Modifications with other synthetic polymers are also being researched, such as PVP, polyacrylic acid (PAA), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) covalently linked to poly(2-methyl-2-oxazoline) or poly(2-ethyl-2-oxazoline) [55].

Liposomes have undergone further development, resulting in new types with improved properties and various designations. The following are some examples of the variety of "somes" that have already been developed and deployed. These include niosomes, which are a combination of a non-ionic surfactant and cholesterol, transfersomes consisting of phospholipids and surfactants or ethosomes consisting of ethanol in addition to phospholipids [11]. Encapsulation of a UV endonuclease enzyme in a liposome is called ultrasomes, which are used in cosmetic products [57], as well as photosomes, which encapsulate the enzyme photolyase to protect the skin from sun exposure [56], Asymmetric Oxygen Carrier System (AOCS) liposomes, which carry oxygen to the skin and consist of phospholipids and perfluorocarbon, and yeast-based liposomes, which are used to repair and oxygenate the skin [16]. Bilosomes are a modification of niosomes that also contain bile salts [121]. Spongosomes are sponge-like liposomes composed of lipids and surfactants [58], and phytosomes are composed of phospholipids and flavonoids derived from plants [16]. Currently under research for drug delivery are so-called vesosomes and dendrosomes, which encapsulate smaller liposomes resp. dendrimers [60]. Nanocarrier systems of a drug attached to a phospholipid are called pharmacosomes [61]. Cubosomes and hexosomes are non-lamellar liquid crystalline vesicles and belong to the group of ISAsomes (Internally Self-Assembled Somes) [66].

Other liposomal nanocarriers are, e.g., nanotopes, vesicles in the size range of 20–40 nm. They are similar to liposomes but have only a monolayer phospholipid membrane and improved stability [63]. They are designed to deliver cosmetic ingredients across the skin barrier. Liposomes made of cationic lipids are suitable for delivering nucleic acids for gene therapy in medicine. Such complexes of DNA or RNA and lipids are called lipoplexes and have been successfully investigated for cancer therapy [62]. Lipofectamin™ is a commercially available transfection agent based on cationic lipids for delivering nucleic acids into cells. In an aqueous medium the lipids form liposomes in which DNA or RNA can be encapsulated to improve their stability and efficiency [59].

In addition to liposomes, other lipid-based nanocarriers such as lipid nanoparticles (LNPs), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have been developed. They are already being used for drug and gene delivery, vaccines, and for the delivery of cosmetic ingredients to the skin. LNPs have micellar

structures in their core and typically consist of cationic lipids, phospholipids, and cholesterol [10]. SLNs have a core of glycerides and waxes surrounded by a monolayer membrane, and they are stabilized with polymers or surfactants [64]. SLNs are suitable for encapsulation and sustained release of lipophilic substances. SLNs with multiple phospholipid layers called emulsomes have also been developed [65]. NLCs are formulated with a mixture of solid lipids such as stearic acid or cocoa butter, liquid lipids such as glycerin or corn oil, and surfactants. They have been developed to overcome some of the limitations of SLNs and show improved stability, a better safety profile, and a higher loading capacity [64].

Nanobubbles are nanocarriers in which phospholipids, polymers or proteins can be used as the carrier material, and the entrapped active ingredient is a gas. Nanobubbles range in size from 10 to 200 nm and are of interest for the delivery of a therapeutic medical gas such as oxygen. They have also been investigated for drug and gene delivery by attaching the cargo to the surface of the nanobubbles [67].

Drug molecules can be chemically modified with lipids such as fatty acids, cholesterol or phospholipids. Such lipid-drug conjugates (LDCs) improve drug bioavailability, reduce their toxicity, and enhance tumor targeting in cancer therapy [68].

Emulsions are a mixture of water and oil stabilized by an emulsifier that can increase the solubility of poorly water-soluble active ingredients and protect them from degradation. There is an abundance of literature on lipid-based emulsions, such as microemulsions, nanoemulsions, and self-micro- and nanoemulsifying drug delivery systems (SMEDDS, SNEDDS) used in medical, cosmetic, and food products [69]. So-called double or multi-emulsions are actually an "emulsion of an emulsion", e.g. a water-in-oil emulsion dispersed in water. They are particularly interesting to the food industry because unstable hydrophilic substances dissolved in water droplets can be protected from the aqueous environment within the oil droplets [70]. Pickering emulsions are another type of emulsion stabilized by solid particles without an emulsifier, which improves their biocompatibility. They are of particular interest for oral drug delivery in medicine, where the bioavailability of poorly soluble drugs can be increased [71].

Extracellular vesicles (EVs), such as exosomes or endosomes, are produced by cells and are involved in many physiological processes of organisms. Their structure is similar to liposomes, but they are composed of a mixture of different lipids and proteins [72]. EVs are present in all body fluids and have been isolated from various sources, including blood, urine, saliva, breast milk, tears, plant cells, and prokaryotic cell cultures. They exhibit an intrinsic "homing" ability, defined as the ability to migrate to their organ of origin, which makes them interesting candidates for the delivery of drugs or chemotherapeutics to specific cells or diseased tissue [72].

Organogels are three-dimensional semi-solid systems formed by a liquid organic solvent or a lipid and an organogelator [73]. They are promising for drug delivery in medicine and are being investigated, for example, as depot formulations for parenteral extravascular injection. Suitable gelators such as lecithin, sorbitan monostearate or amino acid derivatives ensure the biocompatibility of organogels for drug delivery [73].

Surfactants

Surfactants are widely used in pharmaceuticals, cosmetics, and nutraceuticals to increase the dispersibility of poorly soluble active ingredients in an aqueous medium [74]. Like polymers, amphiphilic surfactants such as polysorbate 80 form micelles above the critical micelle concentration in which hydrophobic substances such as curcumin can be encapsulated [74].

Macrocycles

Macrocycles are chemical compounds that have a ring of twelve or more atoms. Within their ring structure, active ingredients can be encapsulated, protecting them from degradation [75]. They are also interesting for controlled release of the cargo. In particular, cyclodextrins, cucurbiturils, calix[n]arenes, and pillar[n]arenes have been investigated as nanocarriers, while inclusion complexes and hydrogels of cyclodextrins have been the most intensively researched [75] and are widely used in medicine, the cosmetic and food industry, in household products, and pesticide formulations [113].

Cyclodextrins are oligosaccharides consisting of 6 or more α-1,4-linked D-glucopyranose units produced enzymatically from starch [75]. Depending on the number of glucose units, they can be classified as α-, β- and γ-cyclodextrins, which are of particular interest for drug delivery systems in cancer and gene therapy as well as diagnostics. Due to their amphiphilic nature, cyclodextrins can encapsulate a wide range of active ingredients, especially lipophilic and poorly soluble substances [75]. Many derivatives of the three parent types have been developed by modification and functionalization, mainly for medical applications but also for the food industry [113]. Cyclodextrins exhibit many advantageous properties for their use as nanocarriers, such as increased solubility and bioavailability as well as protection of the active ingredient, the possibility of sustained and controlled release, high loading capacity, biocompatibility, site-specific action, and they can even be designed to respond to different stimuli [75].

Further developments of cyclodextrin-based nanocarriers described in the literature include

cyclodextrin-polymer micelles, which exhibit improved stability and can be designed to respond to different stimuli, as well as cyclodextrin nanosponges [76]. These are porous networks of crosslinked cyclodextrins that also show improved stability and allow controlled release of the cargo. Injectable hydrogels made from cyclodextrins and polymers such as PEG, hyaluronic acid or polysaccharides are being researched for medical applications. They can deliver both hydrophilic and hydrophobic drugs and can be designed to respond to NIR [113].

Heterocycles

Heterocycles are compounds characterized by a cyclic structure composed of carbon atoms and containing at least one atom of another chemical element. Spiropyrans (SPs) and porphyrins are two representatives of this group that have been investigated for their use as nanocarriers due to their interesting properties. SPs have the ability to reversibly change their conformation between a closed hydrophobic and an open hydrophilic state by exposure to different external stimuli such as light, pH, heat or metal ions [77]. This ability can be exploited for drug delivery purposes, whereas polymers, inorganic nanoparticles or carbon nanomaterials are functionalized with SPs. Porphyrin-based nanocomposites, such as a composite of gold nanoshells and PLA loaded with an anticancer drug and functionalized with porphyrin, show improved colloidal stability and enable sustained release of the cargo [78]. Such composites with porphyrins are also suitable for "theranostics" because they can simultaneously carry agents for imaging and therapy in medicine. A disadvantage of porphyrins is their low water solubility. To overcome this drawback, various nanoparticles are being investigated for porphyrin transport in aqueous media [78].

Hydrogels based on low weight gelators

Low molecular weight organic gelators (LMOGs) are small molecules, such as derivatives of fatty acids, sugars, amino acids or gemini surfactants, with the ability to gel water or an organic solvent to form a three-dimensional network by self-assembly. They have been explored as an alternative to polymeric gels for drug delivery applications due to their improved biodegradability and low toxicity [122], e.g. hydrogels based on LMOGs for the transport of pharmaceuticals across the skin barrier or such for the pH-responsive delivery of anti-inflammatory drugs [76].

Antibody drug-conjugate

To reduce the systemic exposure of the body to chemotherapeutic drugs and the resulting adverse side effects, the cytotoxic drug can be conjugated via a chemical linker to a monoclonal antibody that directly targets a specific antigen presented on the surface of cancer cells. By carefully selecting the components of such an antibody-drug conjugate, its safety and efficacy can be determined [79].

Inorganic

A wide variety of metallic, semi-metallic, non-metallic nanoparticles, carbon nanomaterials, and semiconductor quantum dots are being explored for use as nanocarriers, and some are already applied for drug delivery in medicine. The majority of inorganic nanocarriers approved for medical use are magnetic iron oxide nanoparticles (IONPs) [10]. Inorganic nanocarriers exhibit advantageous properties such as high loading capacity, biocompatibility, prolonged circulation time in the bloodstream, and the possibility of controlled release of the cargo [13].

Metal, metal oxide, metal sulfide nanoparticles

Metal nanoparticles (MNPs), such as various types of magnetic nanoparticles, silver, gold, palladium, platinum, titanium, zinc, and copper nanoparticles, metal oxide and metal sulfide nanomaterials, are suitable for the delivery of a variety of different drugs, nucleic acids, peptides or antibodies [80]. The active ingredient can be bound to their surface, which can also be easily functionalized with targeting moieties, making MNPs capable of targeted delivery of the cargo [80].

Magnetic nanoparticles such as maghemite (Fe_2O_3), magnetite (Fe_3O_4), iron oxides, metal alloys, rare earth minerals, and transition materials, and to a lesser extent, ferromagnetic nickel and cobalt or antiferromagnetic chromium are suitable for targeted drug delivery in medicine [82]. They can be controlled by the application of an external magnetic field to deliver the cargo to the desired site of action within the body [81]. Surface modifications with different materials, e.g., polymers, lipids, silica, gold, amino groups or other organic substances, are necessary to prevent agglomeration of magnetic nanoparticles, and functionalization with e.g. antibodies or proteins support targeted delivery [2]. Magnetic Drug Delivery Systems (MDDS) have been developed specifically for cancer therapy and the treatment of neurological disorders. In particular, iron oxide nanoparticles (IONPs) and superparamagnetic iron oxide nanoparticles (SPIONs) have been used for magnetic hypothermia treatment, delivery of cytotoxic drugs in cancer and gene therapy. Various targeting moieties, including folic acid, peptides, aptamers or transferrin, are used for their functionalization [13].

Gold nanoparticles (AuNPs) have many beneficial properties for drug delivery, such as low toxicity, biocompatibility, inertness, and high stability [13]. Their surface can be easily modified and functionalized with specific antibodies or folic acid for targeted drug delivery

and other substances such as PEG, transferrin, oligonucleotides or carbohydrates [84]. AuNPs with a chemotherapeutic agent attached to their surface have been successfully investigated for cancer treatment [13], as well as gold "nanoflowers" for NIR photothermal cancer therapy, which are coated with two layers of mesoporous silica to support drug loading [83].

Silver nanoparticles (AgNPs) themselves exhibit antimicrobial and anticancer properties. Due to their low human toxicity and volatility, as well as high thermal stability, they can also be exploited for the delivery of various pharmaceutical agents [85, 86]. To enhance their pharmaceutical properties, they can be functionalized with targeting moieties or coated with polymers [13, 85].

A number of other metals and metal oxides are also the subject of research into their suitability as nanocarriers, for example, palladium nanoparticles have been investigated for their use in medicine due to their high porosity and antibacterial and cytotoxic properties, as have platinum nanoparticles (PtNPs) due to their large surface area, but the use of PtNPs is hampered by their toxicity [80]. Copper nanoparticles are being investigated for cancer treatment and bioimaging due to their interesting chemical, physical, optical and electrical properties, and functionalized zinc oxide nanoparticles have been developed for cancer therapy and treatment of diabetes and inflammation [80]. A variety of different structures of TiO_2, such as nanoparticles, nanotubes, and nanocapsules, are being developed as nanocarriers for the delivery of chemotherapeutic agents. Metal sulfide nanomaterials, such as copper or nickel sulfides, have recently been investigated for drug delivery due to their interesting physicochemical properties and good biocompatibility [80].

Nanoparticles of gold, gadolinium, tungsten, and hafnium oxide exhibit radiosensitizing properties and can also be used for drug delivery [87]. They are potential candidates for cancer treatment with a combination of chemotherapy and radiotherapy. Clinical trials of hafnium oxide nanoparticles for the treatment of cancer are already underway [87].

Semi-metallic nanoparticles

Mesoporous silica nanoparticle (MSN) nanocarriers are degradable and have a high loading capacity [13]. Their surface can be modified with, e.g., PEG to prolong their circulation time in the bloodstream, to increase their stability, and to reduce immune reactions and particle aggregation. MSNs can also be functionalized with appropriate ligands for targeted drug delivery and can be designed to respond to internal or external stimuli [13]. Biodegradable organic bonds between two or more silicon atoms can be incorporated to make MSNs biodegradable. These so-called biodegradable periodic mesoporous organosilicon nanoparticles (BPMOs) also exhibit a large surface area and well-defined pore size, making them interesting for drug delivery [88]. Another form of highly porous silica material are aerogels, which are of particular interest for oral drug delivery due to their ability to improve the stability and dissolution rate of the cargo [89].

Non-metallic nanoparticles

Calcium phosphate nanoparticles are biocompatible, non-toxic and can serve as pH-responsive nanocarriers in cancer therapy [13]. Clay minerals such as kaolinite, montmorillonite, and halloysite are capable of enhancing drug dissolution and are being under investigation for the controlled delivery of a wide range of drugs, proteins, and nucleic acids due to their chemical inertness and large surface area [90]. Halloysite nanotubes have also been successfully investigated for the encapsulation and slow release of vinylene carbonate in lithium-ion batteries to improve their cycling stability [9]. A wide variety of active ingredients can be incorporated into layered double hydroxides, and they are under research for controlled drug delivery in medicine as well as for the delivery of dsRNA for sprayable crop protection products in agriculture [91, 92]. Selenium nanoparticles are promising nanocarriers in biomedicine due to their stability, degradability, and high loading capacity [93]. Hydroxyapatite (HAP) is a ceramic material with high mechanical strength, pH and temperature resistance, stability, and loading capacity [94]. This material can be modified with PEG and functionalized, e.g., with folic acid for anticancer drug delivery. Hollow mesoporous HAP nanoparticles have also been developed as pH-responsive nanocarriers, and HAP microspheres for the sustained release of antibiotics [13]. HAP-urea nanohybrids doped with zinc and magnesium have been shown to be suitable for slow release of nitrogen to crops [94].

Carbon-based nanomaterials

Carbon nanotubes (CNTs), graphene, mesoporous carbon, nanodiamonds, fullerenes, and carbon dots belong to the group of carbon-based nanomaterials (CBNs) that have been intensively studied for their use as nanocarriers due to their favorable structural, physical, and chemical properties not only in medicine but also for agricultural applications [95]. However, there are also some drawbacks such as toxicity, low dispersibility, and the formation of a protein corona in biological media. Surface modifications, for example with polymers, are therefore necessary [95].

CNTs are characterized by high stability and a large surface area to which various active ingredients such as drugs, nucleic acids, enzymes, and antibodies can be attached. They also exhibit strong NIR light absorption

and can be used for photothermal therapy in medicine. They can also be functionalized with thermosensitive polymers for temperature-controlled drug release [95].

Graphene is a 2D CBN consisting of a single layer of carbon atoms arranged in a honeycomb structure with outstanding properties such as high surface area, superior strength, optical transparency and high thermal conductivity [95]. By cutting graphene oxide sheets into fine tiles, so-called nanoribbons can be produced, which have great potential for drug delivery [95]. Graphene quantum dots are small particles of graphene in the size range of 2–20 nm, which exhibit high photothermal stability, dispersibility, and low toxicity, making them interesting for the delivery of chemotherapeutics and nucleic acids in medicine [95]. Graphene oxide surface-modified with polymers has been explored as nanocarriers for pesticide delivery in agriculture [96].

Mesoporous carbon nanomaterials (MCNs), also known as activated carbon, have a specific crystal structure with high surface area and absorbency, and can be easily functionalized. MCNs are commercially available at low cost and are reported to be non-toxic, making them interesting as potential candidates for pesticide nanocarriers in agriculture [97].

Nanodiamonds are core-shell nanoparticles of various sizes and shapes, with a diamond core and a graphite shell [98]. They exhibit good biocompatibility, and their surface can be modified or functionalized with targeting moieties such as antibodies to enable targeted delivery of chemotherapeutics in cancer therapy [123].

Fullerenes are hollow spherical particles consisting of sixty or more carbon atoms. C_{60} fullerenes are also known as "bucky balls" and have been most intensively studied for their use as nanocarriers in medicine, e.g., functionalized with glycine for drug delivery [95]. Carbon dots (CDs) are small spherical particles in size < 10 nm and have only recently become the focus of research for their use as nanocarriers for the delivery of chemotherapeutics, antibiotics, and nucleic acids due to their good dispersibility in water, biocompatibility, and conductivity [95].

Semiconductor quantum dots

Semiconductor quantum dots (QDs) are nanoscale crystalline particles that most commonly exhibit a core-shell structure with an outer organic surface coating for stabilization. They are characterized by a high specific surface area, photostability, and excellent photoluminescence properties [100]. QD-based nanocarriers have been developed by functionalizing their large surface area for controlled and targeted delivery of therapeutic agents [124] such as core-shell QDs composed of CdSe/ZnS, CdTe/CdS, CdTe QDs modified with PEG and CdSe QDs coated with trioctylphosphine oxide (TOPO) [13]. ZnO QDs capped with zwitterionic poly(carboxybetaine methacrylate) (PCBMA) and poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA) and loaded with the chemotherapeutic drug doxorubicin (DOX) are applicable as pH-responsive NCs, whilst imaging based Förster resonance energy transfer (FRET) is possible [125]. Thus, QDs can be used for imaging applications due to their fluorescent properties and high photostability [13]. For instance, the controlled release of drugs can be achieved by using CdSe QDs that have been modified with multiple copies of maltose binding protein (MBP) and bioconjugated with DOX [101]. To avoid the toxic effects of heavy metals used in preparing some semiconductor QDs and to increase their dispersibility in aqueous media, their surface must be modified with organic ligands [124].

Hybrid systems

As briefly presented in the previous chapters, a wide variety of organic and inorganic materials have been researched and developed for potential or actual nanocarrier applications, and each of them has its advantages and disadvantages. Therefore, much research is being done to combine the various materials in different ways to achieve the best possible properties. Such hybrid systems are being investigated for the delivery of drugs, antibacterial agents, genes and vaccines and are also suitable for "theranostics" [103]. Combinations of different polymers, lipids and polymers, polymers or lipids with metals, silica or CBNs are examples of hybrid systems, for which an overview is given below. It should be noted that simple coating of nanoparticles with polymers, e.g., with PEG to impart stealth properties or nanoparticles conjugated with targeting ligands, are often not considered as hybrid systems in the literature [102].

Inorganic/inorganic hybrid systems

The only example of this type of hybrid system found in the literature is a nanocarrier consisting of a core of gold nanorods and a shell of mesoporous silica into which the cargo has been loaded. Single-stranded DNA attached to the surface acts as a kind of switch, opening and closing by turning a NIR laser on and off to allow controlled release of the cargo [104].

Organic/organic hybrid systems

A combination of different polymers or polymers and lipids is the most common type of organic/organic hybrid systems. There is a wide variety of lipids and polymers available and suitable for such nanocarriers, e.g., PLGA/lecithin, PLGA/glyceryl tripalmitate, PLGA/PEG/dextran sulfate, PLA/chitosan, PLGA/phosphatidylcholine/stearic acid, PLGA/modified chitosan, PLA/didodecyldimethylammonium bromide/cetyltrimethylammonium

bromide, or chitosan/hyaluronic acid [102]. In the case of lipid/polymer hybrid nanocarriers, the core usually consists of a polymer encapsulating the drug, and one or two lipid shells enhance biocompatibility and allow targeted delivery of the cargo by attachment of appropriate ligands [102].

Organic/inorganic hybrid systems

In these hybrid systems, organic and inorganic materials are combined to form core/shell nanocarriers to take advantage of the beneficial properties of both building blocks in drug and gene delivery, even allowing combinations of different therapies as well as "theranostics" [103]. Inorganic materials include metals, especially gold and iron oxide nanoparticles, clays, CBNs, QDs, nanoparticles of ZnO or CaP, and mesoporous silica. Polymers, lipids and isolated cell membranes can be used as organic building blocks [103]. For example, a gold shell can increase the physical and chemical stability of a polymer or lipid core, and other metal nanoparticles can be used to make the organic drug carrier, e.g., a liposome, responsive to stimuli and suitable for cancer thermotherapy [102, 103, 105]. Recently, so-called hybrid nanoflowers consisting of proteins or DNA and inorganic materials such as copper, calcium or manganese have been investigated as nanocarriers due to their high efficiency and ability to stabilize enzymes [106].

Nanofluids

Nanofluids are suspensions of nanoparticles in fluids such as ethylene glycol or water and are used for heat transfer in industrial applications [126]. They have recently also gained interest for drug delivery and "theranostic" applications [107], and although the scientific literature on the use of nanofluids as nanocarriers is currently sparse, nanofluids have been included in the present categorization as a distinctive type of carrier. Apart from nanofluids containing single magnetic nanoparticles such as magnetite (Fe_3O_4) or SPIONS, which can be used for magnetic drug delivery as discussed in the previous Chap. 3.2.1 nanofluids containing hybrid nanoparticles are also being developed as nanocarriers. For example, a nanofluid of core/shell Fe_3O_4/oleic acid nanoparticles has been developed for the controlled release of antibiotics [127] and a MWCNT/Fe_30_4 hybrid nanocarrier for magnetic drug delivery [126].

Janus nanoparticles

Janus Particles (JNPs) have two distinct sides made of materials that differ in chemical composition or polarity, which can be used to simultaneously carry active ingredients with different properties, such as drugs or imaging agents, without significant interaction between them [108]. For example, two drugs of opposite polarity and solubility can be loaded on a single JNP, enabling combined chemotherapy and phototherapy as well as "theranostics", and JNPs can also be designed to respond to stimuli, allowing controlled and targeted drug release. Recently, several JNPs with core/shell/shell structure have been developed from different materials such as mesoporous silica, gold and polymers [108].

Janus micro- or nanomotors, which are capable of converting chemical or external energy into motion, are also under investigation and represent an interesting new form of nanocarriers for active drug delivery [106, 108]. For example, a Janus motor based on mesoporous silica nanoparticles coated with a phospholipid layer has been developed that is driven by oxygen and can be functionalized with ligands for targeted drug delivery. Janus motors based on virus capsids, such as Brome mosaic and Cowpea chlorotic mottle viruses, half coated with catalytic platinum, are also under development [108].

Supraparticles

Supraparticles are complex, flexible structures of various shapes and sizes composed of one, two or more different nanoscale building blocks [109, 110]. They exhibit novel combined functionalities that cannot be achieved with single nanoparticles alone, making them interesting nanocarriers for the delivery of active ingredients. For example, supraparticles composed of silica nanoparticles and cellulose nanofribrils have been developed for the delivery of agrochemicals, and those composed of nanodiamonds modified with alkylamine have been developed for the delivery of drugs in medicine [110].

Conclusion

To facilitate the identification of nanocarriers in this characterization of the technological field, we propose a definition based on size and functions. Nanocarriers can be made of any material, material combination, chemical substance, or compound with at least one dimension smaller than 1000 nm capable of encapsulating an active ingredient or binding it, aiming, among other things, to protect, disperse, transport, or sustain the release of the active ingredient and thereby enhancing its properties, efficacy and/or safety. This definition distinguishes nanocarriers from other structures, such as (nano)composites or surface-modified nanoparticles, which lack the functions characteristic of nanocarriers.

Nanocarriers are not only used successfully and beneficially in medicine, but also in many other application areas. Highly complex systems consisting of different organic and inorganic material combinations, core/shell structures with specific surface modifications and functionalization are being developed and research is progressing rapidly. They range from human cells, viruses, bacteria, natural envelopes of pollen or spores to

chemical compounds such as lipids, polymers, macrocycles, heterocycles, surfactants and inorganic nanoparticles, Janus particles, and complex supraparticles. Especially, lipid- and surfactant-based nanocarriers have been used for decades in medicine, food supplements and cosmetics. Macrocyclic compounds such as cyclodextrins have also been used, e.g., in medicine, food supplements or household products. Polymeric nanocarriers are the subject of intensive research, some have already been approved for medical applications and have already entered the agricultural sector. Great expectations are being placed on nanocarriers in the medical sector, especially for cancer therapy, but also for the development of new types of vaccines. Inspired by medical research, nanocarriers are also increasingly being used in other application areas, such as agriculture. The active ingredients transported by nanocarriers are also very diverse, ranging from pharmaceuticals, proteins and enzymes to vitamins, antioxidants, flavors, antimicrobials, cosmetic ingredients, and pesticides. Some are designed to carry "information" in the form of DNA or RNA instead of chemically or enzymatically active substances.

The requirements for nanocarriers can be quite high, depending on the respective application. In the medical field, there are a growing number of approaches that operate at the information level by using therapeutic RNA payloads for, e.g., interference with gene expression or encoding of missing proteins [128]. Efforts are being made to control the behavior of their delivery systems either through specifically applied external physical stimuli such as light of certain wavelengths, ultrasound or magnetic fields or biological stimuli such as the pH value or the activity of certain enzymes [129]. In medicine, however, it is particularly important that the nanocarrier systems created can also be produced in large quantities and function reliably, i.e., reproducibly, in practice, which also means that they can withstand transport and storage.

Advanced nanocarriers for agricultural applications should also respond to stimuli such as pH, light, temperature or enzymes in order to allow a controlled release of the active ingredient [130]. The behavior of nanocarriers or nanomaterials generally depends strongly on the prevailing environmental conditions (pH, ionic strength, organic content, temperature, etc.) as well as specific surface properties (functionalization, coatings for steric or electrostatic stabilization, etc.) [131, 132]. Due to the complex challenges of multiple environmental parameters that need to be considered for efficient application, particularly of pesticides, a range of nanocarriers that respond to more than one stimulus have been developed (for an overview see [133]). However, such complex designs can also be associated with a greater susceptibility to malfunctions. Ma et al. emphasize the need for standardized assessment methods to allow for a more reliable comparison of these intricate and also more expensive delivery techniques [133].

Hofmann et al. pointed out that new materials used as nanocarriers or active ingredients in agriculture should also be sufficiently characterized to be more effective in practice than previous formulations and that they might confront farmers with more challenges in handling than conventional formulations [134].

Due to their direct and intentional use in the environment, nanoagrochemicals are considered particularly critical in terms of potential environmental impacts [135]. The effect that nanocarrier formulations have on the environmental behavior of pesticides is not fully understood [136]. Depending on the function and stability of the nanocarrier, it cannot be excluded that the release, availability, transformation and degradation of the active substance under environmental conditions can be altered in terms of time and location compared to the freely available active substance. Safety concerns about nanoformulations of agrochemicals should be raised especially for those that show altered behavior in terms of degradability or persistence in the environment as well as absorption, biokinetics and toxicity to exposed nontarget organisms compared to conventional formulations [137].

Regarding risk assessment and the approval of drugs, biocides, cosmetics, food supplements or further applications, the labeling of nanocarriers on products is not required by law, so it is often difficult to determine the definitive use of nanocarriers in the various application areas. Especially for environmentally sensitive applications such as in agriculture and for use in consumer products, information and a comprehensive overview of developments are essential to take appropriate regulatory measures for the protection of the environment and consumers – if necessary. Regarding regulations for plant protection products like nanopesticides, Kah et al. highlighted that their durability in biofluids or environmental samples (soil, water, etc.) and the potential for crossing biological barriers are the key factors for human health and environmental risk assessment [138]. From the regulators' point of view, it can be summarized that the durability (stability, biodegradability), mobility through biological barriers or in the environment and the release kinetics of the active ingredients, including the release mechanisms (time-delayed sustained release vs. burst release by a trigger), should be investigated in more detail, especially for new areas of application of nanocarriers such as agriculture or consumer products. For innovators, it is also suggested that design principles that minimize risks to humans and the environment, such as the European Commission's "safe and sustainable by design" guidelines for chemicals and materials

[139], should be applied in the development of nanocarrier products. Their effective implementation would lead to a strategy that is in line with the precautionary principle and would help to avoid negative experiences from the past, such as with persistent organic pollutants or microplastics.

Supplementary Information

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Supplementary Material 1

Author contributions

B.G., C.H., C.Z., F.P., S.G. conceptualized the study. The methodology was developed, and the investigations were carried out by C.H. and S.G. The original draft was written, and all sections were prepared by S.G. F.P. illustrated all figures. B.G., F.P. and S.G. prepared and validated all tables. All co-authors were reviewing and editing the study. A.P., B.G., C.Z., F.P. and S.G. acquired the funds.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

Ethics Declaration

Not applicable.

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